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
Arm title	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.

Arm title	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

Arm title	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 [1]
Response Evaluable Analysis Set	319	120	0 [2]
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	-	-
Withdrew consent	40	63	3
Lost to follow-up	8	5	-

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:	
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	

Primary: Overall Survival (OS)

End point title	Overall Survival (OS)[1]
End point description:	
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. 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:	
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: 177Lu-PSMA-617 + BS/BSOC	Main Study: 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

Statistical analysis title	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

Statistical analysis title	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)[2]

End point description:

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.

End point type	Primary

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:

[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

End point values	Main Study: 177Lu-PSMA-617 + BS/BSOC	Main Study: 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 10.8)	3.4 (2.4 to 4.0)		

Statistical analyses

Statistical analysis title	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: 177Lu-PSMA-617 + BS/BSOC	Main Study: BS/BSOC alone	Sub Study: 177Lu-PSMA-617 + 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-PSMA-617	30	0	2	
TEAE leading to reduction of BSC/BSoC	17	7	1	
TEAE leading to interruption of 177Lu-PSMA-617	85	2	4	
TEAE leading to interruption of BSC/BSoC	50	14	1	
TEAE leading to discontinuation of 177Lu-PSMA-617	63	1	2	
TEAE leading to discontinuation of BSC/BSoC	47	16	0	
Fatal TEAE	19	6	2	

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response (DOR)

End point title	Duration of Response (DOR)[3]

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:

[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

End point values	Main Study: 177Lu-PSMA-617 + BS/BSOC	Main Study: 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: Disease control rate (DCR)

End point title	Disease control rate (DCR)[4]

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

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

Statistical analyses

Statistical analysis title	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: Overall Response Rate (ORR)

End point title	Overall Response Rate (ORR)[5]

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:

[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

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

Statistical analyses

Statistical analysis title	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: 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[6]

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:

[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: 177Lu-PSMA-617 + BS/BSOC	Main Study: 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)[7]

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:

[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

End point values	Main Study: 177Lu-PSMA-617 + BS/BSOC	Main Study: 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

Statistical analysis title	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: Time to first Symptomatic Skeletal Event (SSE)

End point title	Time to first Symptomatic Skeletal Event (SSE)[8]

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:

[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

End point values	Main Study: 177Lu-PSMA-617 + BS/BSOC	Main Study: 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 alkaline phosphatase (ALP) level

End point title	Best percentage change from baseline in alkaline phosphatase (ALP) level[9]

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:

[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

End point values	Main Study: 177Lu-PSMA-617 + BS/BSOC	Main Study: 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: Percentage of participants achieving prostate-specific antigen (PSA) response

End point title	Percentage of participants achieving prostate-specific antigen (PSA) response[10]

End point description:

PSA response was defined as the proportion of patients who had a >= 50% decrease in PSA from baseline confirmed by a PSA measurement >= 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:

[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

End point values	Main Study: 177Lu-PSMA-617 + BS/BSOC	Main Study: 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: Prostate-specific antigen 80 (PSA80) response

End point title	Prostate-specific antigen 80 (PSA80) response[11]

End point description:

PSA80 response was defined as the proportion of participants who had a >= 80% decrease in PSA from baseline confirmed by a PSA measurement >= 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

End point values	Main Study: 177Lu-PSMA-617 + BS/BSOC	Main Study: 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 37.9)	2.0 (0.6 to 5.1)		

Statistical analyses

Statistical analysis title	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: Duration of PSA response

End point title	Duration of PSA response[12]

End point description:

Duration of PSA response was defined as the duration between the date of first document PSA response (i.e. >= 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 >= 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 >= 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:

[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: 177Lu-PSMA-617 + BS/BSOC	Main Study: 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 10.7)	4.4 (2.6 to 10.8)		

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[13]

End point description:

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:

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: 177Lu-PSMA-617 + BS/BSOC	Main Study: 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 intensity scale

End point title	Time to improvement after worsening in BPI-SF pain intensity scale[14]

End point description:

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:

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:

[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: 177Lu-PSMA-617 + BS/BSOC	Main Study: 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: Best percentage change from baseline in lactate dehydrogenase (LDH) level

End point title	Best percentage change from baseline in lactate dehydrogenase (LDH) level[15]

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:

[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.
Justification: Only applicable to study arms for the Main Study

End point values	Main Study: 177Lu-PSMA-617 + BS/BSOC	Main Study: 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 worsening in BPI-SF pain intensity scale

End point title	Time to worsening in BPI-SF pain intensity scale[16]

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 (>=30% of baseline or >=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:

[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.
Justification: Only applicable to study arms for the Main Study

End point values	Main Study: 177Lu-PSMA-617 + BS/BSOC	Main Study: 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: 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[17]

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:

[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

End point values	Main Study: 177Lu-PSMA-617 + BS/BSOC	Main Study: 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: 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)[18]

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 (>=30% of baseline or >=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: 177Lu-PSMA-617 + BS/BSOC	Main Study: 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: 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[19]

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 <= 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:

[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: 177Lu-PSMA-617 + BS/BSOC	Main Study: 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: 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[20]

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: 177Lu-PSMA-617 + BS/BSOC	Main Study: 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[21]

End point description:

Time to worsening was defined as the time from randomization to the first occurring of a >=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: 177Lu-PSMA-617 + BS/BSOC	Main Study: 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[22]

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: 177Lu-PSMA-617 + BS/BSOC	Main Study: 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[23]

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: 177Lu-PSMA-617 + BS/BSOC	Main Study: 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[24]

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: 177Lu-PSMA-617 + BS/BSOC	Main Study: 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[25]

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: 177Lu-PSMA-617 + BS/BSOC	Main Study: 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[26]

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: 177Lu-PSMA-617 + BS/BSOC	Main Study: 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[27]

End point description:

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: 177Lu-PSMA-617 + BS/BSOC	Main Study: BS/BSOC alone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	341	0[28]		
Units: Hours				
arithmetic mean (standard deviation)	28.25 (± 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[29]

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: 177Lu-PSMA-617 + BS/BSOC	Main Study: 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[30]

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 derivates).

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: 177Lu-PSMA-617 + BS/BSOC	Main Study: 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: 177Lu-PSMA-617 + BS/BSOC	Main Study: BS/BSOC alone	Sub Study: 177Lu-PSMA-617 + 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

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			
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
Cardio-respiratory arrest			
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
Myocardial infarction			
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
Supraventricular tachycardia			
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
Ventricular tachycardia			
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
Nervous system disorders			
Brain 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
Cauda equina syndrome			
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
Cerebellar infarction			
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 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
Blood and lymphatic system disorders			
Anaemia			
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
Bone marrow 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	1 / 1	0 / 0	0 / 0
Febrile neutropenia			
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
Leukopenia			
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
Neutropenia			
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
Pancytopenia			
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
Thrombocytopenia			
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
Ear and labyrinth disorders			

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 %

Non-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 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	34 / 529 (6.43%)	1 / 30 (3.33%)	16 / 205 (7.80%)
occurrences (all)	48	1	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	36 / 529 (6.81%)	2 / 30 (6.67%)	4 / 205 (1.95%)
occurrences (all)	40	2	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	1 / 529 (0.19%)	2 / 30 (6.67%)	1 / 205 (0.49%)
occurrences (all)	1	2	1
Dry mouth			
subjects affected / exposed	205 / 529 (38.75%)	5 / 30 (16.67%)	1 / 205 (0.49%)
occurrences (all)	231	5	2
Diarrhoea			
subjects affected / exposed	101 / 529 (19.09%)	3 / 30 (10.00%)	5 / 205 (2.44%)
occurrences (all)	128	3	7
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	4 / 529 (0.76%)	2 / 30 (6.67%)	0 / 205 (0.00%)
occurrences (all)	5	2	0
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	37 / 529 (6.99%)	2 / 30 (6.67%)	8 / 205 (3.90%)
occurrences (all)	38	2	8
Urinary retention			
subjects affected / exposed	8 / 529 (1.51%)	3 / 30 (10.00%)	4 / 205 (1.95%)
occurrences (all)	8	4	4
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	117 / 529 (22.12%)	3 / 30 (10.00%)	26 / 205 (12.68%)
occurrences (all)	154	4	30
Back pain			
subjects affected / exposed	122 / 529 (23.06%)	4 / 30 (13.33%)	29 / 205 (14.15%)
occurrences (all)	141	4	29
Bone pain			
subjects affected / exposed	54 / 529 (10.21%)	3 / 30 (10.00%)	15 / 205 (7.32%)
occurrences (all)	60	3	16
Osteonecrosis of jaw			
subjects affected / exposed	7 / 529 (1.32%)	2 / 30 (6.67%)	1 / 205 (0.49%)
occurrences (all)	7	2	1
Pain in extremity			
subjects affected / exposed	45 / 529 (8.51%)	2 / 30 (6.67%)	12 / 205 (5.85%)
occurrences (all)	55	2	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	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. Details of the protocol amendments are as follows: · V5 extended the long-term follow-up by one year. · V6 extended further the long-term follow-up until a separate long-term follow-up study is available. 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.

Notes:

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: