Clinical trial results:
Multinational, Phase 3, Randomized, Double-blind, Placebo-controlled Efficacy and Safety Study of Enzalutamide Plus Androgen Deprivation Therapy (ADT) Versus Placebo Plus ADT in Patients With Metastatic Hormone Sensitive Prostate Cancer (mHSPC)

Summary

EudraCT number	2015-003869-28
Trial protocol	NL BE ES DK FI SE DE SK GB FR IT
Global end of trial date	

Results information

Result version number	v2 (current)
This version publication date	18 April 2022
First version publication date	23 April 2020
Version creation reason	

Trial information

Trial identification

Sponsor protocol code	9785-CL-0335

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02677896
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Astellas Pharma Global Development, Inc. (APGD)
Sponsor organisation address	1 Astellas Way, Northbrook, IL, United States, 60062
Public contact	Clinical Trial Disclosure, Astellas Pharma Global Development, Inc. (APGD), astellas.resultsdisclosure@astellas.com
Scientific contact	Clinical Trial Disclosure, Astellas Pharma Global Development, Inc. (APGD), astellas.resultsdisclosure@astellas.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	28 May 2021
Is this the analysis of the primary completion data?	No

Global end of trial reached?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to determine the benefit of enzalutamide plus ADT as compared to placebo plus ADT as assessed by radiographic progression-free survival (rPFS) based on independent central review (ICR).

Protection of trial subjects:

This clinical study was written, conducted and reported in accordance with the protocol, International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP) Guidelines, and applicable local regulations, including the European Directive 2001/20/EC, on the protection of human rights, and with the ethical principles that have their origin in the Declaration of Helsinki. Astellas ensures that the use and disclosure of protected health information (PHI) obtained during a research study complies with the federal, national and/or regional legislation related to the privacy and protection of personal information.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	09 March 2016
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	31 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Japan: 92
Country: Number of subjects enrolled	Taiwan: 30
Country: Number of subjects enrolled	Korea, Republic of: 25
Country: Number of subjects enrolled	Australia: 47
Country: Number of subjects enrolled	New Zealand: 23
Country: Number of subjects enrolled	Russian Federation: 139
Country: Number of subjects enrolled	Slovakia: 81
Country: Number of subjects enrolled	Italy: 68
Country: Number of subjects enrolled	Denmark: 62
Country: Number of subjects enrolled	Romania: 57
Country: Number of subjects enrolled	Spain: 55
Country: Number of subjects enrolled	Netherlands: 54
Country: Number of subjects enrolled	Poland: 47
Country: Number of subjects enrolled	France: 44
Country: Number of subjects enrolled	Finland: 39
Country: Number of subjects enrolled	Belgium: 15

Country: Number of subjects enrolled	Sweden: 12
Country: Number of subjects enrolled	Germany: 10
Country: Number of subjects enrolled	United Kingdom: 2
Country: Number of subjects enrolled	United States: 122
Country: Number of subjects enrolled	Canada: 41
Country: Number of subjects enrolled	Argentina: 10
Country: Number of subjects enrolled	Chile: 52
Country: Number of subjects enrolled	Israel: 23
Worldwide total number of subjects	1150
EEA total number of subjects	544

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)	300
From 65 to 84 years	824
85 years and over	26

Subject disposition

Recruitment

Recruitment details:

Participants with metastatic hormone sensitive prostate cancer (mHSPC) were enrolled in 204 study sites worldwide.

Pre-assignment

Screening details:

The randomization was stratified by volume of disease (low vs high) and prior docetaxel therapy for prostate cancer (no prior docetaxel, 1 to 5 cycles, 6 cycles).

Period 1

Period 1 title	Double Blind Period (up to 35 months)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Carer

Arms

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

Arm description:

Participants received 160 mg of enzalutamide orally once daily during double blind treatment period until radiographic progression was documented or until the participants started an investigational agent or new therapy for treatment of prostate cancer or until any other discontinuation criterion was met. Eligible participants who received enzalutamide during double blind treatment period and provided informed consent to take part in open-label period continued to receive 160 mg enzalutamide orally once daily in open-label period until disease progression, unacceptable toxicity or any other discontinuation criteria were met. ADT (either bilateral orchiectomy or luteinizing hormone-releasing hormone (LHRH) agonist/antagonist) was maintained during study treatment as per standard of care and provided by the site’s pharmacy stock.

Arm type	Experimental
Investigational medicinal product name	Enzalutamide
Investigational medicinal product code	MDV3100
Other name	Xtandi
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Participants received 4 capsules (40 mg each) of enzalutamide orally once a day, for a total daily dose of 160 mg. Treatment was given with or without food and as close as possible to the same time each day.

Arm title	Placebo + Androgen Deprivation Therapy (ADT)

Arm description:

Participants received enzalutamide matching placebo orally once daily during double blind treatment period until radiographic progression was documented or until the participants started an investigational agent or new therapy for treatment of prostate cancer or until any other discontinuation criterion was met. Eligible participants who received enzalutamide matching placebo during double blind treatment period and provided informed consent to take part in open-label period switched to receive 160 mg enzalutamide orally once daily in open-label period until disease progression, unacceptable toxicity or any other discontinuation criteria were met. ADT (either bilateral orchiectomy or LHRH agonist/antagonist) was maintained during study treatment as per standard of care and provided by the site’s pharmacy stock.

Arm type	Placebo

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Participants received 4 capsules of matching placebo orally once a day. Treatment was given with or without food and as close as possible to the same time each day.

Number of subjects in period 1	Enzalutamide + Androgen Deprivation Therapy (ADT)	Placebo + Androgen Deprivation Therapy (ADT)
Started	574	576
Completed	0	0
Not completed	574	576
Death	113	189
Progressive Disease	3	4
Miscellaneous	9	14
Followed-up for OS	31	108
Lost to follow-up	12	12
Continued in OLE	365	180
Withdrawal by subject	41	69

Period 2

Period 2 title	Open-Label Extension (up to 25 months)
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	No
Arm title	Enzalutamide + Androgen Deprivation Therapy (ADT)

Arm description:

Participants received 160 mg of enzalutamide orally once daily during double blind treatment period until radiographic progression was documented or until the participants started an investigational agent or new therapy for treatment of prostate cancer or until any other discontinuation criterion was met. Eligible participants who received enzalutamide during double blind treatment period and provided informed consent to take part in open-label period continued to receive 160 mg enzalutamide orally once daily in open-label period until disease progression, unacceptable toxicity or any other discontinuation criteria were met. ADT (either bilateral orchiectomy or luteinizing hormone-releasing hormone (LHRH) agonist/antagonist) was maintained during study treatment as per standard of care and provided by the site’s pharmacy stock.

Arm type	Experimental

Investigational medicinal product name	Enzalutamide
Investigational medicinal product code	MDV3100
Other name	Xtandi
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Participants received 4 capsules (40 mg each) of enzalutamide orally once a day, for a total daily dose of 160 mg. Treatment was given with or without food and as close as possible to the same time each day.

Arm title	Placebo + Androgen Deprivation Therapy (ADT)

Arm description:

Participants received enzalutamide matching placebo orally once daily during double blind treatment period until radiographic progression was documented or until the participants started an investigational agent or new therapy for treatment of prostate cancer or until any other discontinuation criterion was met. Eligible participants who received enzalutamide matching placebo during double blind treatment period and provided informed consent to take part in open-label period switched to receive 160 mg enzalutamide orally once daily in open-label period until disease progression, unacceptable toxicity or any other discontinuation criteria were met. ADT (either bilateral orchiectomy or LHRH agonist/antagonist) was maintained during study treatment as per standard of care and provided by the site's pharmacy stock.

Arm type	Experimental
Investigational medicinal product name	Enzalutamide
Investigational medicinal product code	MDV3100
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Participants received 4 capsules (40 mg each) of enzalutamide orally once a day, for a total daily dose of 160 mg. Treatment was given with or without food and as close as possible to the same time each day.

Number of subjects in period 2	Enzalutamide + Androgen Deprivation Therapy (ADT)	Placebo + Androgen Deprivation Therapy (ADT)
Started	365	180
Completed	0	0
Not completed	365	180
Followed up for OS	49	18
Death	40	14
Progressive Disease	3	1
Miscellaneous	-	1
Lost to follow-up	2	1
OLE treatment ongoing	261	136
Withdrawal by subject	10	9

Baseline characteristics

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

Reporting group description:

Participants received 160 mg of enzalutamide orally once daily during double blind treatment period until radiographic progression was documented or until the participants started an investigational agent or new therapy for treatment of prostate cancer or until any other discontinuation criterion was met. Eligible participants who received enzalutamide during double blind treatment period and provided informed consent to take part in open-label period continued to receive 160 mg enzalutamide orally once daily in open-label period until disease progression, unacceptable toxicity or any other discontinuation criteria were met. ADT (either bilateral orchiectomy or luteinizing hormone-releasing hormone (LHRH) agonist/antagonist) was maintained during study treatment as per standard of care and provided by the site's pharmacy stock.

Reporting group title	Placebo + Androgen Deprivation Therapy (ADT)

Reporting group description:

Participants received enzalutamide matching placebo orally once daily during double blind treatment period until radiographic progression was documented or until the participants started an investigational agent or new therapy for treatment of prostate cancer or until any other discontinuation criterion was met. Eligible participants who received enzalutamide matching placebo during double blind treatment period and provided informed consent to take part in open-label period switched to receive 160 mg enzalutamide orally once daily in open-label period until disease progression, unacceptable toxicity or any other discontinuation criteria were met. ADT (either bilateral orchiectomy or LHRH agonist/antagonist) was maintained during study treatment as per standard of care and provided by the site's pharmacy stock.

Reporting group values	Enzalutamide + Androgen Deprivation Therapy (ADT)	Placebo + Androgen Deprivation Therapy (ADT)	Total
Number of subjects	574	576	1150
Age categorical			
Units: Subjects			
Age continuous			
All randomized participants.			
Units: years			
arithmetic mean	69.5	69.5	
standard deviation	± 8	± 8.4	-
Gender categorical			
All randomized participants.			
Units: Subjects			
Female	0	0	0
Male	574	576	1150
Race (NIH/OMB)			
All randomized participants.			
Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	75	80	155
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	8	8	16
White	466	460	926
More than one race	0	0	0
Unknown or Not Reported	25	28	53

Ethnicity (NIH/OMB)			
All randomized participants.			
Units: Subjects			
Hispanic or Latino	46	37	83
Not Hispanic or Latino	504	514	1018
Unknown or Not Reported	24	25	49
Volume of Disease			
High volume of disease was defined as metastases involving the viscera or, in the absence of visceral lesions, 4 or more bone lesions, at least 1 of which was in a bony structure beyond the vertebral column and pelvic bone. Low volume was anything that wasn't considered high volume by definition provided. Intent-to-Treat (ITT) population is defined as all participants who were randomized in this study.			
Units: Subjects			
Low	220	203	423
High	354	373	727
Prior Docetaxel Therapy Use			
ITT			
Units: Subjects			
None	471	474	945
1 to 5 cycles	14	11	25
6 cycles	89	91	180

End points

End points reporting groups

Reporting group title	Enzalutamide + Androgen Deprivation Therapy (ADT)

Reporting group description:

Participants received 160 mg of enzalutamide orally once daily during double blind treatment period until radiographic progression was documented or until the participants started an investigational agent or new therapy for treatment of prostate cancer or until any other discontinuation criterion was met. Eligible participants who received enzalutamide during double blind treatment period and provided informed consent to take part in open-label period continued to receive 160 mg enzalutamide orally once daily in open-label period until disease progression, unacceptable toxicity or any other discontinuation criteria were met. ADT (either bilateral orchiectomy or luteinizing hormone-releasing hormone (LHRH) agonist/antagonist) was maintained during study treatment as per standard of care and provided by the site’s pharmacy stock.

Reporting group title	Placebo + Androgen Deprivation Therapy (ADT)

Reporting group description:

Participants received enzalutamide matching placebo orally once daily during double blind treatment period until radiographic progression was documented or until the participants started an investigational agent or new therapy for treatment of prostate cancer or until any other discontinuation criterion was met. Eligible participants who received enzalutamide matching placebo during double blind treatment period and provided informed consent to take part in open-label period switched to receive 160 mg enzalutamide orally once daily in open-label period until disease progression, unacceptable toxicity or any other discontinuation criteria were met. ADT (either bilateral orchiectomy or LHRH agonist/antagonist) was maintained during study treatment as per standard of care and provided by the site’s pharmacy stock.

Reporting group title	Enzalutamide + Androgen Deprivation Therapy (ADT)

Reporting group description:

Participants received 160 mg of enzalutamide orally once daily during double blind treatment period until radiographic progression was documented or until the participants started an investigational agent or new therapy for treatment of prostate cancer or until any other discontinuation criterion was met. Eligible participants who received enzalutamide during double blind treatment period and provided informed consent to take part in open-label period continued to receive 160 mg enzalutamide orally once daily in open-label period until disease progression, unacceptable toxicity or any other discontinuation criteria were met. ADT (either bilateral orchiectomy or luteinizing hormone-releasing hormone (LHRH) agonist/antagonist) was maintained during study treatment as per standard of care and provided by the site’s pharmacy stock.

Reporting group title	Placebo + Androgen Deprivation Therapy (ADT)

Reporting group description:

Participants received enzalutamide matching placebo orally once daily during double blind treatment period until radiographic progression was documented or until the participants started an investigational agent or new therapy for treatment of prostate cancer or until any other discontinuation criterion was met. Eligible participants who received enzalutamide matching placebo during double blind treatment period and provided informed consent to take part in open-label period switched to receive 160 mg enzalutamide orally once daily in open-label period until disease progression, unacceptable toxicity or any other discontinuation criteria were met. ADT (either bilateral orchiectomy or LHRH agonist/antagonist) was maintained during study treatment as per standard of care and provided by the site’s pharmacy stock.

Subject analysis set title	Enzalutamide + Androgen Deprivation Therapy (ADT)
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Participants received 160 mg of enzalutamide orally once daily during double blind treatment period until radiographic progression was documented or until the Participants started an investigational agent or new therapy for treatment of prostate cancer or until any other discontinuation criterion was met. Eligible participants who received enzalutamide during double blind treatment period and provided informed consent to take part in open-label period continued to receive 160 mg enzalutamide orally once daily in open-label period until disease progression, unacceptable toxicity or any other discontinuation criteria were met. ADT (either bilateral orchiectomy or LHRH agonist/antagonist) was maintained during study treatment as per standard of care and provided by the site’s pharmacy stock.

Subject analysis set title	Placebo + Androgen Deprivation Therapy
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Participants received enzalutamide matching placebo orally once daily during double blind treatment period until radiographic progression was documented or until the Participants started an investigational agent or new therapy for treatment of prostate cancer or until any other discontinuation criterion was met. Eligible participants who received enzalutamide matching placebo during double blind treatment period and provided informed consent to take part in open-label period switched to receive 160 mg enzalutamide orally once daily in open-label period until disease progression, unacceptable toxicity or any other discontinuation criteria were met. ADT (either bilateral orchiectomy or LHRH agonist/antagonist) was maintained during study treatment as per standard of care and provided by the site's pharmacy stock.

Primary: Radiographic Progression-Free Survival (rPFS) Based on Independent Central Review (ICR) of Bone Scan According to Prostate Cancer Clinical Trials Working Group 2 (PCWG2) Criteria

End point title	Radiographic Progression-Free Survival (rPFS) Based on Independent Central Review (ICR) of Bone Scan According to Prostate Cancer Clinical Trials Working Group 2 (PCWG2) Criteria

End point description:

rPFS was calculated as the time from the date of randomization to the first objective evidence of radiographic progression disease (rPD) at any time or death up to 24 weeks after study drug discontinuation without documented radiographic progression, whichever occurred first. rPD was defined as progressive disease by RECIST version 1.1 for soft tissue disease or by appearance of 2 or more new lesions on bone scan compared to baseline or week 13 according to PCWG2 criteria, as assessed by ICR or death. In participants with no rPFS event, rPFS was censored on the date of last evaluable radiographic assessment prior to the data analysis cutoff date. In participants with no baseline radiographic assessment, participants with no postbaseline radiographic assessments and participants with all postbaseline radiographic assessments documented as "not evaluable (NE)," rPFS was censored on the date of randomization. ITT population. "99999" denotes data not reached due to low number of events.

End point type	Primary

End point timeframe:

From randomization until the data cut-off date of 14 October 2018; maximum duration of treatment was 26.6 months

End point values	Enzalutamide + Androgen Deprivation Therapy (ADT)	Placebo + Androgen Deprivation Therapy		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	574	576		
Units: months				
median (confidence interval 95%)				
months	99999 (99999 to 99999)	19.4 (16.59 to 99999)		

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

rPFS Treatment Comparison

Comparison groups	Placebo + Androgen Deprivation Therapy v Enzalutamide + Androgen Deprivation Therapy (ADT)

Number of subjects included in analysis	1150
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [1]
Method	Logrank
Parameter estimate	Cox hazard ratio
Point estimate	0.39
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.3
upper limit	0.5

Notes:

[1] - Stratified by volume of disease (low vs high) and prior docetaxel use (yes vs no) during screening period.

Primary: rPFS Based on ICR of Bone Scan According to Protocol Assessment Criteria

End point title	rPFS Based on ICR of Bone Scan According to Protocol Assessment Criteria

End point description:

rPFS was calculated as the time from the date of randomization to the first objective evidence of rPD at any time or death up to 24 weeks after study drug discontinuation without documented radiographic progression, whichever occurred first. rPD was defined as progressive disease by RECIST version 1.1 for soft tissue disease or by appearance of 2 or more new lesions on bone scan compared to baseline for week 13 or the best response on treatment for week 25 or later assessments, as assessed by ICR or death. In participants with no rPFS event, rPFS was censored on the date of last evaluable radiographic assessment prior to the data analysis cutoff date. In participants with no baseline radiographic assessment, participants with no postbaseline radiographic assessments & participants with all postbaseline radiographic assessments documented as "not evaluable(NE)," rPFS was censored on the date of randomization.ITT population."99999" denotes data not reached due to low number of events.

End point type	Primary

End point timeframe:

From randomization until the data cut-off date of 14 October 2018; maximum duration of treatment was 26.6 months.

End point values	Enzalutamide + Androgen Deprivation Therapy (ADT)	Placebo + Androgen Deprivation Therapy		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	574	576		
Units: months				
median (confidence interval 95%)				
months	99999 (99999 to 99999)	19.0 (16.59 to 22.24)		

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

rPFS Treatment Comparision

Comparison groups	Enzalutamide + Androgen Deprivation Therapy (ADT) v Placebo + Androgen Deprivation Therapy
Number of subjects included in analysis	1150
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Logrank
Parameter estimate	Cox proportional hazards model
Point estimate	0.39
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.3
upper limit	0.5

Secondary: Overall Survival (OS)

End point title	Overall Survival (OS)

End point description:

OS was defined as the time from randomization to death due to any cause. In participants still alive at the date of the analysis cutoff point, OS was censored on the last date the participant was known to be alive. OS was analyzed using Kaplan-Meier estimates. ITT population

99999 denotes data was not reached due to low number of events.

End point type	Secondary

End point timeframe:

From date of randomization to OS final analysis (28 May 2021); Maximum treatment duration was 58.6 months

End point values	Enzalutamide + Androgen Deprivation Therapy (ADT)	Placebo + Androgen Deprivation Therapy		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	574	576		
Units: months				
median (confidence interval 95%)	99999 (99999 to 99999)	99999 (49.74 to 99999)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Enzalutamide + Androgen Deprivation Therapy (ADT) v Placebo + Androgen Deprivation Therapy

Number of subjects included in analysis	1150
Analysis specification	Pre-specified
Analysis type	superiority[2]
P-value	< 0.0001 [3]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.66
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.53
upper limit	0.81

Notes:

[2] - Significance level is 0.04. Hazard ratio and 95 % CI are estimated by cox proportional hazards model.
[3] - P-value from stratified log-rank test.

Secondary: Time to Prostate Specific Antigen (PSA) Progression

End point title	Time to Prostate Specific Antigen (PSA) Progression

End point description:

Time to PSA progression was calculated as the time from the date of randomization to the first observation of PSA progression. A PSA progression was defined as a ≥ 25% increase and an absolute increase of ≥ 2 ng/mL above the nadir, which was confirmed by a second consecutive value at least 3 weeks later. In participants with no PSA progression, time to PSA progression was censored on the date of the last PSA sample taken (or last value prior to 2 or more consecutive missed PSA assessments). ITT population. "99999" denotes data not reached due to low number of events.

End point type	Secondary

End point timeframe:

From randomization until the data cut-off date of 14 October 2018; maximum duration of treatment was 26.6 months

End point values	Enzalutamide + Androgen Deprivation Therapy (ADT)	Placebo + Androgen Deprivation Therapy		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	574	576		
Units: months				
median (confidence interval 95%)				
months	99999 (99999 to 99999)	99999 (16.59 to 99999)		

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

Time to PSA Progression Treatment Comparison

Comparison groups	Enzalutamide + Androgen Deprivation Therapy (ADT) v Placebo + Androgen Deprivation Therapy

Number of subjects included in analysis	1150
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [4]
Method	Logrank
Parameter estimate	Cox hazard ratio
Point estimate	0.19
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.13
upper limit	0.26

Notes:

[4] - Stratified by volume of disease (low vs high) and prior docetaxel use (yes vs no) during screening period.

Secondary: Time to Start of New Antineoplastic Therapy

End point title	Time to Start of New Antineoplastic Therapy

End point description:

In participants with a new antineoplastic therapy initiated for prostate cancer after randomization, time to start of a new antineoplastic therapy was defined as the time interval from randomization to the date of the first dose administration of the first antineoplastic therapy. In participants with no new antineoplastic therapy initiated for prostate cancer after randomization, time to start of new antineoplastic therapy was censored on the last visit date or the date of randomization, whichever occurred last. ITT population. 99999 denotes data not reached due to low number of events. Time to start of new antineoplastic therapy was analyzed using Kaplan-Meier estimates.

End point type	Secondary

End point timeframe:

From date of randomization to data cut-off date (28 May 2021); Maximum treatment duration was 58.6 months

End point values	Enzalutamide + Androgen Deprivation Therapy (ADT)	Placebo + Androgen Deprivation Therapy		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	574	576		
Units: months				
median (confidence interval 95%)				
months	99999 (99999 to 99999)	40.5 (26.25 to 99999)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Enzalutamide + Androgen Deprivation Therapy (ADT) v Placebo + Androgen Deprivation Therapy

Number of subjects included in analysis	1150
Analysis specification	Pre-specified
Analysis type	superiority[5]
Parameter estimate	Hazard ratio (HR)
Point estimate	0.38
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.31
upper limit	0.48

Notes:

[5] - Hazard ratio and 95 % CI are estimated by cox proportional hazards model.

Secondary: PSA Undetectable Rate

End point title	PSA Undetectable Rate

End point description:

The PSA undetectable rate was defined as the percentage of participants with undetectable (< 0.2 ng/mL) PSA values at any time during study treatment, of those participants with detectable (≥ 0.2 ng/mL) PSA values at baseline. ITT with detectable PSA at baseline.

End point type	Secondary

End point timeframe:

Up to the data cut-off date of 14 October 2018; maximum duration of treatment was 26.6 months

End point values	Enzalutamide + Androgen Deprivation Therapy (ADT)	Placebo + Androgen Deprivation Therapy		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	511	506		
Units: percentage of participants				
number (confidence interval 95%)				
percentage of participants	68.1 (63.9 to 72.1)	17.6 (14.4 to 21.2)		

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

PSA Undetectable Rate Treatment Comparison

Comparison groups	Enzalutamide + Androgen Deprivation Therapy (ADT) v Placebo + Androgen Deprivation Therapy
Number of subjects included in analysis	1017
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [6]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in rate
Point estimate	50.5

Confidence interval	
level	95 %
sides	2-sided
lower limit	45.3
upper limit	55.7

Notes:

[6] - Stratified by volume of disease (low vs high) and prior docetaxel use (yes vs no) during screening period.

Secondary: Objective Response Rate (ORR)

End point title	Objective Response Rate (ORR)

End point description:

The ORR was calculated as the percentage of participants who achieved a completed response (CR) or a partial response (PR) (unconfirmed responses) in their soft tissue disease using the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 assessed by ICR. ITT participants with measurable disease at baseline.

End point type	Secondary

End point timeframe:

Up to the data cut-off date of 14 October 2018; maximum duration of treatment was 26.6 months

End point values	Enzalutamide + Androgen Deprivation Therapy (ADT)	Placebo + Androgen Deprivation Therapy		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	177	182		
Units: percentage of participants				
number (confidence interval 95%)				
percentage of participants	83.1 (76.7 to 88.3)	63.7 (56.3 to 70.7)		

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

ORR Treatment Comparison

Comparison groups	Placebo + Androgen Deprivation Therapy v Enzalutamide + Androgen Deprivation Therapy (ADT)
Number of subjects included in analysis	359
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [7]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in rate
Point estimate	19.3

Confidence interval	
level	95 %
sides	2-sided
lower limit	10.4
upper limit	28.2

Notes:

[7] - Stratified by volume of disease (low vs high) and prior docetaxel use (yes vs no) during screening period.

Secondary: Time to Deterioration in Urinary Symptoms

End point title	Time to Deterioration in Urinary Symptoms

End point description:

In participants with deterioration, time to deterioration was calculated as the time interval between randomization and the first deterioration in urinary symptoms at any postbaseline visit. Deterioration in urinary symptoms was defined as an increase in the Quality of Life Prostate-specific Questionnaire(QLQ-PR25) modified urinary symptoms. Subscale score by ≥50% of the standard deviation observed in the QLQ-PR25 modified urinary symptoms subscale score at baseline. Modified urinary symptoms subscale score consisted of 3-items(Q31–Q33) from the QLQ-PR25,each scored from 1(not at all) to 4(very much). Total modified urinary symptoms subscale score ranges from 0-100,higher scores represents a higher level of symptomatology/problems. In participants without deterioration in urinary symptoms, the time to deterioration in urinary symptoms was censored on the date the last urinary symptoms QLQ-PR25 score was calculable. ITT. "99999" denotes data not reached due to low number of events.

End point type	Secondary

End point timeframe:

From randomization to the data cut-off date of 14 October 2018; maximum duration of treatment was 26.6 months

End point values	Enzalutamide + Androgen Deprivation Therapy (ADT)	Placebo + Androgen Deprivation Therapy		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	574	576		
Units: months				
median (confidence interval 95%)				
months	99999 (19.35 to 99999)	16.8 (14.06 to 99999)		

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

Time to Deterioration of Urinary Symptoms Treatment Comparison

Comparison groups	Placebo + Androgen Deprivation Therapy v Enzalutamide + Androgen Deprivation Therapy (ADT)

Number of subjects included in analysis	1150
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2162 [8]
Method	Logrank
Parameter estimate	Cox hazard ratio
Point estimate	0.88
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.72
upper limit	1.08

Notes:

[8] - Stratified by volume of disease (low vs high) and prior docetaxel use (yes vs no) during screening period.

Secondary: Time to First Symptomatic Skeletal Event (SSE)

End point title	Time to First Symptomatic Skeletal Event (SSE)

End point description:

Time to first SSE was calculated as the time from randomization to the occurrence of the first SSE prior to the data analysis cut-off date. An SSE was defined as radiation to bone, surgery to bone, clinically apparent pathological bone fracture, or spinal cord compression. In participants with no SSE by the time of the data cut-off point, time to SSE was censored on the last visit date or the date of randomization, whichever occurred last. ITT population. "99999" denotes data not reached due to low number of events.

End point type	Secondary

End point timeframe:

From randomization to the data cut-off date of 14 October 2018; maximum duration of treatment was 26.6 months

End point values	Enzalutamide + Androgen Deprivation Therapy (ADT)	Placebo + Androgen Deprivation Therapy		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	574	576		
Units: months				
median (confidence interval 95%)				
months	99999 (99999 to 99999)	99999 (99999 to 99999)		

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

Time to SSE Treatment Comparison

Comparison groups	Placebo + Androgen Deprivation Therapy v Enzalutamide + Androgen Deprivation Therapy (ADT)

Number of subjects included in analysis	1150
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0026
Method	Logrank
Parameter estimate	Cox hazard ratio
Point estimate	0.52
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.33
upper limit	0.8

Secondary: Time to Castration Resistance

End point title	Time to Castration Resistance

End point description:

Time to castration resistance was calculated as the time from randomization to the first castration-resistant event. A castration resistance event was defined as any of the following in the presence of castrate levels of testosterone (< 50 ng/dL): radiographic disease progression, PSA progression or SSE, whichever occurred first. In participants with no documented castration resistance event, the time to castration resistance was censored on the latest date from: the date of last radiologic assessment, the last PSA sample taken prior to the start of any new prostate cancer therapy and prior to 2 or more consecutive missed PSA assessments (if applicable), and the last visit date performed. ITT population. "99999" denotes data not reached due to low number of events.

End point type	Secondary

End point timeframe:

From randomization to the data cut-off date of 14 October 2018; maximum duration of treatment was 26.6 months

End point values	Enzalutamide + Androgen Deprivation Therapy (ADT)	Placebo + Androgen Deprivation Therapy		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	574	576		
Units: months				
median (confidence interval 95%)				
months	99999 (99999 to 99999)	13.9 (11.40 to 17.18)		

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

Time to Castration Resistance Treatment Comparison

Comparison groups	Enzalutamide + Androgen Deprivation Therapy (ADT) v Placebo + Androgen Deprivation Therapy

Number of subjects included in analysis	1150
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Logrank
Parameter estimate	Cox hazard ratio
Point estimate	0.28
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.22
upper limit	0.36

Secondary: Time to Deterioration of Quality of Life (QoL) in Functional Assessment of Cancer Therapy-Prostate (FACT-P)

End point title	Time to Deterioration of Quality of Life (QoL) in Functional Assessment of Cancer Therapy-Prostate (FACT-P)

End point description:

Time to deterioration of QoL was calculated as the time interval from the date of randomization to the first date a decline from baseline of 10 points or more in the FACT-P total score was recorded. The FACT-P consists of 27 core items that assess participant function in 4 domains and 12 prostate cancer-related items grouped into 5 subscales as follows: physical wellbeing, social/family wellbeing, emotional wellbeing, functional wellbeing and prostate cancer subscale. Each item is rated on a 0 to 4 Likert-type scale. The FACT-P total score is the sum of all 5 subscale scores of the FACT-P questionnaire and ranges from 0 to 156), where high score represent better quality of life. In participants without FACT-P progression, the time to deterioration of QoL was censored on the date of the last FACT-P total score was calculable. ITT population.

End point type	Secondary

End point timeframe:

From randomization to the data cut-off date of 14 October 2018; maximum duration of treatment was 26.6 months

End point values	Enzalutamide + Androgen Deprivation Therapy (ADT)	Placebo + Androgen Deprivation Therapy		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	574	576		
Units: months				
median (confidence interval 95%)				
months	11.3 (11.04 to 13.83)	11.1 (8.48 to 13.83)		

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

Time to Deterioration of QoL in FACT-P Treatment Comparison

Comparison groups	Placebo + Androgen Deprivation Therapy v Enzalutamide + Androgen Deprivation Therapy (ADT)
Number of subjects included in analysis	1150
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6548
Method	Logrank
Parameter estimate	Cox hazard ratio
Point estimate	0.96
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.81
upper limit	1.14

Secondary: Time to Pain Progression Based on Brief Pain Inventory-Short Form (BPI-SF)

End point title	Time to Pain Progression Based on Brief Pain Inventory-Short Form (BPI-SF)

End point description:

Time to pain progression was defined as time from randomization to the first pain progression event. Pain progression was defined as an increase of ≥ 30% from baseline in the average BPI-SF pain severity score. BPI-SF contains 9 questions with rating scales from 0 (no pain/no interference) to 10 (worst pain/interferes completely). Total score was calculated as the average of each question. Higher scores represent a higher level of pain or interference. In participants with no pain progression event, time to pain progression was censored on the last visit date where BPI-SF was collected. ITT population.

End point type	Secondary

End point timeframe:

From randomization to the data cut-off date of 14 October 2018; maximum duration of treatment was 26.6 months

End point values	Enzalutamide + Androgen Deprivation Therapy (ADT)	Placebo + Androgen Deprivation Therapy		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	574	576		
Units: months				
median (confidence interval 95%)				
months	8.3 (8.25 to 10.91)	8.3 (5.65 to 8.38)		

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

Time to Pain Progression Based on BPI-SF Treatment Comparison

Comparison groups	Enzalutamide + Androgen Deprivation Therapy (ADT) v Placebo

	+ Androgen Deprivation Therapy
Number of subjects included in analysis	1150
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2715
Method	Logrank
Parameter estimate	Cox hazard ratio
Point estimate	0.92
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.78
upper limit	1.07

Adverse events information

Timeframe for reporting adverse events:

From first dose of study drug up to 30 days after last dose of study or prior to initiation of new therapy for prostate cancer, whichever occurred first. Maximum duration of treatment to the data cut-off date of 28 May 2021 was 58.6 months

Adverse event reporting additional description:

Safety Analysis Set (SAF) consisted of all randomized participants who received at least one dose of study drug.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	v23

Reporting groups

Reporting group title	Enzalutamide + Androgen Deprivation Therapy (ADT)

Reporting group description:

Participants received 160 mg of enzalutamide orally once daily during double blind treatment period until radiographic progression was documented or until the participants started an investigational agent or new therapy for treatment of prostate cancer or until any other discontinuation criterion was met. Eligible participants who received enzalutamide during double blind treatment period and provided informed consent to take part in open-label period continued to receive 160 mg enzalutamide orally once daily in open-label period until disease progression, unacceptable toxicity or any other discontinuation criteria were met. ADT (either bilateral orchiectomy or LHRH agonist/antagonist) was maintained during study treatment as per standard of care and provided by the site’s pharmacy stock.

Reporting group title	Placebo + Androgen Deprivation Therapy

Reporting group description:

Participants received enzalutamide matching placebo orally once daily during double blind treatment period until radiographic progression was documented or until the participants started an investigational agent or new therapy for treatment of prostate cancer or until any other discontinuation criterion was met. This arm represents only double blind period.

Reporting group title	Placebo cross-over Enzalutamide

Reporting group description:

Eligible participants who received enzalutamide matching placebo during double blind treatment period and provided informed consent to take part in open-label period switched to receive 160 mg enzalutamide orally once daily in open-label period until disease progression, unacceptable toxicity or any other discontinuation criteria were met. ADT (either bilateral orchiectomy or LHRH agonist/antagonist) was maintained during study treatment as per standard of care and provided by the site’s pharmacy stock. This arm represents only the open-label extension period.

Serious adverse events	Enzalutamide + Androgen Deprivation Therapy (ADT)	Placebo + Androgen Deprivation Therapy	Placebo cross-over Enzalutamide
Total subjects affected by serious adverse events			
subjects affected / exposed	197 / 572 (34.44%)	128 / 574 (22.30%)	36 / 180 (20.00%)
number of deaths (all causes)	154	189	14
number of deaths resulting from adverse events	30	12	3
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenocarcinoma gastric			

subjects affected / exposed	1 / 572 (0.17%)	0 / 574 (0.00%)	0 / 180 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Basal cell carcinoma			
subjects affected / exposed	4 / 572 (0.70%)	5 / 574 (0.87%)	1 / 180 (0.56%)
occurrences causally related to treatment / all	0 / 5	0 / 5	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Benign pancreatic neoplasm			
subjects affected / exposed	0 / 572 (0.00%)	1 / 574 (0.17%)	0 / 180 (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
Bladder cancer			
subjects affected / exposed	3 / 572 (0.52%)	0 / 574 (0.00%)	0 / 180 (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
Bone cancer			
subjects affected / exposed	1 / 572 (0.17%)	0 / 574 (0.00%)	0 / 180 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchial carcinoma			
subjects affected / exposed	0 / 572 (0.00%)	1 / 574 (0.17%)	0 / 180 (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	2 / 572 (0.35%)	1 / 574 (0.17%)	0 / 180 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colon cancer			
subjects affected / exposed	2 / 572 (0.35%)	3 / 574 (0.52%)	1 / 180 (0.56%)
occurrences causally related to treatment / all	0 / 2	0 / 5	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diffuse large B-cell lymphoma			

subjects affected / exposed	0 / 572 (0.00%)	1 / 574 (0.17%)	0 / 180 (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
Gastric cancer			
subjects affected / exposed	0 / 572 (0.00%)	1 / 574 (0.17%)	0 / 180 (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
Laryngeal squamous cell carcinoma			
subjects affected / exposed	1 / 572 (0.17%)	0 / 574 (0.00%)	0 / 180 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung adenocarcinoma			
subjects affected / exposed	0 / 572 (0.00%)	1 / 574 (0.17%)	0 / 180 (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 adenocarcinoma stage 0			
subjects affected / exposed	1 / 572 (0.17%)	1 / 574 (0.17%)	0 / 180 (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
Lung adenocarcinoma stage I			
subjects affected / exposed	1 / 572 (0.17%)	0 / 574 (0.00%)	0 / 180 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung neoplasm malignant			
subjects affected / exposed	3 / 572 (0.52%)	1 / 574 (0.17%)	0 / 180 (0.00%)
occurrences causally related to treatment / all	0 / 6	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Malignant melanoma in situ			
subjects affected / exposed	0 / 572 (0.00%)	1 / 574 (0.17%)	0 / 180 (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
Malignant neoplasm progression			

subjects affected / exposed	11 / 572 (1.92%)	3 / 574 (0.52%)	2 / 180 (1.11%)
occurrences causally related to treatment / all	0 / 12	0 / 4	0 / 4
deaths causally related to treatment / all	0 / 7	0 / 2	0 / 2
Metastases to liver			
subjects affected / exposed	2 / 572 (0.35%)	0 / 574 (0.00%)	1 / 180 (0.56%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Monoclonal gammopathy			
subjects affected / exposed	0 / 572 (0.00%)	1 / 574 (0.17%)	0 / 180 (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
Neuroendocrine carcinoma			
subjects affected / exposed	2 / 572 (0.35%)	1 / 574 (0.17%)	0 / 180 (0.00%)
occurrences causally related to treatment / all	1 / 2	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Non-small cell lung cancer			
subjects affected / exposed	1 / 572 (0.17%)	0 / 574 (0.00%)	1 / 180 (0.56%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Paraproteinaemia			
subjects affected / exposed	0 / 572 (0.00%)	1 / 574 (0.17%)	0 / 180 (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
Plasmacytoma			
subjects affected / exposed	0 / 572 (0.00%)	1 / 574 (0.17%)	0 / 180 (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	1 / 572 (0.17%)	1 / 574 (0.17%)	0 / 180 (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
Squamous cell carcinoma of head and neck			

subjects affected / exposed	0 / 572 (0.00%)	1 / 574 (0.17%)	0 / 180 (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 of skin			
subjects affected / exposed	0 / 572 (0.00%)	1 / 574 (0.17%)	0 / 180 (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
Transitional cell carcinoma			
subjects affected / exposed	0 / 572 (0.00%)	1 / 574 (0.17%)	0 / 180 (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
Tumour pain			
subjects affected / exposed	0 / 572 (0.00%)	1 / 574 (0.17%)	0 / 180 (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
Adenocarcinoma			
subjects affected / exposed	1 / 572 (0.17%)	0 / 574 (0.00%)	0 / 180 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
B-cell lymphoma			
subjects affected / exposed	1 / 572 (0.17%)	0 / 574 (0.00%)	0 / 180 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bowen's disease			
subjects affected / exposed	1 / 572 (0.17%)	0 / 574 (0.00%)	1 / 180 (0.56%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colorectal adenocarcinoma			
subjects affected / exposed	1 / 572 (0.17%)	0 / 574 (0.00%)	0 / 180 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malignant melanoma			

subjects affected / exposed	2 / 572 (0.35%)	0 / 574 (0.00%)	1 / 180 (0.56%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Meningioma			
subjects affected / exposed	0 / 572 (0.00%)	0 / 574 (0.00%)	1 / 180 (0.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metastases to adrenals			
subjects affected / exposed	1 / 572 (0.17%)	0 / 574 (0.00%)	0 / 180 (0.00%)
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 / 572 (0.17%)	0 / 574 (0.00%)	0 / 180 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oesophageal squamous cell carcinoma			
subjects affected / exposed	1 / 572 (0.17%)	0 / 574 (0.00%)	0 / 180 (0.00%)
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 cancer			
subjects affected / exposed	1 / 572 (0.17%)	0 / 574 (0.00%)	0 / 180 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Squamous cell carcinoma of lung			
subjects affected / exposed	1 / 572 (0.17%)	0 / 574 (0.00%)	0 / 180 (0.00%)
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 aneurysm			
subjects affected / exposed	2 / 572 (0.35%)	1 / 574 (0.17%)	0 / 180 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aortic dissection			

subjects affected / exposed	2 / 572 (0.35%)	0 / 574 (0.00%)	0 / 180 (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
Aortic dissection rupture			
subjects affected / exposed	1 / 572 (0.17%)	0 / 574 (0.00%)	0 / 180 (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
Deep vein thrombosis			
subjects affected / exposed	0 / 572 (0.00%)	1 / 574 (0.17%)	1 / 180 (0.56%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Granulomatosis with polyangiitis			
subjects affected / exposed	1 / 572 (0.17%)	0 / 574 (0.00%)	0 / 180 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertensive crisis			
subjects affected / exposed	1 / 572 (0.17%)	1 / 574 (0.17%)	0 / 180 (0.00%)
occurrences causally related to treatment / all	0 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral ischaemia			
subjects affected / exposed	1 / 572 (0.17%)	1 / 574 (0.17%)	0 / 180 (0.00%)
occurrences causally related to treatment / all	0 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Phlebitis			
subjects affected / exposed	1 / 572 (0.17%)	0 / 574 (0.00%)	0 / 180 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombosis			
subjects affected / exposed	1 / 572 (0.17%)	0 / 574 (0.00%)	0 / 180 (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
Vena cava thrombosis			

subjects affected / exposed	0 / 572 (0.00%)	1 / 574 (0.17%)	0 / 180 (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
Circulatory collapse			
subjects affected / exposed	1 / 572 (0.17%)	0 / 574 (0.00%)	1 / 180 (0.56%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Embolism			
subjects affected / exposed	1 / 572 (0.17%)	0 / 574 (0.00%)	0 / 180 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Essential hypertension			
subjects affected / exposed	1 / 572 (0.17%)	0 / 574 (0.00%)	0 / 180 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematoma			
subjects affected / exposed	2 / 572 (0.35%)	0 / 574 (0.00%)	1 / 180 (0.56%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypotension			
subjects affected / exposed	1 / 572 (0.17%)	0 / 574 (0.00%)	0 / 180 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypovolaemic shock			
subjects affected / exposed	1 / 572 (0.17%)	0 / 574 (0.00%)	0 / 180 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lymphoedema			
subjects affected / exposed	1 / 572 (0.17%)	0 / 574 (0.00%)	0 / 180 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral arterial occlusive disease			

subjects affected / exposed	0 / 572 (0.00%)	0 / 574 (0.00%)	1 / 180 (0.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral embolism			
subjects affected / exposed	1 / 572 (0.17%)	0 / 574 (0.00%)	0 / 180 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Venous thrombosis			
subjects affected / exposed	1 / 572 (0.17%)	0 / 574 (0.00%)	0 / 180 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Surgical and medical procedures			
Bone lesion excision			
subjects affected / exposed	1 / 572 (0.17%)	0 / 574 (0.00%)	0 / 180 (0.00%)
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	1 / 572 (0.17%)	2 / 574 (0.35%)	0 / 180 (0.00%)
occurrences causally related to treatment / all	0 / 1	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Death			
subjects affected / exposed	1 / 572 (0.17%)	0 / 574 (0.00%)	0 / 180 (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
Euthanasia			
subjects affected / exposed	1 / 572 (0.17%)	1 / 574 (0.17%)	0 / 180 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0
Fatigue			
subjects affected / exposed	3 / 572 (0.52%)	0 / 574 (0.00%)	0 / 180 (0.00%)
occurrences causally related to treatment / all	3 / 4	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

General physical health deterioration			
subjects affected / exposed	3 / 572 (0.52%)	2 / 574 (0.35%)	0 / 180 (0.00%)
occurrences causally related to treatment / all	0 / 3	3 / 3	0 / 0
deaths causally related to treatment / all	0 / 1	1 / 1	0 / 0
Malaise			
subjects affected / exposed	1 / 572 (0.17%)	0 / 574 (0.00%)	0 / 180 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			
subjects affected / exposed	0 / 572 (0.00%)	1 / 574 (0.17%)	0 / 180 (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
Sudden cardiac death			
subjects affected / exposed	0 / 572 (0.00%)	1 / 574 (0.17%)	0 / 180 (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
Sudden death			
subjects affected / exposed	0 / 572 (0.00%)	2 / 574 (0.35%)	0 / 180 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 2	0 / 0
Chills			
subjects affected / exposed	1 / 572 (0.17%)	0 / 574 (0.00%)	0 / 180 (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
Drowning			
subjects affected / exposed	1 / 572 (0.17%)	0 / 574 (0.00%)	0 / 180 (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
Implant site dehiscence			
subjects affected / exposed	1 / 572 (0.17%)	0 / 574 (0.00%)	0 / 180 (0.00%)
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	2 / 572 (0.35%)	1 / 574 (0.17%)	0 / 180 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pelvic pain			
subjects affected / exposed	1 / 572 (0.17%)	1 / 574 (0.17%)	0 / 180 (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
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 572 (0.00%)	1 / 574 (0.17%)	0 / 180 (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
Dyspnoea			
subjects affected / exposed	0 / 572 (0.00%)	2 / 574 (0.35%)	0 / 180 (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
Interstitial lung disease			
subjects affected / exposed	2 / 572 (0.35%)	0 / 574 (0.00%)	0 / 180 (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
Pneumonia aspiration			
subjects affected / exposed	0 / 572 (0.00%)	1 / 574 (0.17%)	0 / 180 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed	5 / 572 (0.87%)	3 / 574 (0.52%)	1 / 180 (0.56%)
occurrences causally related to treatment / all	1 / 6	0 / 3	0 / 1
deaths causally related to treatment / all	0 / 4	0 / 0	0 / 0
Acute respiratory failure			
subjects affected / exposed	1 / 572 (0.17%)	0 / 574 (0.00%)	1 / 180 (0.56%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Diaphragmatic paralysis			
subjects affected / exposed	1 / 572 (0.17%)	0 / 574 (0.00%)	0 / 180 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eosinophilic pneumonia			
subjects affected / exposed	1 / 572 (0.17%)	0 / 574 (0.00%)	0 / 180 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Epistaxis			
subjects affected / exposed	1 / 572 (0.17%)	0 / 574 (0.00%)	0 / 180 (0.00%)
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 / 572 (0.17%)	0 / 574 (0.00%)	0 / 180 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonitis			
subjects affected / exposed	1 / 572 (0.17%)	0 / 574 (0.00%)	0 / 180 (0.00%)
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			
subjects affected / exposed	3 / 572 (0.52%)	0 / 574 (0.00%)	1 / 180 (0.56%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary haemorrhage			
subjects affected / exposed	1 / 572 (0.17%)	0 / 574 (0.00%)	0 / 180 (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
Respiratory distress			
subjects affected / exposed	1 / 572 (0.17%)	0 / 574 (0.00%)	0 / 180 (0.00%)
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 / 572 (0.17%)	0 / 574 (0.00%)	0 / 180 (0.00%)
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			
Completed suicide			
subjects affected / exposed	1 / 572 (0.17%)	0 / 574 (0.00%)	0 / 180 (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
Confusional state			
subjects affected / exposed	1 / 572 (0.17%)	0 / 574 (0.00%)	0 / 180 (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
Delirium			
subjects affected / exposed	2 / 572 (0.35%)	2 / 574 (0.35%)	1 / 180 (0.56%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Product issues			
Device occlusion			
subjects affected / exposed	0 / 572 (0.00%)	0 / 574 (0.00%)	1 / 180 (0.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	2 / 572 (0.35%)	0 / 574 (0.00%)	0 / 180 (0.00%)
occurrences causally related to treatment / all	3 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Antineutrophil cytoplasmic antibody increased			
subjects affected / exposed	1 / 572 (0.17%)	0 / 574 (0.00%)	0 / 180 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aspartate aminotransferase increased			

subjects affected / exposed	2 / 572 (0.35%)	0 / 574 (0.00%)	0 / 180 (0.00%)
occurrences causally related to treatment / all	3 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood alkaline phosphatase increased			
subjects affected / exposed	1 / 572 (0.17%)	0 / 574 (0.00%)	0 / 180 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood bilirubin increased			
subjects affected / exposed	1 / 572 (0.17%)	0 / 574 (0.00%)	0 / 180 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood creatinine increased			
subjects affected / exposed	2 / 572 (0.35%)	1 / 574 (0.17%)	0 / 180 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood testosterone increased			
subjects affected / exposed	0 / 572 (0.00%)	1 / 574 (0.17%)	0 / 180 (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
Intraocular pressure increased			
subjects affected / exposed	1 / 572 (0.17%)	0 / 574 (0.00%)	0 / 180 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Liver function test abnormal			
subjects affected / exposed	1 / 572 (0.17%)	0 / 574 (0.00%)	0 / 180 (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
Transaminases increased			
subjects affected / exposed	1 / 572 (0.17%)	0 / 574 (0.00%)	0 / 180 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Accidental overdose			

subjects affected / exposed	2 / 572 (0.35%)	1 / 574 (0.17%)	0 / 180 (0.00%)
occurrences causally related to treatment / all	2 / 2	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bone fissure			
subjects affected / exposed	1 / 572 (0.17%)	0 / 574 (0.00%)	0 / 180 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cervical vertebral fracture			
subjects affected / exposed	0 / 572 (0.00%)	2 / 574 (0.35%)	0 / 180 (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
Clavicle fracture			
subjects affected / exposed	1 / 572 (0.17%)	1 / 574 (0.17%)	0 / 180 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Comminuted fracture			
subjects affected / exposed	1 / 572 (0.17%)	0 / 574 (0.00%)	0 / 180 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coronary artery restenosis			
subjects affected / exposed	0 / 572 (0.00%)	1 / 574 (0.17%)	0 / 180 (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	8 / 572 (1.40%)	4 / 574 (0.70%)	1 / 180 (0.56%)
occurrences causally related to treatment / all	4 / 8	1 / 4	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Femoral neck fracture			
subjects affected / exposed	2 / 572 (0.35%)	3 / 574 (0.52%)	0 / 180 (0.00%)
occurrences causally related to treatment / all	1 / 2	1 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fracture displacement			

subjects affected / exposed	1 / 572 (0.17%)	0 / 574 (0.00%)	0 / 180 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Limb injury			
subjects affected / exposed	1 / 572 (0.17%)	1 / 574 (0.17%)	0 / 180 (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 vertebral fracture			
subjects affected / exposed	0 / 572 (0.00%)	1 / 574 (0.17%)	0 / 180 (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
Multiple fractures			
subjects affected / exposed	1 / 572 (0.17%)	0 / 574 (0.00%)	0 / 180 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral artery restenosis			
subjects affected / exposed	1 / 572 (0.17%)	0 / 574 (0.00%)	0 / 180 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Radius fracture			
subjects affected / exposed	1 / 572 (0.17%)	1 / 574 (0.17%)	0 / 180 (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
Road traffic accident			
subjects affected / exposed	1 / 572 (0.17%)	1 / 574 (0.17%)	0 / 180 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Stenosis of vesicourethral anastomosis			
subjects affected / exposed	0 / 572 (0.00%)	1 / 574 (0.17%)	0 / 180 (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 / 572 (0.00%)	1 / 574 (0.17%)	0 / 180 (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
Thoracic vertebral fracture			
subjects affected / exposed	2 / 572 (0.35%)	1 / 574 (0.17%)	0 / 180 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ulna fracture			
subjects affected / exposed	0 / 572 (0.00%)	1 / 574 (0.17%)	0 / 180 (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 postoperative			
subjects affected / exposed	0 / 572 (0.00%)	1 / 574 (0.17%)	0 / 180 (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 tract stoma complication			
subjects affected / exposed	1 / 572 (0.17%)	0 / 574 (0.00%)	0 / 180 (0.00%)
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			
subjects affected / exposed	0 / 572 (0.00%)	1 / 574 (0.17%)	0 / 180 (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 / 572 (0.17%)	0 / 574 (0.00%)	0 / 180 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Concussion			
subjects affected / exposed	2 / 572 (0.35%)	0 / 574 (0.00%)	0 / 180 (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
Craniocerebral injury			

subjects affected / exposed	1 / 572 (0.17%)	0 / 574 (0.00%)	0 / 180 (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
Femur fracture			
subjects affected / exposed	4 / 572 (0.70%)	1 / 574 (0.17%)	0 / 180 (0.00%)
occurrences causally related to treatment / all	1 / 4	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Head injury			
subjects affected / exposed	1 / 572 (0.17%)	0 / 574 (0.00%)	0 / 180 (0.00%)
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 / 572 (0.17%)	0 / 574 (0.00%)	0 / 180 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Humerus fracture			
subjects affected / exposed	1 / 572 (0.17%)	0 / 574 (0.00%)	0 / 180 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infusion related reaction			
subjects affected / exposed	1 / 572 (0.17%)	0 / 574 (0.00%)	0 / 180 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Jaw fracture			
subjects affected / exposed	1 / 572 (0.17%)	0 / 574 (0.00%)	0 / 180 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Overdose			
subjects affected / exposed	1 / 572 (0.17%)	0 / 574 (0.00%)	0 / 180 (0.00%)
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	1 / 572 (0.17%)	0 / 574 (0.00%)	1 / 180 (0.56%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rib fracture			
subjects affected / exposed	1 / 572 (0.17%)	0 / 574 (0.00%)	0 / 180 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Scapula fracture			
subjects affected / exposed	1 / 572 (0.17%)	0 / 574 (0.00%)	0 / 180 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skull fractured base			
subjects affected / exposed	1 / 572 (0.17%)	0 / 574 (0.00%)	0 / 180 (0.00%)
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	2 / 572 (0.35%)	0 / 574 (0.00%)	0 / 180 (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
Thermal burn			
subjects affected / exposed	1 / 572 (0.17%)	0 / 574 (0.00%)	0 / 180 (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
Wound haemorrhage			
subjects affected / exposed	1 / 572 (0.17%)	0 / 574 (0.00%)	0 / 180 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wrong dose			
subjects affected / exposed	1 / 572 (0.17%)	0 / 574 (0.00%)	1 / 180 (0.56%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Acute coronary syndrome			

subjects affected / exposed	2 / 572 (0.35%)	2 / 574 (0.35%)	0 / 180 (0.00%)
occurrences causally related to treatment / all	0 / 2	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Angina pectoris			
subjects affected / exposed	2 / 572 (0.35%)	0 / 574 (0.00%)	0 / 180 (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
Angina unstable			
subjects affected / exposed	1 / 572 (0.17%)	1 / 574 (0.17%)	0 / 180 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arteriosclerosis coronary artery			
subjects affected / exposed	0 / 572 (0.00%)	1 / 574 (0.17%)	0 / 180 (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	8 / 572 (1.40%)	7 / 574 (1.22%)	1 / 180 (0.56%)
occurrences causally related to treatment / all	2 / 10	0 / 10	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial flutter			
subjects affected / exposed	1 / 572 (0.17%)	2 / 574 (0.35%)	0 / 180 (0.00%)
occurrences causally related to treatment / all	0 / 1	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrioventricular block			
subjects affected / exposed	1 / 572 (0.17%)	1 / 574 (0.17%)	0 / 180 (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
Atrioventricular block complete			
subjects affected / exposed	1 / 572 (0.17%)	0 / 574 (0.00%)	1 / 180 (0.56%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrioventricular block second degree			

subjects affected / exposed	1 / 572 (0.17%)	1 / 574 (0.17%)	0 / 180 (0.00%)
occurrences causally related to treatment / all	0 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac arrest			
subjects affected / exposed	2 / 572 (0.35%)	1 / 574 (0.17%)	0 / 180 (0.00%)
occurrences causally related to treatment / all	0 / 2	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure			
subjects affected / exposed	3 / 572 (0.52%)	1 / 574 (0.17%)	1 / 180 (0.56%)
occurrences causally related to treatment / all	2 / 3	0 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure chronic			
subjects affected / exposed	1 / 572 (0.17%)	0 / 574 (0.00%)	0 / 180 (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	1 / 572 (0.17%)	1 / 574 (0.17%)	0 / 180 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0
Cardiopulmonary failure			
subjects affected / exposed	2 / 572 (0.35%)	0 / 574 (0.00%)	0 / 180 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 2	0 / 0	0 / 0
Myocardial infarction			
subjects affected / exposed	3 / 572 (0.52%)	2 / 574 (0.35%)	2 / 180 (1.11%)
occurrences causally related to treatment / all	0 / 3	2 / 2	2 / 2
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Ventricular fibrillation			
subjects affected / exposed	0 / 572 (0.00%)	1 / 574 (0.17%)	0 / 180 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute myocardial infarction			

subjects affected / exposed	3 / 572 (0.52%)	1 / 574 (0.17%)	2 / 180 (1.11%)
occurrences causally related to treatment / all	1 / 3	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Aortic valve incompetence			
subjects affected / exposed	1 / 572 (0.17%)	0 / 574 (0.00%)	0 / 180 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bradycardia			
subjects affected / exposed	1 / 572 (0.17%)	1 / 574 (0.17%)	0 / 180 (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
Coronary artery disease			
subjects affected / exposed	2 / 572 (0.35%)	0 / 574 (0.00%)	1 / 180 (0.56%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Coronary artery stenosis			
subjects affected / exposed	1 / 572 (0.17%)	0 / 574 (0.00%)	1 / 180 (0.56%)
occurrences causally related to treatment / all	0 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial ischaemia			
subjects affected / exposed	0 / 572 (0.00%)	1 / 574 (0.17%)	0 / 180 (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	2 / 572 (0.35%)	0 / 574 (0.00%)	0 / 180 (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
Supraventricular tachycardia			
subjects affected / exposed	0 / 572 (0.00%)	1 / 574 (0.17%)	0 / 180 (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
Trifascicular block			

subjects affected / exposed	1 / 572 (0.17%)	0 / 574 (0.00%)	0 / 180 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Subarachnoid haemorrhage			
subjects affected / exposed	1 / 572 (0.17%)	1 / 574 (0.17%)	0 / 180 (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
Carotid arteriosclerosis			
subjects affected / exposed	1 / 572 (0.17%)	0 / 574 (0.00%)	0 / 180 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebellar infarction			
subjects affected / exposed	1 / 572 (0.17%)	0 / 574 (0.00%)	0 / 180 (0.00%)
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 / 572 (0.17%)	0 / 574 (0.00%)	0 / 180 (0.00%)
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 ischaemia			
subjects affected / exposed	0 / 572 (0.00%)	1 / 574 (0.17%)	0 / 180 (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
Cerebrovascular accident			
subjects affected / exposed	0 / 572 (0.00%)	1 / 574 (0.17%)	1 / 180 (0.56%)
occurrences causally related to treatment / all	0 / 0	0 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Cervicobrachial syndrome			
subjects affected / exposed	0 / 572 (0.00%)	1 / 574 (0.17%)	0 / 180 (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
Dementia			

subjects affected / exposed	1 / 572 (0.17%)	1 / 574 (0.17%)	1 / 180 (0.56%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Guillain-Barre syndrome			
subjects affected / exposed	1 / 572 (0.17%)	0 / 574 (0.00%)	0 / 180 (0.00%)
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	1 / 572 (0.17%)	1 / 574 (0.17%)	0 / 180 (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
Lethargy			
subjects affected / exposed	0 / 572 (0.00%)	1 / 574 (0.17%)	0 / 180 (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
Monoparesis			
subjects affected / exposed	1 / 572 (0.17%)	1 / 574 (0.17%)	0 / 180 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Paraparesis			
subjects affected / exposed	1 / 572 (0.17%)	1 / 574 (0.17%)	0 / 180 (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
Seizure			
subjects affected / exposed	3 / 572 (0.52%)	2 / 574 (0.35%)	0 / 180 (0.00%)
occurrences causally related to treatment / all	2 / 3	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal cord compression			
subjects affected / exposed	3 / 572 (0.52%)	7 / 574 (1.22%)	1 / 180 (0.56%)
occurrences causally related to treatment / all	2 / 3	0 / 7	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			

subjects affected / exposed	5 / 572 (0.87%)	0 / 574 (0.00%)	0 / 180 (0.00%)
occurrences causally related to treatment / all	3 / 5	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Toxic encephalopathy			
subjects affected / exposed	0 / 572 (0.00%)	1 / 574 (0.17%)	0 / 180 (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
Transient global amnesia			
subjects affected / exposed	1 / 572 (0.17%)	0 / 574 (0.00%)	0 / 180 (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
Transient ischaemic attack			
subjects affected / exposed	4 / 572 (0.70%)	2 / 574 (0.35%)	0 / 180 (0.00%)
occurrences causally related to treatment / all	2 / 4	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Altered state of consciousness			
subjects affected / exposed	0 / 572 (0.00%)	0 / 574 (0.00%)	1 / 180 (0.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aphasia			
subjects affected / exposed	1 / 572 (0.17%)	0 / 574 (0.00%)	0 / 180 (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
Brain stem haemorrhage			
subjects affected / exposed	1 / 572 (0.17%)	0 / 574 (0.00%)	0 / 180 (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
Cerebral infarction			
subjects affected / exposed	2 / 572 (0.35%)	0 / 574 (0.00%)	0 / 180 (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
Cognitive disorder			

subjects affected / exposed	0 / 572 (0.00%)	1 / 574 (0.17%)	0 / 180 (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
Dementia Alzheimer's type			
subjects affected / exposed	1 / 572 (0.17%)	0 / 574 (0.00%)	0 / 180 (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
Dizziness			
subjects affected / exposed	1 / 572 (0.17%)	0 / 574 (0.00%)	1 / 180 (0.56%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Facial paralysis			
subjects affected / exposed	1 / 572 (0.17%)	0 / 574 (0.00%)	0 / 180 (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
Headache			
subjects affected / exposed	1 / 572 (0.17%)	0 / 574 (0.00%)	1 / 180 (0.56%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hemianopia			
subjects affected / exposed	1 / 572 (0.17%)	0 / 574 (0.00%)	0 / 180 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoglycaemic seizure			
subjects affected / exposed	0 / 572 (0.00%)	1 / 574 (0.17%)	0 / 180 (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
Loss of consciousness			
subjects affected / exposed	0 / 572 (0.00%)	0 / 574 (0.00%)	1 / 180 (0.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lumbar radiculopathy			

subjects affected / exposed	1 / 572 (0.17%)	0 / 574 (0.00%)	0 / 180 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Memory impairment			
subjects affected / exposed	1 / 572 (0.17%)	0 / 574 (0.00%)	0 / 180 (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
Thalamus haemorrhage			
subjects affected / exposed	0 / 572 (0.00%)	0 / 574 (0.00%)	1 / 180 (0.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	5 / 572 (0.87%)	2 / 574 (0.35%)	1 / 180 (0.56%)
occurrences causally related to treatment / all	0 / 5	0 / 4	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood loss anaemia			
subjects affected / exposed	0 / 572 (0.00%)	1 / 574 (0.17%)	0 / 180 (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	1 / 572 (0.17%)	0 / 574 (0.00%)	0 / 180 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune thrombocytopenia			
subjects affected / exposed	1 / 572 (0.17%)	0 / 574 (0.00%)	0 / 180 (0.00%)
occurrences causally related to treatment / all	6 / 6	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Iron deficiency anaemia			
subjects affected / exposed	1 / 572 (0.17%)	0 / 574 (0.00%)	0 / 180 (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
Lymphadenopathy			

subjects affected / exposed	2 / 572 (0.35%)	0 / 574 (0.00%)	0 / 180 (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
Pancytopenia			
subjects affected / exposed	3 / 572 (0.52%)	1 / 574 (0.17%)	0 / 180 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear and labyrinth disorders			
Deafness			
subjects affected / exposed	1 / 572 (0.17%)	0 / 574 (0.00%)	0 / 180 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Deafness neurosensory			
subjects affected / exposed	0 / 572 (0.00%)	0 / 574 (0.00%)	1 / 180 (0.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Eye haemorrhage			
subjects affected / exposed	1 / 572 (0.17%)	0 / 574 (0.00%)	0 / 180 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Retinal detachment			
subjects affected / exposed	1 / 572 (0.17%)	1 / 574 (0.17%)	0 / 180 (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
Ulcerative keratitis			
subjects affected / exposed	1 / 572 (0.17%)	0 / 574 (0.00%)	0 / 180 (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
Cataract			
subjects affected / exposed	0 / 572 (0.00%)	0 / 574 (0.00%)	1 / 180 (0.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			

Abdominal pain			
subjects affected / exposed	3 / 572 (0.52%)	2 / 574 (0.35%)	0 / 180 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colitis ischaemic			
subjects affected / exposed	0 / 572 (0.00%)	1 / 574 (0.17%)	0 / 180 (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
Diarrhoea			
subjects affected / exposed	0 / 572 (0.00%)	1 / 574 (0.17%)	0 / 180 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diverticulum intestinal haemorrhagic			
subjects affected / exposed	1 / 572 (0.17%)	0 / 574 (0.00%)	0 / 180 (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
Duodenal ulcer perforation			
subjects affected / exposed	1 / 572 (0.17%)	0 / 574 (0.00%)	0 / 180 (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
Duodenitis			
subjects affected / exposed	1 / 572 (0.17%)	0 / 574 (0.00%)	0 / 180 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspepsia			
subjects affected / exposed	1 / 572 (0.17%)	2 / 574 (0.35%)	1 / 180 (0.56%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Epiploic appendagitis			
subjects affected / exposed	1 / 572 (0.17%)	0 / 574 (0.00%)	0 / 180 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastritis			

subjects affected / exposed	1 / 572 (0.17%)	0 / 574 (0.00%)	0 / 180 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastritis erosive			
subjects affected / exposed	1 / 572 (0.17%)	0 / 574 (0.00%)	0 / 180 (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
Gastrointestinal haemorrhage			
subjects affected / exposed	1 / 572 (0.17%)	1 / 574 (0.17%)	0 / 180 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Impaired gastric emptying			
subjects affected / exposed	1 / 572 (0.17%)	0 / 574 (0.00%)	0 / 180 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Incarcerated inguinal hernia			
subjects affected / exposed	2 / 572 (0.35%)	0 / 574 (0.00%)	0 / 180 (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
Inguinal hernia			
subjects affected / exposed	1 / 572 (0.17%)	1 / 574 (0.17%)	1 / 180 (0.56%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Large intestinal obstruction			
subjects affected / exposed	2 / 572 (0.35%)	0 / 574 (0.00%)	0 / 180 (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
Large intestine perforation			
subjects affected / exposed	1 / 572 (0.17%)	0 / 574 (0.00%)	0 / 180 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			

subjects affected / exposed	1 / 572 (0.17%)	0 / 574 (0.00%)	0 / 180 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumoperitoneum			
subjects affected / exposed	1 / 572 (0.17%)	0 / 574 (0.00%)	0 / 180 (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
Proctalgia			
subjects affected / exposed	1 / 572 (0.17%)	0 / 574 (0.00%)	0 / 180 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Retroperitoneal fibrosis			
subjects affected / exposed	1 / 572 (0.17%)	0 / 574 (0.00%)	0 / 180 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Small intestinal obstruction			
subjects affected / exposed	1 / 572 (0.17%)	0 / 574 (0.00%)	0 / 180 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subileus			
subjects affected / exposed	1 / 572 (0.17%)	0 / 574 (0.00%)	0 / 180 (0.00%)
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	0 / 572 (0.00%)	1 / 574 (0.17%)	1 / 180 (0.56%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Duodenal ulcer haemorrhage			
subjects affected / exposed	1 / 572 (0.17%)	0 / 574 (0.00%)	0 / 180 (0.00%)
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 / 572 (0.17%)	0 / 574 (0.00%)	0 / 180 (0.00%)
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 intestine polyp			
subjects affected / exposed	1 / 572 (0.17%)	0 / 574 (0.00%)	0 / 180 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Retroperitoneal haematoma			
subjects affected / exposed	1 / 572 (0.17%)	0 / 574 (0.00%)	0 / 180 (0.00%)
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	2 / 572 (0.35%)	1 / 574 (0.17%)	1 / 180 (0.56%)
occurrences causally related to treatment / all	0 / 4	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholecystitis acute			
subjects affected / exposed	1 / 572 (0.17%)	1 / 574 (0.17%)	0 / 180 (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
Hepatic function abnormal			
subjects affected / exposed	1 / 572 (0.17%)	0 / 574 (0.00%)	3 / 180 (1.67%)
occurrences causally related to treatment / all	1 / 1	0 / 0	4 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Jaundice cholestatic			
subjects affected / exposed	0 / 572 (0.00%)	1 / 574 (0.17%)	0 / 180 (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			
subjects affected / exposed	1 / 572 (0.17%)	0 / 574 (0.00%)	0 / 180 (0.00%)
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	1 / 572 (0.17%)	0 / 574 (0.00%)	0 / 180 (0.00%)
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	6 / 572 (1.05%)	3 / 574 (0.52%)	1 / 180 (0.56%)
occurrences causally related to treatment / all	3 / 9	0 / 3	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bladder perforation			
subjects affected / exposed	1 / 572 (0.17%)	0 / 574 (0.00%)	0 / 180 (0.00%)
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 / 572 (0.17%)	1 / 574 (0.17%)	0 / 180 (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
Dysuria			
subjects affected / exposed	1 / 572 (0.17%)	0 / 574 (0.00%)	0 / 180 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematuria			
subjects affected / exposed	8 / 572 (1.40%)	2 / 574 (0.35%)	1 / 180 (0.56%)
occurrences causally related to treatment / all	0 / 12	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hydronephrosis			
subjects affected / exposed	4 / 572 (0.70%)	3 / 574 (0.52%)	1 / 180 (0.56%)
occurrences causally related to treatment / all	0 / 4	0 / 4	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal colic			
subjects affected / exposed	1 / 572 (0.17%)	0 / 574 (0.00%)	0 / 180 (0.00%)
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	2 / 572 (0.35%)	0 / 574 (0.00%)	0 / 180 (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
Renal impairment			
subjects affected / exposed	1 / 572 (0.17%)	1 / 574 (0.17%)	0 / 180 (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
Ureterolithiasis			
subjects affected / exposed	1 / 572 (0.17%)	0 / 574 (0.00%)	1 / 180 (0.56%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urethral obstruction			
subjects affected / exposed	0 / 572 (0.00%)	1 / 574 (0.17%)	0 / 180 (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
Urethral stenosis			
subjects affected / exposed	0 / 572 (0.00%)	1 / 574 (0.17%)	0 / 180 (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 retention			
subjects affected / exposed	7 / 572 (1.22%)	4 / 574 (0.70%)	2 / 180 (1.11%)
occurrences causally related to treatment / all	0 / 7	0 / 4	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract obstruction			
subjects affected / exposed	2 / 572 (0.35%)	0 / 574 (0.00%)	1 / 180 (0.56%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bladder mass			
subjects affected / exposed	1 / 572 (0.17%)	0 / 574 (0.00%)	0 / 180 (0.00%)
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 / 572 (0.17%)	0 / 574 (0.00%)	1 / 180 (0.56%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary bladder haemorrhage			
subjects affected / exposed	0 / 572 (0.00%)	0 / 574 (0.00%)	1 / 180 (0.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary incontinence			
subjects affected / exposed	2 / 572 (0.35%)	0 / 574 (0.00%)	0 / 180 (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
Endocrine disorders			
Goitre			
subjects affected / exposed	1 / 572 (0.17%)	0 / 574 (0.00%)	0 / 180 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperparathyroidism			
subjects affected / exposed	1 / 572 (0.17%)	0 / 574 (0.00%)	0 / 180 (0.00%)
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			
Back pain			
subjects affected / exposed	3 / 572 (0.52%)	2 / 574 (0.35%)	1 / 180 (0.56%)
occurrences causally related to treatment / all	0 / 3	1 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bone pain			
subjects affected / exposed	2 / 572 (0.35%)	0 / 574 (0.00%)	0 / 180 (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 / 572 (0.17%)	2 / 574 (0.35%)	0 / 180 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Musculoskeletal chest pain			
subjects affected / exposed	0 / 572 (0.00%)	1 / 574 (0.17%)	0 / 180 (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
Neck pain			
subjects affected / exposed	0 / 572 (0.00%)	1 / 574 (0.17%)	0 / 180 (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	3 / 572 (0.52%)	2 / 574 (0.35%)	0 / 180 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain in extremity			
subjects affected / exposed	1 / 572 (0.17%)	1 / 574 (0.17%)	1 / 180 (0.56%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pathological fracture			
subjects affected / exposed	1 / 572 (0.17%)	1 / 574 (0.17%)	0 / 180 (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 osteoarthritis			
subjects affected / exposed	1 / 572 (0.17%)	0 / 574 (0.00%)	0 / 180 (0.00%)
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	0 / 572 (0.00%)	0 / 574 (0.00%)	1 / 180 (0.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arthritis			
subjects affected / exposed	1 / 572 (0.17%)	0 / 574 (0.00%)	0 / 180 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Compartment syndrome			

subjects affected / exposed	0 / 572 (0.00%)	0 / 574 (0.00%)	1 / 180 (0.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Flank pain			
subjects affected / exposed	1 / 572 (0.17%)	0 / 574 (0.00%)	0 / 180 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Groin pain			
subjects affected / exposed	0 / 572 (0.00%)	0 / 574 (0.00%)	1 / 180 (0.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Muscle spasms			
subjects affected / exposed	0 / 572 (0.00%)	0 / 574 (0.00%)	1 / 180 (0.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteonecrosis of jaw			
subjects affected / exposed	2 / 572 (0.35%)	0 / 574 (0.00%)	0 / 180 (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
Osteoporotic fracture			
subjects affected / exposed	0 / 572 (0.00%)	0 / 574 (0.00%)	1 / 180 (0.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Anorectal infection			
subjects affected / exposed	0 / 572 (0.00%)	1 / 574 (0.17%)	0 / 180 (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
Appendicitis			
subjects affected / exposed	2 / 572 (0.35%)	1 / 574 (0.17%)	0 / 180 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchitis			

subjects affected / exposed	1 / 572 (0.17%)	1 / 574 (0.17%)	0 / 180 (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
Bronchopulmonary aspergillosis			
subjects affected / exposed	0 / 572 (0.00%)	1 / 574 (0.17%)	0 / 180 (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 infective			
subjects affected / exposed	0 / 572 (0.00%)	1 / 574 (0.17%)	0 / 180 (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
Cellulitis			
subjects affected / exposed	2 / 572 (0.35%)	1 / 574 (0.17%)	0 / 180 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Device related infection			
subjects affected / exposed	0 / 572 (0.00%)	1 / 574 (0.17%)	0 / 180 (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
Diverticulitis			
subjects affected / exposed	1 / 572 (0.17%)	0 / 574 (0.00%)	0 / 180 (0.00%)
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	1 / 572 (0.17%)	2 / 574 (0.35%)	1 / 180 (0.56%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Escherichia pyelonephritis			
subjects affected / exposed	0 / 572 (0.00%)	1 / 574 (0.17%)	0 / 180 (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
Escherichia urinary tract infection			

subjects affected / exposed	0 / 572 (0.00%)	1 / 574 (0.17%)	1 / 180 (0.56%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Genital abscess			
subjects affected / exposed	0 / 572 (0.00%)	1 / 574 (0.17%)	0 / 180 (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
Groin abscess			
subjects affected / exposed	0 / 572 (0.00%)	1 / 574 (0.17%)	0 / 180 (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
Infected lymphocele			
subjects affected / exposed	0 / 572 (0.00%)	1 / 574 (0.17%)	0 / 180 (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
Influenza			
subjects affected / exposed	1 / 572 (0.17%)	0 / 574 (0.00%)	0 / 180 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Otitis media chronic			
subjects affected / exposed	1 / 572 (0.17%)	0 / 574 (0.00%)	0 / 180 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	5 / 572 (0.87%)	5 / 574 (0.87%)	1 / 180 (0.56%)
occurrences causally related to treatment / all	0 / 8	0 / 6	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyelonephritis			
subjects affected / exposed	1 / 572 (0.17%)	0 / 574 (0.00%)	0 / 180 (0.00%)
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	4 / 572 (0.70%)	3 / 574 (0.52%)	2 / 180 (1.11%)
occurrences causally related to treatment / all	0 / 5	0 / 3	0 / 3
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0
Septic shock			
subjects affected / exposed	1 / 572 (0.17%)	0 / 574 (0.00%)	0 / 180 (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
Urinary tract infection			
subjects affected / exposed	1 / 572 (0.17%)	2 / 574 (0.35%)	0 / 180 (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
Urinary tract infection bacterial			
subjects affected / exposed	0 / 572 (0.00%)	1 / 574 (0.17%)	0 / 180 (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
Urosepsis			
subjects affected / exposed	2 / 572 (0.35%)	1 / 574 (0.17%)	0 / 180 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
COVID-19			
subjects affected / exposed	2 / 572 (0.35%)	0 / 574 (0.00%)	2 / 180 (1.11%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
COVID-19 pneumonia			
subjects affected / exposed	3 / 572 (0.52%)	0 / 574 (0.00%)	1 / 180 (0.56%)
occurrences causally related to treatment / all	0 / 4	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Cystitis			
subjects affected / exposed	1 / 572 (0.17%)	0 / 574 (0.00%)	0 / 180 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocarditis			

subjects affected / exposed	1 / 572 (0.17%)	0 / 574 (0.00%)	0 / 180 (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
Gangrene			
subjects affected / exposed	1 / 572 (0.17%)	0 / 574 (0.00%)	0 / 180 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			
subjects affected / exposed	2 / 572 (0.35%)	0 / 574 (0.00%)	0 / 180 (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
Infection			
subjects affected / exposed	0 / 572 (0.00%)	1 / 574 (0.17%)	0 / 180 (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
Osteomyelitis			
subjects affected / exposed	1 / 572 (0.17%)	0 / 574 (0.00%)	0 / 180 (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
Spinal cord infection			
subjects affected / exposed	1 / 572 (0.17%)	0 / 574 (0.00%)	0 / 180 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subcutaneous abscess			
subjects affected / exposed	1 / 572 (0.17%)	0 / 574 (0.00%)	0 / 180 (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
Systemic candida			
subjects affected / exposed	1 / 572 (0.17%)	0 / 574 (0.00%)	0 / 180 (0.00%)
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 staphylococcal			

subjects affected / exposed	0 / 572 (0.00%)	0 / 574 (0.00%)	1 / 180 (0.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Cachexia			
subjects affected / exposed	1 / 572 (0.17%)	1 / 574 (0.17%)	0 / 180 (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
Dehydration			
subjects affected / exposed	0 / 572 (0.00%)	1 / 574 (0.17%)	1 / 180 (0.56%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypercalcaemia			
subjects affected / exposed	1 / 572 (0.17%)	0 / 574 (0.00%)	0 / 180 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoglycaemia			
subjects affected / exposed	0 / 572 (0.00%)	1 / 574 (0.17%)	0 / 180 (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
Adult failure to thrive			
subjects affected / exposed	1 / 572 (0.17%)	0 / 574 (0.00%)	0 / 180 (0.00%)
occurrences causally related to treatment / all	0 / 1	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	Enzalutamide + Androgen Deprivation Therapy (ADT)	Placebo + Androgen Deprivation Therapy	Placebo cross-over Enzalutamide
Total subjects affected by non-serious adverse events			
subjects affected / exposed	443 / 572 (77.45%)	396 / 574 (68.99%)	110 / 180 (61.11%)
Investigations			
Weight increased			

subjects affected / exposed	46 / 572 (8.04%)	45 / 574 (7.84%)	2 / 180 (1.11%)
occurrences (all)	83	51	2
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	52 / 572 (9.09%)	16 / 574 (2.79%)	12 / 180 (6.67%)
occurrences (all)	78	16	18
Vascular disorders			
Hot flush			
subjects affected / exposed	171 / 572 (29.90%)	131 / 574 (22.82%)	15 / 180 (8.33%)
occurrences (all)	196	137	16
Hypertension			
subjects affected / exposed	75 / 572 (13.11%)	35 / 574 (6.10%)	13 / 180 (7.22%)
occurrences (all)	87	37	15
Nervous system disorders			
Dizziness			
subjects affected / exposed	44 / 572 (7.69%)	22 / 574 (3.83%)	7 / 180 (3.89%)
occurrences (all)	47	24	7
Headache			
subjects affected / exposed	46 / 572 (8.04%)	22 / 574 (3.83%)	5 / 180 (2.78%)
occurrences (all)	52	27	6
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	49 / 572 (8.57%)	28 / 574 (4.88%)	4 / 180 (2.22%)
occurrences (all)	70	35	5
Fatigue			
subjects affected / exposed	141 / 572 (24.65%)	92 / 574 (16.03%)	39 / 180 (21.67%)
occurrences (all)	180	103	45
Oedema peripheral			
subjects affected / exposed	46 / 572 (8.04%)	40 / 574 (6.97%)	7 / 180 (3.89%)
occurrences (all)	60	48	7
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	38 / 572 (6.64%)	28 / 574 (4.88%)	4 / 180 (2.22%)
occurrences (all)	55	39	5
Gastrointestinal disorders			

Constipation			
subjects affected / exposed	52 / 572 (9.09%)	34 / 574 (5.92%)	8 / 180 (4.44%)
occurrences (all)	60	34	8
Diarrhoea			
subjects affected / exposed	48 / 572 (8.39%)	34 / 574 (5.92%)	6 / 180 (3.33%)
occurrences (all)	60	35	7
Nausea			
subjects affected / exposed	51 / 572 (8.92%)	34 / 574 (5.92%)	12 / 180 (6.67%)
occurrences (all)	62	35	16
Reproductive system and breast disorders			
Gynaecomastia			
subjects affected / exposed	33 / 572 (5.77%)	8 / 574 (1.39%)	3 / 180 (1.67%)
occurrences (all)	37	8	3
Psychiatric disorders			
Insomnia			
subjects affected / exposed	29 / 572 (5.07%)	20 / 574 (3.48%)	4 / 180 (2.22%)
occurrences (all)	31	21	4
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	104 / 572 (18.18%)	65 / 574 (11.32%)	11 / 180 (6.11%)
occurrences (all)	136	78	14
Back pain			
subjects affected / exposed	74 / 572 (12.94%)	67 / 574 (11.67%)	19 / 180 (10.56%)
occurrences (all)	98	70	22
Musculoskeletal pain			
subjects affected / exposed	50 / 572 (8.74%)	26 / 574 (4.53%)	7 / 180 (3.89%)
occurrences (all)	59	30	10
Bone pain			
subjects affected / exposed	34 / 572 (5.94%)	31 / 574 (5.40%)	2 / 180 (1.11%)
occurrences (all)	42	34	2
Pain in extremity			
subjects affected / exposed	37 / 572 (6.47%)	27 / 574 (4.70%)	7 / 180 (3.89%)
occurrences (all)	45	28	7
Infections and infestations			
Nasopharyngitis			

subjects affected / exposed	48 / 572 (8.39%)	33 / 574 (5.75%)	13 / 180 (7.22%)
occurrences (all)	57	39	17
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	39 / 572 (6.82%)	18 / 574 (3.14%)	12 / 180 (6.67%)
occurrences (all)	41	20	13

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
02 June 2016	The changes included: ● Added 2 exclusion criteria to o exclude patients who had not received bisphosphonates or denosumab at a stable dose (unless diagnosed with osteoporosis) and o exclude patients who had shown a hypersensitivity reaction to any of the study capsule components. ● Revised test drug information to remove information related to tablet formulations and add information related to the capsule formulation of study drug and placebo (chemical name, physical description and storage requirements).
14 December 2017	The changes included: ● Revised the number of events required for the primary endpoint to reflect that primary analysis was to occur when 262 rPD events were confirmed by independent central imaging review. All secondary endpoints were to be evaluated at the time of primary analysis (and are considered final, except for OS [Section 5.5.5]). ● Specified a step-wise approach for the statistical testing of the key secondary endpoints. To maintain the family-wise 2-sided type I error rate at 0.05, a parallel testing strategy between OS (with allocated type I error rate 0.04) and the other 4 endpoints (with allocated type I error rate 0.01) was developed. If the interim results of the OS analysis were statistically significant, no further analysis of OS would be completed. ● Specified that unblinding of study treatment assignment could have been performed if a patient discontinued due to disease progression and in the investigator's opinion this information was necessary to determine the next course of therapy.
10 December 2018	The changes included: ● Added an open-label extension period. Following unblinding at the end of the doubleblind period and demonstration of a statistically significant advantage of enzalutamide over placebo when added to ADT, as assessed by the primary endpoint, all eligible patients could be treated on study with open-label enzalutamide at the discretion of the patient and investigator. ● Specific QoL assessments related to deterioration of urinary symptoms and QoL were added to the secondary endpoints.
31 March 2021	The Changes included: ● Survival follow-up is considered complete and patients will be discontinued from long term follow-up when a final number of OS events has been reached. Sites will no longer be required to collect assessments at that time. ● Following the final OS analysis, patients continuing to receive clinical benefit from enzalutamide treatment may continue open-label treatment in another Astellas-sponsored study, provided they have not met any discontinuation criteria.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/31329516