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

Summary

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

Results information

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

Trial information

Trial identification

Sponsor protocol code	56021927PCR3002

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Aragon Pharmaceuticals, Inc
Sponsor organisation address	10990 Wilshire Blvd., Suite 440, Los Angeles, CA, United States, 90024
Public contact	Clinical Registry Group, Aragon Pharmaceuticals, Inc, ClinicalTrialsEU@its.jnj.com
Scientific contact	Clinical Registry Group, Aragon Pharmaceuticals, Inc, ClinicalTrialsEU@its.jnj.com

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Interim
Date of interim/final analysis	07 September 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	07 September 2020
Global end of trial reached?	No

Notes:

General information about the trial

Main objective of the trial:

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

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

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

Notes:

Population of trial subjects

Subjects enrolled per country

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

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

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	331
From 65 to 84 years	701
85 years and over	20

Subject disposition

Recruitment

Recruitment details:

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

Pre-assignment

Screening details:

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

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo + Androgen Deprivation Therapy (ADT)

Arm description:

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

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

Dosage and administration details:

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

Arm title	Apalutamide + ADT

Arm description:

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

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

Dosage and administration details:

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

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

Period 2

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo + Androgen Deprivation Therapy (ADT)

Arm description:

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

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

Dosage and administration details:

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

Arm title	Apalutamide + ADT

Arm description:

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

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

Dosage and administration details:

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

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

Baseline characteristics

Reporting groups	
Reporting group title	Placebo + Androgen Deprivation Therapy (ADT)

Reporting group description:

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

Reporting group title	Apalutamide + ADT

Reporting group description:

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

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

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

End points

End points reporting groups

Reporting group title	Placebo + Androgen Deprivation Therapy (ADT)

Reporting group description:

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

Reporting group title	Apalutamide + ADT

Reporting group description:

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

Reporting group title	Placebo + Androgen Deprivation Therapy (ADT)

Reporting group description:

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

Reporting group title	Apalutamide + ADT

Reporting group description:

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

Primary: Radiographic Progression-free Survival (rPFS)

End point title	Radiographic Progression-free Survival (rPFS)

End point description:

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

End point type	Primary

End point timeframe:

Up to 35 months

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

Statistical analyses

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

Primary: Overall Survival (OS)

End point title	Overall Survival (OS)

End point description:

OS was defined as the time from date of randomization to date of death from any cause. ITT population included all randomized subjects classified according to their assigned treatment group, regardless of the actual treatment received. Here "99999" signifies that the upper limit of CI was not estimable due to lesser number of events for Placebo + Androgen Deprivation Therapy [ADT] arm and the median, lower limit and upper limit of CI were not estimable due to lesser number of events for Apalutamide + ADT arm.

End point type	Primary

End point timeframe:

Up to 57 months

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

Statistical analyses

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

Secondary: Time to Initiation of Cytotoxic Chemotherapy

End point title	Time to Initiation of Cytotoxic Chemotherapy

End point description:

Time to initiation of cytotoxic chemotherapy was defined as the time from date of randomization to the date of initiation of cytotoxic chemotherapy for prostate cancer. ITT population included all randomized subjects classified according to their assigned treatment group, regardless of the actual treatment received. Here "99999" signifies that the median, lower limit and upper limit of CI were not estimable due to lesser number of events for both the arms.

End point type	Secondary

End point timeframe:

Up to 57 months

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

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

Statistical analyses

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

Secondary: Time to Pain Progression

End point title	Time to Pain Progression

End point description:

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

End point type	Secondary

End point timeframe:

Up to 57 months

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

Statistical analyses

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

Secondary: Time to Chronic Opioid Use

End point title	Time to Chronic Opioid Use

End point description:

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

End point type	Secondary

End point timeframe:

Up to 57 months

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

Statistical analyses

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

Secondary: Time to Skeletal-related Event (SRE)

End point title	Time to Skeletal-related Event (SRE)

End point description:

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

End point type	Secondary

End point timeframe:

Up to 57 months

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

Statistical analyses

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

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to 57 months

Adverse event reporting additional description:

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

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23.0

Reporting groups

Reporting group title	Placebo + Androgen Deprivation Therapy (ADT)

Reporting group description:

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

Reporting group title	Apalutamide + ADT

Reporting group description:

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

Reporting group title	Placebo + ADT to Apalutamide + ADT

Reporting group description:

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

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

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported