Clinical trial results:
A Phase 4, randomized, double-Blind, placebo-Controlled Study of continued enzalutamide treatment beyond progression in subjects with chemotherapy-naïve metastatic castration-resistant prostate cancer (CRPC).

Summary

EudraCT number	2013-000722-54
Trial protocol	GB ES FI DE SK BE SE IT DK
Global end of trial date	

Results information

Result version number	v1
This version publication date	30 October 2017
First version publication date	30 October 2017

Trial information

Trial identification

Sponsor protocol code	MDV3100-10

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01995513
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Pfizer, Inc.
Sponsor organisation address	235 E 42nd Street, New York, United States, NY 110017
Public contact	Pfizer Inc., Pfizer ClinicalTrials.gov Call Center, 001 18007181021, ClinicalTrials.gov_Inquiries@pfizer.com
Scientific contact	Pfizer ClinicalTrials.gov Call Center, Pfizer, Inc., 001 18007181021, ClinicalTrials.gov_Inquiries@pfizer.com
Sponsor organisation name	Pfizer, Inc.
Sponsor organisation address	235 E 42nd Street, New York, United States, 10017
Public contact	Pfizer, Inc., Pfizer ClinicalTrials.gov Call Center, 001 18007181021, ClinicalTrials.gov_Inquiries@pfizer.com
Scientific contact	Pfizer, Inc., Pfizer ClinicalTrials.gov Call Center, 001 18007181021, ClinicalTrials.gov_Inquiries@pfizer.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	16 May 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	15 November 2016
Global end of trial reached?	No

Notes:

General information about the trial

Main objective of the trial:

To determine the efficacy of combination treatment with continued enzalutamide plus abiraterone and prednisone (or prednisolone) compared with placebo plus abiraterone and prednisone as measured by progression free survival (PFS) after prostate specific antigen (PSA) progression on treatment with enzalutamide in subjects with chemotherapy-naïve metastatic castration-resistant prostate cancer (CRPC).

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and in compliance with all International Council for Harmonization (ICH) Good Clinical Practice (GCP) Guidelines. All the local regulatory requirements pertinent to safety of trial subjects were followed.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	12 November 2013
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	4 Months
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Australia: 234
Country: Number of subjects enrolled	United States: 16
Country: Number of subjects enrolled	Belgium: 16
Country: Number of subjects enrolled	Denmark: 39
Country: Number of subjects enrolled	Finland: 35
Country: Number of subjects enrolled	France: 6
Country: Number of subjects enrolled	Italy: 43
Country: Number of subjects enrolled	Slovakia: 16
Country: Number of subjects enrolled	Spain: 34
Country: Number of subjects enrolled	Sweden: 18
Country: Number of subjects enrolled	United Kingdom: 52
Worldwide total number of subjects	509
EEA total number of subjects	259

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)	95
From 65 to 84 years	385
85 years and over	29

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

The study comprised of consecutive periods of open-label treatment with enzalutamide (period 1) followed by randomized, double-blind treatment with enzalutamide or placebo, each in combination with open-label abiraterone and prednisone (period 2).

Period 1

Period 1 title	Open label Treatment Period
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Enzalutamide 160 mg

Arm description:

Subjects received enzalutamide 160 milligram (mg) as four 40 mg capsules, orally once daily until disease progression (as defined by radiographic imaging or unequivocal clinical progression or death on study), intolerable toxicity, or subject withdrawal, whichever occurred first. Subjects were followed-up until 30 days after last dose of study drug or before initiation of a new antitumor treatment, whichever occurred first.

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

Dosage and administration details:

Enzalutamide 160 mg was administered orally, once daily.

Number of subjects in period 1	Enzalutamide 160 mg
Started	509
Completed	251
Not completed	258
Adverse event, serious fatal	8
Consent withdrawn by subject	14
No PSA response at week 13	43
Adverse event, non-fatal	35
Ongoing as of data cutoff (07 Oct 2016)	84
Unspecified	9
Disease Progression	64
Protocol deviation	1

Period 2

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Enzalutamide 160mg+Abiraterone 1000mg+ Prednisone 10mg

Arm description:

Subjects with confirmed prostate-specific antigen (PSA) progression at Week 21 in open label period, received enzalutamide 160 mg as four 40 mg capsules, orally once daily along with abiraterone 1000 mg as four 250-mg tablets, orally once daily and prednisone 5 mg tablet, orally twice daily in double blind treatment period, up to disease progression (as defined by radiographic imaging or unequivocal clinical progression or death on study), intolerable toxicity, or subject withdrawal, whichever occurred first. Subjects were followed up for 16 weeks at 4-week interval after discontinuation of study drug for survival and subsequent antineoplastic therapy for prostate cancer.

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

Dosage and administration details:

Enzalutamide 160 mg was administered orally, once daily.

Investigational medicinal product name	Abiraterone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Abiraterone 1000 mg as four 250 mg tablets were administered orally, once daily.

Investigational medicinal product name	Prednisone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Prednisone 10 mg as two 5 mg tablets were administered orally, once daily.

Arm title	Placebo+Abiraterone 1000mg+ Prednisone 10mg

Arm description:

Subjects with confirmed PSA progression at Week 21 in open label period, received placebo matched to enzalutamide as four 40 mg capsules, orally once daily along with abiraterone 1000 mg as four 250-mg tablets, orally once daily and prednisone 5 mg tablet, orally twice daily in double blind treatment period, up to disease progression (as defined by radiographic imaging or unequivocal clinical progression or death on study), intolerable toxicity, or subject withdrawal, whichever occurred first. Subjects were followed up for 16 weeks at 4-week interval after discontinuation of study drug for survival and subsequent antineoplastic therapy for prostate cancer.

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:

Placebo matched to enzalutamide was administered orally, once daily.

Investigational medicinal product name	Abiraterone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Abiraterone 1000 mg as four 250 mg tablets were administered orally, once daily.

Investigational medicinal product name	Prednisone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Prednisone 10 mg as two 5 mg tablets were administered orally, once daily.

Number of subjects in period 2	Enzalutamide 160mg+Abiraterone 1000mg+ Prednisone 10mg	Placebo+Abiraterone 1000mg+ Prednisone 10mg
Started	126	125
Treated	125	124
Completed	0	0
Not completed	126	125
Adverse event, serious fatal	-	1
Consent withdrawn by subject	4	6
Adverse event, non-fatal	12	5
Ongoing as of data cutoff (07 Oct 2016)	27	18
Unspecified	1	2
Disease Progression	82	93

Baseline characteristics

Reporting groups	
Reporting group title	Enzalutamide 160 mg

Reporting group description:

Subjects received enzalutamide 160 milligram (mg) as four 40 mg capsules, orally once daily until disease progression (as defined by radiographic imaging or unequivocal clinical progression or death on study), intolerable toxicity, or subject withdrawal, whichever occurred first. Subjects were followed-up until 30 days after last dose of study drug or before initiation of a new antitumor treatment, whichever occurred first.

Reporting group values	Enzalutamide 160 mg	Total	
Number of subjects	509	509	
Age Categorical Units: Subjects			
<65 years	95	95	
65 -74 years	203	203	
>=75 years	211	211	
Age continuous Units: years			
arithmetic mean	72.3		
standard deviation	± 8.31	-	
Gender, Male/Female Units: Subjects			
Female	0	0	
Male	509	509	

End points

End points reporting groups

Reporting group title	Enzalutamide 160 mg

Reporting group description:

Subjects received enzalutamide 160 milligram (mg) as four 40 mg capsules, orally once daily until disease progression (as defined by radiographic imaging or unequivocal clinical progression or death on study), intolerable toxicity, or subject withdrawal, whichever occurred first. Subjects were followed-up until 30 days after last dose of study drug or before initiation of a new antitumor treatment, whichever occurred first.

Reporting group title	Enzalutamide 160mg+Abiraterone 1000mg+ Prednisone 10mg

Reporting group description:

Subjects with confirmed prostate-specific antigen (PSA) progression at Week 21 in open label period, received enzalutamide 160 mg as four 40 mg capsules, orally once daily along with abiraterone 1000 mg as four 250-mg tablets, orally once daily and prednisone 5 mg tablet, orally twice daily in double blind treatment period, up to disease progression (as defined by radiographic imaging or unequivocal clinical progression or death on study), intolerable toxicity, or subject withdrawal, whichever occurred first. Subjects were followed up for 16 weeks at 4-week interval after discontinuation of study drug for survival and subsequent antineoplastic therapy for prostate cancer.

Reporting group title	Placebo+Abiraterone 1000mg+ Prednisone 10mg

Reporting group description:

Subjects with confirmed PSA progression at Week 21 in open label period, received placebo matched to enzalutamide as four 40 mg capsules, orally once daily along with abiraterone 1000 mg as four 250-mg tablets, orally once daily and prednisone 5 mg tablet, orally twice daily in double blind treatment period, up to disease progression (as defined by radiographic imaging or unequivocal clinical progression or death on study), intolerable toxicity, or subject withdrawal, whichever occurred first. Subjects were followed up for 16 weeks at 4-week interval after discontinuation of study drug for survival and subsequent antineoplastic therapy for prostate cancer.

Primary: Progression Free Survival (PFS)

End point title	Progression Free Survival (PFS)

End point description:

PFS = time from randomization to first documentation of radiographic progression (RP),unequivocal clinical progression or death due to any cause (death within 112 days of treatment discontinuation without objective evidence of RP),whichever occurred first as per investigator. Unequivocal disease progression was pain requiring chronic administration of analgesics, decline of prostate cancer of Eastern Cooperative Oncology Group (ECOG) performance status score to 3 or higher or initiation of new anticancer therapy/radiation therapy or surgical intervention due to tumor progression. ECOG score range= 0(no severity) to 5(maximum severity).RP for bone disease was evaluated by appearance of 2 or more new bone lesions as per Prostate Cancer Clinical Trials Working Group 2 (PCWG2) or for soft tissue disease according to RECIST v1.1. Subjects with no PFS event at analysis date were censored at last tumor assessment date prior to data cutoff date. Intent to treat (ITT) analysis set.

End point type	Primary

End point timeframe:

From randomization until disease progression, last tumor assessment without disease progression or death due to any cause, whichever occurred first (up to the data cutoff date [07 Oct 2016])

End point values	Enzalutamide 160mg+Abiraterone 1000mg+ Prednisone 10mg	Placebo+Abiraterone 1000mg+ Prednisone 10mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	126	125		
Units: months				
median (confidence interval 95%)	5.7 (4.6 to 8.1)	5.6 (4.5 to 7.3)		

Statistical analyses

Statistical analysis title	Enzalutamide vs Placebo
Comparison groups	Placebo+Abiraterone 1000mg+ Prednisone 10mg v Enzalutamide 160mg+Abiraterone 1000mg+ Prednisone 10mg
Number of subjects included in analysis	251
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2176 [1]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.828
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.612
upper limit	1.119

Notes:

[1] - P-value was based on log-rank test stratified by PSA response (greater than or equal to [>=] 0 percent [%] to less than [<] 30% vs >=30%) at Week 13 in the open-label period.

Secondary: Time to Prostate Specific Antigen (PSA) Progression

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

End point description:

Time from date of randomization to the date of first confirmed PSA progression as per Prostate Cancer Clinical Trials Working Group 2 (PCWG2). For subject whose PSA decreased at Week 13 after randomization, progression was defined as 25 percent (%) PSA increase relative to nadir or absolute increase of >=2 nanogram/milliliter (ng/mL) above nadir. Progression was confirmed if another assessment measured at least 3 weeks later met the criterion as well. For subject whose PSA did not decrease at Week 13 after randomization, progression was defined as 25% PSA increase relative to baseline assessed 12 weeks after baseline. Subjects who were not known to have had a PFS event at the analysis date were censored at last PSA assessment date prior to data cutoff date. ITT analysis set.

End point type	Secondary

End point timeframe:

From randomization until disease progression, last tumor assessment without disease progression, whichever occurred first (up to the data cutoff date [07 Oct 2016])

End point values	Enzalutamide 160mg+Abiraterone 1000mg+ Prednisone 10mg	Placebo+Abiraterone 1000mg+ Prednisone 10mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	126	125		
Units: months				
median (confidence interval 95%)	2.8 (2.8 to 2.9)	2.8 (2.8 to 2.8)		

Statistical analyses

Statistical analysis title	Enzalutamide vs Placebo
Comparison groups	Enzalutamide 160mg+Abiraterone 1000mg+ Prednisone 10mg v Placebo+Abiraterone 1000mg+ Prednisone 10mg
Number of subjects included in analysis	251
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.45 [2]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.874
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.617
upper limit	1.239

Notes:

[2] - P-value was based on log-rank test stratified by PSA response (>=0% to <30% vs >=30%) at Week 13 in the open-label period.

Secondary: Prostate Specific Antigen (PSA) Response Rate

End point title	Prostate Specific Antigen (PSA) Response Rate

End point description:

PSA response rate was defined as percentage of subjects with >=30% and >=50% decrease in PSA from baseline at randomization to the maximal PSA response with a threshold of 30% and 50% respectively. PSA response was confirmed if another assessment measured at least 3 weeks later met the criterion as well. Evaluable ITT population included all subjects with a PSA value at baseline of Period 2 and at least 1 post baseline assessment. Here, N signifies those subjects who were evaluable for this outcome measure.

End point type	Secondary

End point timeframe:

From randomization until disease progression, last tumor assessment without disease progression, whichever occurred first (up to the data cutoff date [07 Oct 2016])

End point values	Enzalutamide 160mg+Abiraterone 1000mg+ Prednisone 10mg	Placebo+Abiraterone 1000mg+ Prednisone 10mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	124	122		
Units: percentage of subjects				
number (confidence interval 95%)				
>= 50%	0.8 (0.0 to 4.4)	2.5 (0.5 to 7.0)		
>= 30%	2.4 (0.5 to 6.9)	2.5 (0.5 to 7.0)		

Statistical analyses

Statistical analysis title	Enzalutamide vs Placebo
Statistical analysis description:	
This analysis is reported for subjects with >=50% decrease from baseline in PSA response.	
Comparison groups	Enzalutamide 160mg+Abiraterone 1000mg+ Prednisone 10mg v Placebo+Abiraterone 1000mg+ Prednisone 10mg
Number of subjects included in analysis	246
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3101 [3]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in Response Rate
Point estimate	-1.65
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.82
upper limit	-1.51

Notes:

[3] - P-value was based on Cochran-Mantel-Haenszel mean score test stratified by PSA response (>=0% to <30% vs >=30%) at Week 13 in the open-label period.

Statistical analysis title	Enzalutamide vs Placebo
Statistical analysis description:	
This analysis is reported for subjects with >=30% decrease from baseline in PSA response.	
Comparison groups	Enzalutamide 160mg+Abiraterone 1000mg+ Prednisone 10mg v Placebo+Abiraterone 1000mg+ Prednisone 10mg
Number of subjects included in analysis	246
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9917 [4]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in Response Rate
Point estimate	-0.04

Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.9
upper limit	3.82

Notes:

[4] - P-value was based on Cochran-Mantel-Haenszel mean score test stratified by PSA response (>=0% to <30% vs >=30%) at Week 13 in the open-label period.

Secondary: Objective Response Rate (ORR)

End point title	Objective Response Rate (ORR)

End point description:

Objective response rate as assessed by the investigator according to Response Evaluation Criteria in Solid Tumor version 1.1 (RECIST v1.1) was defined as 1) Percentage of subjects with confirmed best overall complete response (CR) and partial response (PR); 2) Percentage of subjects with CR, PR and stable disease (SD) for target lesions or non-progressive disease for non-target lesions. CR: Disappearance of all non-nodal target and non-target lesions, including target and non-target lymph nodes reduction to <10 millimeter (mm) in short axis. No new lesions and disappearance of all non-target lesions. PR: >= 30% decrease in sum of diameters of target lesions, compared to the sum at baseline. The short axis was used in the sum for target nodes, while the longest diameter was used in the sum for all other target lesions. ITT population (with measurable disease at screening) included all subjects randomly assigned to study treatment. N= subjects evaluable for this endpoint.

End point type	Secondary

End point timeframe:

From randomization until CR or PR, whichever occurred first (up to the data cutoff date [07 Oct 2016])

End point values	Enzalutamide 160mg+Abiraterone 1000mg+ Prednisone 10mg	Placebo+Abiraterone 1000mg+ Prednisone 10mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	38	40		
Units: percentage of subjects				
number (confidence interval 95%)				
CR + PR	0.0 (0.00 to 9.25)	5.0 (0.61 to 16.92)		
CR + PR + SD	68.4 (51.35 to 82.50)	57.5 (40.89 to 72.96)		

Statistical analyses

Statistical analysis title	Enzalutamide vs Placebo

Statistical analysis description:

This analysis is reported for subjects with CR+PR.

Comparison groups	Enzalutamide 160mg+Abiraterone 1000mg+ Prednisone 10mg v Placebo+Abiraterone 1000mg+ Prednisone 10mg

Number of subjects included in analysis	78
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1653 [5]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in Objective Response Rate
Point estimate	-5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-11.75
upper limit	1.75

Notes:

[5] - P-value was based on Cochran-Mantel-Haenszel mean score test stratified by PSA response (>=0% to <30% vs >=30%) at Week 13 in the open-label period.

Statistical analysis title	Enzalutamide vs Placebo

Statistical analysis description:

This analysis is reported for subjects with CR+PR+SD.

Comparison groups	Enzalutamide 160mg+Abiraterone 1000mg+ Prednisone 10mg v Placebo+Abiraterone 1000mg+ Prednisone 10mg
Number of subjects included in analysis	78
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3216 [6]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in Objective Response Rate
Point estimate	10.92
Confidence interval	
level	95 %
sides	2-sided
lower limit	-10.37
upper limit	32.21

Notes:

[6] - P-value was based on Cochran-Mantel-Haenszel mean score test stratified by PSA response (>=0% to <30% vs >=30%) at Week 13 in the open-label period.

Secondary: Rate of Pain Progression

End point title	Rate of Pain Progression

End point description:

Rate of pain progression was defined as percentage of subjects with an increase of >=30% from baseline in the mean Brief Pain Inventory-Short Form (BPI-SF) pain intensity item scores of 4 items assessing average, worst, least, and intermediate pain severity. BPI-SF is an 11-item self-report questionnaire that is designed to assess the severity and impact of pain on daily functions of a subject. BPI-sf includes 4 questions that assess pain intensity (worst, least, average, right now) and 7 questions that assess impact of pain on daily functions (general activity, mood, walking ability, normal work, relations with other people, sleep, enjoyment of life). BPI-sf score range for each item was from 0=no pain to 10=worst possible pain. Total score was reported as average of individual questions ranges from 0 to 10, where lower scores indicated less pain or less pain interference. ITT analysis set. N=subjects evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Month 6

End point values	Enzalutamide 160mg+Abiraterone 1000mg+ Prednisone 10mg	Placebo+Abiraterone 1000mg+ Prednisone 10mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	58	59		
Units: percentage of subjects				
number (confidence interval 95%)	36.2 (24.0 to 49.9)	27.1 (16.4 to 40.3)		

Statistical analyses

Statistical analysis title	Enzalutamide vs Placebo
Comparison groups	Enzalutamide 160mg+Abiraterone 1000mg+ Prednisone 10mg v Placebo+Abiraterone 1000mg+ Prednisone 10mg
Number of subjects included in analysis	117
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2963 [7]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in Progression Rate
Point estimate	9.09
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.69
upper limit	25.87

Notes:

[7] - P-value was based on Cochran-Mantel-Haenszel mean score test stratified by PSA response (>=0% to <30% vs >=30%) at Week 13 in the open-label period.

Secondary: Time to First Use of New Antineoplastic Therapy for Prostate Cancer

End point title	Time to First Use of New Antineoplastic Therapy for Prostate Cancer

End point description:

It was defined as time from randomization to the date of first use of subsequent antineoplastic therapy for prostate cancer. For subjects who had not started subsequent antineoplastic therapy as of data analysis cutoff date, the time to first use of subsequent antineoplastic therapy was censored at the date of last assessment. ITT population included all subjects randomly assigned to study treatment.

End point type	Secondary

End point timeframe:

From randomization until date of first use of any antineoplastic therapy (after last dose date of Period 2, up to the data cutoff date [07 Oct 2016])

End point values	Enzalutamide 160mg+Abiraterone 1000mg+ Prednisone 10mg	Placebo+Abiraterone 1000mg+ Prednisone 10mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	126	125		
Units: months				
median (confidence interval 95%)	10.3 (8.7 to 12.1)	8.6 (7.4 to 11.7)		

Statistical analyses

Statistical analysis title	Enzalutamide vs Placebo
Comparison groups	Enzalutamide 160mg+Abiraterone 1000mg+ Prednisone 10mg v Placebo+Abiraterone 1000mg+ Prednisone 10mg
Number of subjects included in analysis	251
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3818 [8]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.861
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.616
upper limit	1.204

Notes:

[8] - P-value was based on log-rank test stratified by PSA response (>=0% to <30% vs >=30%) at Week 13 in the open-label period.

Secondary: Change From Baseline in Quality of Life as Assessed by Functional Assessment of Cancer Therapy-Prostate (FACT-P) Global Score

End point title	Change From Baseline in Quality of Life as Assessed by Functional Assessment of Cancer Therapy-Prostate (FACT-P) Global Score

End point description:

The FACT-P is a multidimensional, self-reported quality of life instrument consisting of 27 core items that assess subject function in 4 domains: physical, social/family, emotional, and functional well-being, and supplemented by 12 site-specific items to assess for prostate-related symptoms. Each item is rated on a 0 to 4 Likert-type scale, and then combined to produce subscale scores for each domain, as well as a global quality of life score which is the sum of all 5 domain scores and ranges from 0 to 156 with higher scores representing better quality of life. ITT population included all subjects randomly assigned to study treatment. Here, n signifies those subjects who were evaluable at specified time points.

End point type	Secondary

End point timeframe:

Baseline, Week 9, 13, 17, 21, 25, 29, 33, 37, 41, 45, 49, 53, 57, 61, 65, 69, 73, 77, 81, 85, 89

End point values	Enzalutamide 160mg+Abiraterone 1000mg+ Prednisone 10mg	Placebo+Abiraterone 1000mg+ Prednisone 10mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	126	125		
Units: units on a scale				
arithmetic mean (standard deviation)				
Baseline (n =125, 123)	116.4 (± 20.10)	119.0 (± 19.08)		
Change at Week 9 (n =102, 105)	-3.3 (± 14.90)	-2.2 (± 13.90)		
Change at Week 13 (n =88, 87)	-4.4 (± 14.44)	-0.5 (± 13.02)		
Change at Week 17 (n =83, 77)	-3.7 (± 12.40)	-2.3 (± 13.90)		
Change at Week 21 (n =69, 65)	-2.5 (± 12.33)	-2.7 (± 13.57)		
Change at Week 25 (n =61, 61)	-3.1 (± 13.47)	-2.1 (± 10.87)		
Change at Week 29 (n =51, 49)	-6.8 (± 13.98)	0.3 (± 12.10)		
Change at Week 33 (n =44, 43)	-5.9 (± 15.35)	-0.2 (± 12.90)		
Change at Week 37 (n =35, 33)	-6.1 (± 14.25)	0.9 (± 12.57)		
Change at Week 41 (n =31, 29)	-5.7 (± 12.17)	1.3 (± 14.13)		
Change at Week 45 (n =28, 26)	-6.0 (± 9.56)	-2.6 (± 16.27)		
Change at Week 49 (n =27, 18)	-4.2 (± 11.36)	1.8 (± 10.74)		
Change at Week 53 (n =20, 15)	-4.8 (± 10.17)	1.8 (± 14.68)		
Change at Week 57 (n =17, 13)	-4.3 (± 9.73)	0.1 (± 7.45)		
Change at Week 61 (n =13, 10)	-5.5 (± 10.63)	0.6 (± 12.94)		
Change at Week 65 (n =13, 7)	-7.0 (± 7.86)	1.9 (± 9.50)		
Change at Week 69 (n =10, 7)	-3.5 (± 11.37)	4.4 (± 13.29)		
Change at Week 73 (n =8, 1)	-0.7 (± 7.26)	-35.0 (± 99999)		
Change at Week 77 (n =7, 2)	-4.0 (± 9.81)	6.5 (± 30.41)		
Change at Week 81 (n =2, 0)	10.8 (± 9.24)	99999 (± 99999)		
Change at Week 85 (n =2, 0)	-5.5 (± 3.54)	99999 (± 99999)		
Change at Week 89 (n =1, 0)	-2.0 (± 99999)	99999 (± 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Quality of Life as Assessed by Functional Assessment of Cancer Therapy-Prostate (FACT-P) Social/Family Well-Being Domain Scores

End point title	Change From Baseline in Quality of Life as Assessed by Functional Assessment of Cancer Therapy-Prostate (FACT-P) Social/Family Well-Being Domain Scores

End point description:

The FACT-P is a multidimensional, self-reported quality of life instrument consisting of 27 core items that assess subject function in 4 domains: physical, social/family, emotional, and functional well-being, and supplemented by 12 site-specific items to assess for prostate-related symptoms. Each item is rated on a 0 to 4 Likert-type scale, and then combined to produce subscale scores for each domain. Total subscale score range for social/family well-being domain is from 0 (worst response) to 32 (best response), where higher score indicate better quality of life. ITT population included all subjects

randomly assigned to study treatment. Here, n signifies those subjects who were evaluable at specified time points.

End point type	Secondary

End point timeframe:

Baseline, Week 9, 13, 17, 21, 25, 29, 33, 37, 41, 45, 49, 53, 57, 61, 65, 69, 73, 77, 81, 85, 89

End point values	Enzalutamide 160mg+Abiraterone 1000mg+ Prednisone 10mg	Placebo+Abiraterone 1000mg+ Prednisone 10mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	126	125		
Units: units on a scale				
arithmetic mean (standard deviation)				
Baseline (n =125, 123)	22.1 (± 5.80)	22.4 (± 4.84)		
Change at Week 9 (n =104, 108)	-0.5 (± 4.33)	-0.8 (± 4.13)		
Change at Week 13 (n =89, 89)	-0.4 (± 3.46)	-0.4 (± 3.86)		
Change at Week 17 (n =84, 80)	-0.1 (± 3.68)	-0.6 (± 4.64)		
Change at Week 21 (n =70, 67)	-0.5 (± 3.24)	-1.2 (± 5.75)		
Change at Week 25 (n =62, 62)	0.1 (± 2.79)	-1.0 (± 5.25)		
Change at Week 29 (n =51, 50)	-0.1 (± 3.20)	-0.2 (± 5.18)		
Change at Week 33 (n =44, 44)	-0.2 (± 3.21)	0.0 (± 4.95)		
Change at Week 37 (n =36, 33)	-0.8 (± 3.04)	0.8 (± 2.79)		
Change at Week 41 (n =31, 29)	-1.4 (± 3.75)	-0.1 (± 3.51)		
Change at Week 45 (n =28, 27)	-0.9 (± 3.36)	-0.8 (± 3.75)		
Change at Week 49 (n =27, 18)	-0.6 (± 2.88)	0.0 (± 2.65)		
Change at Week 53 (n =21, 15)	-1.0 (± 3.15)	0.4 (± 2.56)		
Change at Week 57 (n =17, 13)	-2.0 (± 3.06)	0.2 (± 1.29)		
Change at Week 61 (n =13, 10)	-1.5 (± 2.77)	-0.2 (± 1.80)		
Change at Week 65 (n =13, 7)	-1.5 (± 2.54)	-0.5 (± 0.96)		
Change at Week 69 (n =10, 7)	-1.4 (± 2.03)	-0.5 (± 0.96)		
Change at Week 73 (n =8, 1)	-0.6 (± 3.22)	-1.0 (± 99999)		
Change at Week 77 (n =7, 2)	-0.9 (± 3.41)	-0.5 (± 0.71)		
Change at Week 81 (n =2, 0)	6.2 (± 5.42)	99999 (± 99999)		
Change at Week 85 (n =2, 0)	-1.0 (± 1.41)	99999 (± 99999)		
Change at Week 89 (n =1, 0)	0.0 (± 99999)	99999 (± 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Quality of Life as Assessed by Functional Assessment of Cancer Therapy-Prostate (FACT-P) Emotional Well-Being Domain Scores

End point title	Change From Baseline in Quality of Life as Assessed by Functional Assessment of Cancer Therapy-Prostate (FACT-P) Emotional Well-Being Domain Scores

End point description:

The FACT-P is a multidimensional, self-reported quality of life instrument consisting of 27 core items that assess subject function in 4 domains: physical, social/family, emotional, and functional well-being, and supplemented by 12 site-specific items to assess for prostate-related symptoms. Each item is rated on a 0 to 4 Likert-type scale, and then combined to produce subscale scores for each domain. Total subscale score range for emotional well-being domain is from 0 (worst response) to 24 (best response), where higher score indicates better quality of life. ITT population included all subjects randomly assigned to study treatment. Here, n signifies those subjects who were evaluable at specified time points.

End point type	Secondary

End point timeframe:

Baseline, Week 9, 13, 17, 21, 25, 29, 33, 37, 41, 45, 49, 53, 57, 61, 65, 69, 73, 77, 81, 85, 89

End point values	Enzalutamide 160mg+Abiraterone 1000mg+ Prednisone 10mg	Placebo+Abiraterone 1000mg+ Prednisone 10mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	126	125		
Units: units on a scale				
arithmetic mean (standard deviation)				
Baseline (n =126,124)	18.1 (± 3.80)	18.5 (± 4.06)		
Change at Week 9 (n =104, 107)	-0.1 (± 2.81)	0.1 (± 3.40)		
Change at Week 13 (n =91, 88)	-0.1 (± 3.55)	0.2 (± 3.09)		
Change at Week 17 (n =84, 79)	-0.2 (± 3.44)	0.4 (± 2.88)		
Change at Week 21 (n =71, 67)	0.3 (± 3.48)	0.1 (± 3.36)		
Change at Week 25 (n =62, 63)	0.3 (± 2.58)	0.3 (± 3.33)		
Change at Week 29 (n =51, 51)	-0.5 (± 3.56)	0.3 (± 3.27)		
Change at Week 33 (n =44, 45)	0.1 (± 3.33)	0.9 (± 2.99)		
Change at Week 37 (n =36, 34)	-0.7 (± 4.04)	0.9 (± 2.49)		
Change at Week 41 (n =31, 30)	0.1 (± 2.99)	1.4 (± 2.60)		
Change at Week 45 (n =28, 27)	-0.5 (± 3.23)	1.2 (± 2.76)		
Change at Week 49 (n =27, 19)	0.0 (± 3.00)	1.3 (± 2.75)		
Change at Week 53 (n =21, 16)	0.1 (± 2.72)	1.2 (± 3.23)		
Change at Week 57 (n =17, 14)	-0.4 (± 2.32)	1.6 (± 2.53)		
Change at Week 61 (n =13, 11)	-0.3 (± 3.14)	1.1 (± 3.62)		
Change at Week 65 (n =13, 7)	-0.9 (± 3.57)	2.9 (± 2.54)		
Change at Week 69 (n =10, 8)	-0.5 (± 2.93)	1.5 (± 2.93)		
Change at Week 73 (n =8, 2)	1.0 (± 2.83)	-5.0 (± 5.66)		
Change at Week 77 (n =7, 2)	0.1 (± 2.67)	2.0 (± 2.83)		
Change at Week 81 (n =2, 0)	1.5 (± 3.54)	99999 (± 99999)		
Change at Week 85 (n =2, 0)	-1.5 (± 0.71)	99999 (± 99999)		
Change at Week 89 (n =1, 0)	-3.0 (± 99999)	99999 (± 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Quality of Life as Assessed by Functional Assessment of Cancer Therapy-Prostate (FACT-P) Functional Well-Being Domain Scores

End point title	Change From Baseline in Quality of Life as Assessed by Functional Assessment of Cancer Therapy-Prostate (FACT-P) Functional Well-Being Domain Scores

End point description:

The FACT-P is a multidimensional, self-reported quality of life instrument consisting of 27 core items that assess subject function in 4 domains: physical, social/family, emotional, and functional well-being, and supplemented by 12 site-specific items to assess for prostate-related symptoms. Each item is rated on a 0 to 4 Likert-type scale, and then combined to produce subscale scores for each domain. Total subscale score range for functional well-being domain is from 0 (worst response) to 28 (best response), where higher score indicate better quality of life. ITT population included all subjects randomly assigned to study treatment. Here, n signifies those subjects who were evaluable at specified time points.

End point type	Secondary

End point timeframe:

Baseline, Week 9, 13, 17, 21, 25, 29, 33, 37, 41, 45, 49, 53, 57, 61, 65, 69, 73, 77, 81, 85, 89

End point values	Enzalutamide 160mg+Abiraterone 1000mg+ Prednisone 10mg	Placebo+Abiraterone 1000mg+ Prednisone 10mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	126	125		
Units: units on a scale				
arithmetic mean (standard deviation)				
Baseline (n =126, 124)	20.2 (± 5.54)	20.3 (± 5.84)		
Change at Week 9 (n =104, 107)	-1.0 (± 4.23)	-0.7 (± 4.62)		
Change at Week 13 (n =91, 87)	-1.2 (± 4.07)	-0.4 (± 4.54)		
Change at Week 17 (n =84, 78)	-1.3 (± 4.00)	-0.5 (± 4.11)		
Change at Week 21 (n =71, 67)	-1.2 (± 5.03)	-0.7 (± 4.03)		
Change at Week 25 (n =62, 63)	-1.0 (± 3.41)	-0.3 (± 4.41)		
Change at Week 29 (n =51, 51)	-2.4 (± 4.67)	-0.2 (± 4.38)		
Change at Week 33 (n =44, 44)	-2.0 (± 5.14)	-0.7 (± 4.49)		
Change at Week 37 (n =36, 34)	-1.5 (± 5.22)	0.2 (± 5.72)		
Change at Week 41 (n =31, 30)	-2.1 (± 4.44)	0.8 (± 5.74)		
Change at Week 45 (n =28, 28)	-2.0 (± 3.37)	-0.3 (± 6.28)		
Change at Week 49 (n =27, 19)	-2.1 (± 4.55)	1.5 (± 5.02)		
Change at Week 53 (n =21, 16)	-1.6 (± 4.67)	1.3 (± 4.92)		
Change at Week 57 (n =17, 14)	-1.4 (± 4.06)	2.0 (± 4.37)		

Change at Week 61 (n =13, 11)	-0.8 (± 3.34)	2.9 (± 5.56)		
Change at Week 65 (n =13, 7)	-1.2 (± 2.21)	1.7 (± 2.75)		
Change at Week 69 (n =10, 8)	0.2 (± 1.48)	2.3 (± 4.23)		
Change at Week 73 (n =8, 2)	-0.6 (± 3.02)	4.0 (± 12.73)		
Change at Week 77 (n =7, 2)	-1.6 (± 3.91)	2.5 (± 9.19)		
Change at Week 81 (n =2, 0)	-1.5 (± 7.78)	99999 (± 99999)		
Change at Week 85 (n =2, 0)	-1.5 (± 2.12)	99999 (± 99999)		
Change at Week 89 (n =1, 0)	1.0 (± 99999)	99999 (± 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Quality of Life as Assessed by Functional Assessment of Cancer Therapy-Prostate (FACT-P) Prostate Cancer Domain Scores

End point title	Change From Baseline in Quality of Life as Assessed by Functional Assessment of Cancer Therapy-Prostate (FACT-P) Prostate Cancer Domain Scores

End point description:

The FACT-P is a multidimensional, self-reported quality of life instrument consisting of 27 core items that assess subject function in 4 domains: physical, social/family, emotional, and functional well-being, and supplemented by 12 site-specific items to assess for prostate-related symptoms. Each item is rated on a 0 to 4 Likert-type scale, and then combined to produce subscale scores for each domain. Total subscale score range for prostate cancer domain is from 0 (worst response) to 48 (best response), where higher score indicated better quality of life with fewer symptoms. ITT population included all subjects randomly assigned to study treatment. Here, n signifies those subjects who were evaluable at specified time points.

End point type	Secondary

End point timeframe:

Baseline, Week 9, 13, 17, 21, 25, 29, 33, 37, 41, 45, 49, 53, 57, 61, 65, 69, 73, 77, 81, 85, 89

End point values	Enzalutamide 160mg+Abiraterone 1000mg+ Prednisone 10mg	Placebo+Abiraterone 1000mg+ Prednisone 10mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	126	125		
Units: units on a scale				
arithmetic mean (standard deviation)				
Baseline (n =126, 124)	33.2 (± 6.85)	34.2 (± 6.45)		
Change at Week 9 (n =104, 107)	-0.7 (± 5.97)	-0.9 (± 5.18)		
Change at Week 13 (n =90, 89)	-1.9 (± 5.91)	-0.1 (± 5.36)		
Change at Week 17 (n =84, 79)	-1.0 (± 5.36)	-1.4 (± 5.10)		
Change at Week 21 (n =71, 67)	-0.4 (± 5.13)	-0.6 (± 4.83)		
Change at Week 25 (n =61, 63)	-0.8 (± 6.93)	-0.8 (± 4.42)		
Change at Week 29 (n =52, 51)	-1.3 (± 5.75)	-0.3 (± 4.77)		

Change at Week 33 (n =44, 45)	-1.4 (± 5.16)	-0.6 (± 4.88)		
Change at Week 37 (n =35, 34)	-1.5 (± 4.88)	-0.8 (± 4.32)		
Change at Week 41 (n =31, 30)	-1.0 (± 5.13)	-0.7 (± 5.34)		
Change at Week 45 (n =28, 28)	-0.8 (± 4.88)	-1.7 (± 7.02)		
Change at Week 49 (n =27, 19)	-0.8 (± 4.26)	-0.9 (± 4.63)		
Change at Week 53 (n =20, 16)	-1.1 (± 3.65)	-1.8 (± 5.78)		
Change at Week 57 (n =17, 14)	-0.5 (± 3.67)	-3.3 (± 4.48)		
Change at Week 61 (n =13, 11)	-2.1 (± 4.29)	-3.1 (± 5.68)		
Change at Week 65 (n =13, 7)	-2.0 (± 4.05)	-2.6 (± 6.32)		
Change at Week 69 (n =10, 8)	-1.5 (± 3.30)	1.1 (± 5.79)		
Change at Week 73 (n =8, 2)	-0.2 (± 3.17)	-6.4 (± 9.32)		
Change at Week 77 (n =7, 2)	-1.0 (± 3.71)	-1.5 (± 13.44)		
Change at Week 81 (n =2, 0)	3.1 (± 1.22)	99999 (± 99999)		
Change at Week 85 (n =2, 0)	-0.5 (± 0.71)	99999 (± 99999)		
Change at Week 89 (n =1, 0)	0.0 (± 99999)	99999 (± 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Quality of Life as Assessed by Functional Assessment of Cancer Therapy-Prostate (FACT-P) Physical Well-Being Domain Scores

End point title	Change From Baseline in Quality of Life as Assessed by Functional Assessment of Cancer Therapy-Prostate (FACT-P) Physical Well-Being Domain Scores

End point description:

The FACT-P is a multidimensional, self-reported quality of life instrument consisting of 27 core items that assess subject function in 4 domains: physical, social/family, emotional, and functional well-being, and supplemented by 12 site-specific items to assess for prostate-related symptoms. Each item is rated on a 0 to 4 Likert-type scale, and then combined to produce subscale scores for each domain. Total subscale score range for physical well-being domain is from 0 (worst response) to 28 (best response), where higher score indicates better quality of life. ITT population included all subjects randomly assigned to study treatment. Here, n signifies those subjects who were evaluable at specified time points.

End point type	Secondary

End point timeframe:

Baseline, Week 9, 13, 17, 21, 25, 29, 33, 37, 41, 45, 49, 53, 57, 61, 65, 69, 73, 77, 81, 85, 89

End point values	Enzalutamide 160mg+Abiraterone 1000mg+ Prednisone 10mg	Placebo+Abiraterone 1000mg+ Prednisone 10mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	126	125		
Units: units on a scale				
arithmetic mean (standard deviation)				

Baseline (n =126,124)	22.9 (± 4.50)	23.6 (± 4.42)		
Change at Week 9 (n =105, 109)	-0.8 (± 4.04)	0.1 (± 3.20)		
Change at Week 13 (n =91, 89)	-1.0 (± 4.11)	0.0 (± 2.63)		
Change at Week 17 (n =85, 80)	-1.1 (± 3.26)	-0.3 (± 2.97)		
Change at Week 21 (n =70, 68)	-0.8 (± 3.11)	-0.8 (± 4.48)		
Change at Week 25 (n =62, 63)	-1.7 (± 4.23)	-0.4 (± 2.90)		
Change at Week 29 (n =51, 51)	-2.5 (± 4.89)	0.3 (± 2.67)		
Change at Week 33 (n =44, 45)	-2.5 (± 5.37)	0.1 (± 3.18)		
Change at Week 37 (n =36, 34)	-1.8 (± 4.50)	0.4 (± 3.13)		
Change at Week 41 (n =31, 30)	-1.5 (± 3.94)	0.4 (± 2.80)		
Change at Week 45 (n =28, 28)	-2.0 (± 3.72)	-0.4 (± 3.59)		
Change at Week 49 (n =27, 19)	-0.9 (± 3.78)	0.6 (± 2.12)		
Change at Week 53 (n =21, 16)	-0.2 (± 3.78)	0.7 (± 2.85)		
Change at Week 57 (n =17, 14)	-0.4 (± 3.25)	0.4 (± 2.37)		
Change at Week 61 (n =13, 11)	-0.8 (± 3.11)	0.4 (± 2.32)		
Change at Week 65 (n =13, 7)	-1.9 (± 4.25)	0.4 (± 1.99)		
Change at Week 69 (n =10, 8)	-0.3 (± 4.08)	-0.5 (± 2.67)		
Change at Week 73 (n =8, 2)	-0.3 (± 2.05)	-3.0 (± 5.66)		
Change at Week 77 (n =7, 2)	-0.7 (± 2.81)	4.0 (± 4.24)		
Change at Week 81 (n =2, 0)	1.5 (± 2.12)	99999 (± 99999)		
Change at Week 85 (n =2, 0)	-1.0 (± 0.0)	99999 (± 99999)		
Change at Week 89 (n =1, 0)	0.0 (± 99999)	99999 (± 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Degradation of the Functional Assessment of Cancer Therapy-Prostate (FACT-P) Global Score

End point title	Time to Degradation of the Functional Assessment of Cancer Therapy-Prostate (FACT-P) Global Score

End point description:

Time to degradation of FACT-P was defined as the time from randomization to first assessment with at least a 10-point decrease from baseline in the global FACT-P score for each subject. The FACT-P is a multidimensional, self-reported quality of life instrument consisting of 27 core items that assess subject function in 4 domains: physical, social/family, emotional, and functional well-being, and supplemented by 12 site-specific items to assess for prostate-related symptoms (prostate cancer domain). Each item is rated on a 0 to 4 Likert-type scale, and then combined to produce subscale scores for each domain, as well as a global quality of life score which is the sum of all 5 domain scores and ranges from 0 to 156 with higher scores representing better quality of life. Subjects with no score degradation at the time of analysis data cutoff were censored at the date of last assessment showing no degradation. Evaluable ITT analysis set.

End point type	Secondary

End point timeframe:

From randomization up to data cutoff date (07 Oct 2016)

End point values	Enzalutamide 160mg+Abiraterone 1000mg+ Prednisone 10mg	Placebo+Abiraterone 1000mg+ Prednisone 10mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	126	125		
Units: months				
median (confidence interval 95%)	4.6 (3.7 to 6.5)	6.4 (5.5 to 13.9)		

Statistical analyses

Statistical analysis title	Enzalutamide vs Placebo
Comparison groups	Enzalutamide 160mg+Abiraterone 1000mg+ Prednisone 10mg v Placebo+Abiraterone 1000mg+ Prednisone 10mg
Number of subjects included in analysis	251
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0739 [9]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.399
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.967
upper limit	2.025

Notes:

[9] - P-value was based on log-rank test stratified by PSA response (>=0% to <30% vs >=30%) at Week 13 in the open-label period

Other pre-specified: Percentage of Subjects With Treatment-Emergent Adverse Events (AEs) and Serious Adverse Events (SAEs)

End point title	Percentage of Subjects With Treatment-Emergent Adverse Events (AEs) and Serious Adverse Events (SAEs)

End point description:

An AE was any untoward medical occurrence in a subject who received study drug without regard to possibility of causal relationship. SAE was an AE resulting in any of the following outcomes or deemed significant for any other reason: death; initial or prolonged inpatient hospitalization; life threatening experience (immediate risk of dying); persistent or significant disability/incapacity; congenital anomaly. Treatment emergent are events between first dose of study drug and up to 30 days after last dose of study drug that was absent before treatment, or worsened during the treatment period relative to the pretreatment state. AEs included both serious and non-serious. Safety population included all subjects who received any amount of study drug. Here, N signifies those subjects who were evaluable for this endpoint.

End point type	Other pre-specified

End point timeframe:

Baseline up to 30 days after the last dose of study drug or before initiation of a new antitumor treatment, whichever occurred first (up to data cutoff date [07 Oct 2016])

End point values	Enzalutamide 160 mg	Enzalutamide 160mg+Abiraterone 1000mg+ Prednisone 10mg	Placebo+Abiraterone 1000mg+ Prednisone 10mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	509	125	124	
Units: percentage of subjects				
number (not applicable)				
AEs	93.3	89.6	91.1	
SAEs	27.9	30.4	28.2	

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Percentage of Subjects With Adverse Events (AEs) Leading to Study Drug Discontinuation

End point title	Percentage of Subjects With Adverse Events (AEs) Leading to Study Drug Discontinuation

End point description:

An AE was any untoward medical occurrence in a subject who received study drug without regard to possibility of causal relationship. Outcome of an AE was response to a question answered by the investigator: 'Is the AE leading to study discontinuation or death?' as 'yes'. Safety population included all subjects who received any amount of study drug. Here, N signifies those subjects who were evaluable for this endpoint.

End point type	Other pre-specified

End point timeframe:

Baseline up to 30 days after the last dose of study drug or before initiation of a new antitumor treatment, whichever occurred first (up to data cutoff date [07 Oct 2016])

End point values	Enzalutamide 160 mg	Enzalutamide 160mg+Abiraterone 1000mg+ Prednisone 10mg	Placebo+Abiraterone 1000mg+ Prednisone 10mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	509	125	124	
Units: percentage of subjects				
number (not applicable)	9.8	19.2	12.1	

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Percentage of Subjects With Adverse Events (AEs) Leading to Death

End point title	Percentage of Subjects With Adverse Events (AEs) Leading to Death

End point description:

An AE was any untoward medical occurrence in a subject who received study drug without regard to possibility of causal relationship. Outcome of an AE was response to a question answered by the investigator: 'Is the AE leading to study discontinuation or death?' as 'yes'. Safety population included all subjects who received any amount of study drug. Here, N signifies those subjects who were evaluable for this endpoint.

End point type	Other pre-specified

End point timeframe:

Baseline up to 30 days after the last dose of study drug or before initiation of a new antitumor treatment, whichever occurred first (up to data cutoff date [07 Oct 2016])

End point values	Enzalutamide 160 mg	Enzalutamide 160mg+Abiraterone 1000mg+ Prednisone 10mg	Placebo+Abiraterone 1000mg+ Prednisone 10mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	509	125	124	
Units: percentage of subjects				
number (not applicable)	4.7	3.2	2.4	

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Percentage of Subjects With Treatment-Emergent Treatment-Related Adverse Events (AEs) and Serious Adverse Events (SAEs)

End point title	Percentage of Subjects With Treatment-Emergent Treatment-Related Adverse Events (AEs) and Serious Adverse Events (SAEs)

End point description:

Treatment-related AE was any untoward medical occurrence attributed to study drug in a subject who received study drug. SAE was an AE resulting in any of the following outcomes or deemed significant for any other reason: death; initial or prolonged inpatient hospitalization; life-threatening experience (immediate risk of dying); persistent or significant disability/incapacity; congenital anomaly. Treatment-emergent were events between first dose of study drug and up to 30 days after last dose of study drug that were absent before treatment or that worsened relative to pre-treatment state. Relatedness to study drug was assessed by the investigator. Safety population included all subjects who received any amount of study drug. Here, N signifies those subjects who were evaluable for this endpoint.

End point type	Other pre-specified

End point timeframe:

Baseline up to 30 days after the last dose of study drug or before initiation of a new antitumor treatment, whichever occurred first (up to data cutoff date [07 Oct 2016])

End point values	Enzalutamide 160 mg	Enzalutamide 160mg+Abiraterone 1000mg+ Prednisone 10mg	Placebo+Abiraterone 1000mg+ Prednisone 10mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	509	125	124	
Units: percentage of subjects				
number (not applicable)				
AEs	65.4	43.2	35.5	
SAEs	3.5	4.8	4.8	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Baseline up to 30 days after the last dose of study drug or before initiation of a new antitumor treatment, whichever occurred first (up to data cutoff date [07 Oct 2016])

Adverse event reporting additional description:

Same event may appear as both an AE and SAE. However, what is presented are distinct events. An event may be categorized as serious in one subject and as non-serious in another, or a subject may have experienced both a serious and non-serious event.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	16.1

Reporting groups

Reporting group title	Enzalutamide 160 mg

Reporting group description:

Subjects received enzalutamide 160 mg as four 40 mg capsules, orally once daily until disease progression (as defined by radiographic imaging or unequivocal clinical progression or death on study), intolerable toxicity, or patient withdrawal, whichever occurs first. Subjects were followed-up until 30 days after last dose of study drug or before initiation of a new antitumor treatment, whichever occurred first.

Reporting group title	Enzalutamide 160mg+Abiraterone 1000mg+ Prednisone 10mg

Reporting group description:

Subjects with confirmed PSA progression at Week 21 in open label period, received enzalutamide 160 mg as four 40 mg capsules, orally once daily along with abiraterone 1000 mg as four 250-mg tablets, orally once daily and prednisone 5 mg tablet, orally twice daily in double blind treatment period, up to disease progression (as defined by radiographic imaging or unequivocal clinical progression or death on study), intolerable toxicity, or patient withdrawal, whichever occurs first. Subjects were followed-up until 30 days after last dose of study drug or before initiation of a new antitumor treatment, whichever occurred first.

Reporting group title	Placebo+Abiraterone 1000mg+ Prednisone 10mg

Reporting group description:

Subject with confirmed PSA progression at Week 21 in open label period, received placebo matched to enzalutamide as four 40 mg capsules, orally once daily along with abiraterone 1000 mg as four 250-mg tablets, orally once daily and prednisone 5 mg tablet, orally twice daily in double blind treatment period, up to disease progression (as defined by radiographic imaging or unequivocal clinical progression or death on study), intolerable toxicity, or patient withdrawal, whichever occurs first. Subjects were followed-up until 30 days after last dose of study drug or before initiation of a new antitumor treatment, whichever occurred first.

Serious adverse events	Enzalutamide 160 mg	Enzalutamide 160mg+Abiraterone 1000mg+ Prednisone 10mg	Placebo+Abiraterone 1000mg+ Prednisone 10mg
Total subjects affected by serious adverse events			
subjects affected / exposed	142 / 509 (27.90%)	38 / 125 (30.40%)	35 / 124 (28.23%)
number of deaths (all causes)	24	10	10
number of deaths resulting from adverse events	1	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenocarcinoma of colon			

subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
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	0 / 509 (0.00%)	1 / 125 (0.80%)	0 / 124 (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 transitional cell carcinoma			
subjects affected / exposed	0 / 509 (0.00%)	0 / 125 (0.00%)	1 / 124 (0.81%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cancer pain			
subjects affected / exposed	0 / 509 (0.00%)	1 / 125 (0.80%)	0 / 124 (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
Bowen's disease			
subjects affected / exposed	2 / 509 (0.39%)	0 / 125 (0.00%)	0 / 124 (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
Chronic myelomonocytic leukaemia			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Laryngeal squamous cell carcinoma			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lentigo maligna			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
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 / 509 (0.00%)	1 / 125 (0.80%)	0 / 124 (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	0 / 509 (0.00%)	1 / 125 (0.80%)	0 / 124 (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 squamous cell carcinoma stage 0			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
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 pleural effusion			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (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
Metastases to bone			
subjects affected / exposed	2 / 509 (0.39%)	0 / 125 (0.00%)	0 / 124 (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
Metastases to central nervous system			
subjects affected / exposed	3 / 509 (0.59%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 2	0 / 0	0 / 0
Metastases to liver			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (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
Metastases to spine			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	1 / 124 (0.81%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metastasis			

subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metastatic pain			
subjects affected / exposed	3 / 509 (0.59%)	3 / 125 (2.40%)	2 / 124 (1.61%)
occurrences causally related to treatment / all	1 / 4	0 / 4	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neuroendocrine carcinoma metastatic			
subjects affected / exposed	1 / 509 (0.20%)	1 / 125 (0.80%)	0 / 124 (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
Pancreatic carcinoma			
subjects affected / exposed	2 / 509 (0.39%)	0 / 125 (0.00%)	0 / 124 (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
Prostate cancer			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (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
Prostate cancer metastatic			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (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
Renal cell carcinoma			
subjects affected / exposed	0 / 509 (0.00%)	0 / 125 (0.00%)	1 / 124 (0.81%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Squamous cell carcinoma of skin			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transitional cell carcinoma			

subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (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
Transitional cell carcinoma metastatic			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Aortic stenosis			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arterial rupture			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arteriosclerosis			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (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
Circulatory collapse			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (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
Deep vein thrombosis			
subjects affected / exposed	4 / 509 (0.79%)	0 / 125 (0.00%)	1 / 124 (0.81%)
occurrences causally related to treatment / all	1 / 4	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertension			
subjects affected / exposed	1 / 509 (0.20%)	1 / 125 (0.80%)	0 / 124 (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
Hypotension			

subjects affected / exposed	3 / 509 (0.59%)	0 / 125 (0.00%)	1 / 124 (0.81%)
occurrences causally related to treatment / all	1 / 3	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypovolaemic shock			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
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	0 / 509 (0.00%)	0 / 125 (0.00%)	1 / 124 (0.81%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 509 (0.00%)	1 / 125 (0.80%)	0 / 124 (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
Chest pain			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Disease progression			
subjects affected / exposed	5 / 509 (0.98%)	2 / 125 (1.60%)	1 / 124 (0.81%)
occurrences causally related to treatment / all	0 / 5	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 4	0 / 2	0 / 1
Fatigue			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (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
General physical health deterioration			
subjects affected / exposed	4 / 509 (0.79%)	1 / 125 (0.80%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 4	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 2	0 / 1	0 / 0
Malaise			

subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (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
Multi-organ failure			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (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
Oedema peripheral			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (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
Pyrexia			
subjects affected / exposed	3 / 509 (0.59%)	0 / 125 (0.00%)	1 / 124 (0.81%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain			
subjects affected / exposed	1 / 509 (0.20%)	1 / 125 (0.80%)	1 / 124 (0.81%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Balanitis			
subjects affected / exposed	0 / 509 (0.00%)	1 / 125 (0.80%)	0 / 124 (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
Respiratory, thoracic and mediastinal disorders			
Bronchospasm			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic obstructive pulmonary disease			

subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (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
Haemothorax			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleural effusion			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (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
Pneumonia aspiration			
subjects affected / exposed	1 / 509 (0.20%)	1 / 125 (0.80%)	0 / 124 (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
Pneumothorax			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed	4 / 509 (0.79%)	0 / 125 (0.00%)	2 / 124 (1.61%)
occurrences causally related to treatment / all	1 / 4	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory failure			
subjects affected / exposed	0 / 509 (0.00%)	1 / 125 (0.80%)	0 / 124 (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
Psychiatric disorders			
Confusional state			
subjects affected / exposed	2 / 509 (0.39%)	1 / 125 (0.80%)	0 / 124 (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
Delirium			

subjects affected / exposed	2 / 509 (0.39%)	1 / 125 (0.80%)	1 / 124 (0.81%)
occurrences causally related to treatment / all	0 / 2	1 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Depression			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 509 (0.00%)	2 / 125 (1.60%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 509 (0.00%)	1 / 125 (0.80%)	0 / 124 (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
Blood bilirubin increased			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
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 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
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			
Acetabulum fracture			
subjects affected / exposed	2 / 509 (0.39%)	0 / 125 (0.00%)	0 / 124 (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
Burns third degree			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
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	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cystitis radiation			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	1 / 124 (0.81%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fall			
subjects affected / exposed	5 / 509 (0.98%)	1 / 125 (0.80%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	1 / 6	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Femoral neck fracture			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (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
Femur fracture			
subjects affected / exposed	0 / 509 (0.00%)	0 / 125 (0.00%)	1 / 124 (0.81%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hip fracture			
subjects affected / exposed	0 / 509 (0.00%)	1 / 125 (0.80%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower limb fracture			
subjects affected / exposed	0 / 509 (0.00%)	1 / 125 (0.80%)	0 / 124 (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
Musculoskeletal injury			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pelvic fracture			

subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
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 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Road traffic accident			
subjects affected / exposed	0 / 509 (0.00%)	1 / 125 (0.80%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal compression fracture			
subjects affected / exposed	0 / 509 (0.00%)	0 / 125 (0.00%)	1 / 124 (0.81%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal fracture			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Toxicity to various agents			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
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 pseudoaneurysm			
subjects affected / exposed	0 / 509 (0.00%)	1 / 125 (0.80%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	3 / 509 (0.59%)	1 / 125 (0.80%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	1 / 3	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Acute myocardial infarction			

subjects affected / exposed	2 / 509 (0.39%)	1 / 125 (0.80%)	0 / 124 (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
Angina pectoris			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	1 / 124 (0.81%)
occurrences causally related to treatment / all	0 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Angina unstable			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial fibrillation			
subjects affected / exposed	3 / 509 (0.59%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 4	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Atrioventricular block complete			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac arrest			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (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
Cardiac failure			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	1 / 124 (0.81%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Cardiac failure congestive			
subjects affected / exposed	2 / 509 (0.39%)	1 / 125 (0.80%)	0 / 124 (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
Cardio-respiratory arrest			

subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Coronary artery disease			
subjects affected / exposed	2 / 509 (0.39%)	0 / 125 (0.00%)	0 / 124 (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
Coronary artery stenosis			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mitral valve disease			
subjects affected / exposed	0 / 509 (0.00%)	0 / 125 (0.00%)	1 / 124 (0.81%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial infarction			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	2 / 124 (1.61%)
occurrences causally related to treatment / all	0 / 1	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Myocardial ischaemia			
subjects affected / exposed	1 / 509 (0.20%)	1 / 125 (0.80%)	0 / 124 (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
Palpitations			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (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
Pericardial effusion			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (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
Sick sinus syndrome			

subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
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			
Cerebellar infarction			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (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 oedema			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (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
Cerebral haemorrhage			
subjects affected / exposed	3 / 509 (0.59%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	2 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Cerebral infarction			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebrovascular accident			
subjects affected / exposed	1 / 509 (0.20%)	1 / 125 (0.80%)	0 / 124 (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
Cognitive disorder			
subjects affected / exposed	0 / 509 (0.00%)	0 / 125 (0.00%)	1 / 124 (0.81%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dementia			
subjects affected / exposed	0 / 509 (0.00%)	1 / 125 (0.80%)	0 / 124 (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
Dysarthria			

subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
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 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (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
Loss of consciousness			
subjects affected / exposed	2 / 509 (0.39%)	1 / 125 (0.80%)	0 / 124 (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
Nerve root compression			
subjects affected / exposed	2 / 509 (0.39%)	0 / 125 (0.00%)	0 / 124 (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
Presyncope			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal cord compression			
subjects affected / exposed	4 / 509 (0.79%)	4 / 125 (3.20%)	2 / 124 (1.61%)
occurrences causally related to treatment / all	0 / 4	0 / 4	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Stupor			
subjects affected / exposed	0 / 509 (0.00%)	1 / 125 (0.80%)	0 / 124 (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
Syncope			
subjects affected / exposed	5 / 509 (0.98%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 5	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transient ischaemic attack			

subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (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
Unresponsive to stimuli			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
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 and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 509 (0.39%)	1 / 125 (0.80%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 4	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (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
Vertigo positional			
subjects affected / exposed	0 / 509 (0.00%)	0 / 125 (0.00%)	1 / 124 (0.81%)
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			
Exophthalmos			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 509 (0.00%)	0 / 125 (0.00%)	1 / 124 (0.81%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colonic fistula			

subjects affected / exposed	0 / 509 (0.00%)	1 / 125 (0.80%)	0 / 124 (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
Constipation			
subjects affected / exposed	2 / 509 (0.39%)	1 / 125 (0.80%)	0 / 124 (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
Diarrhoea			
subjects affected / exposed	2 / 509 (0.39%)	0 / 125 (0.00%)	0 / 124 (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
Duodenal ulcer haemorrhage			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
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 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastric ulcer			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal perforation			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (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
Haemorrhoidal haemorrhage			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hiatus hernia			

subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
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 perforation			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal ischaemia			
subjects affected / exposed	0 / 509 (0.00%)	0 / 125 (0.00%)	1 / 124 (0.81%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Melaena			
subjects affected / exposed	0 / 509 (0.00%)	0 / 125 (0.00%)	1 / 124 (0.81%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oesophageal perforation			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
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	3 / 509 (0.59%)	0 / 125 (0.00%)	0 / 124 (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
Rectal polyp			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peptic ulcer			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (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
Retroperitoneal haematoma			

subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
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 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper gastrointestinal haemorrhage			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	2 / 509 (0.39%)	0 / 125 (0.00%)	0 / 124 (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
Hepatobiliary disorders			
Bile duct obstruction			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis chronic			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic lesion			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Jaundice cholestatic			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
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			

Calculus bladder			
subjects affected / exposed	3 / 509 (0.59%)	0 / 125 (0.00%)	0 / 124 (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
Calculus ureteric			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	1 / 124 (0.81%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Calculus urethral			
subjects affected / exposed	0 / 509 (0.00%)	0 / 125 (0.00%)	1 / 124 (0.81%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematuria			
subjects affected / exposed	10 / 509 (1.96%)	3 / 125 (2.40%)	1 / 124 (0.81%)
occurrences causally related to treatment / all	0 / 13	0 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hydronephrosis			
subjects affected / exposed	0 / 509 (0.00%)	1 / 125 (0.80%)	1 / 124 (0.81%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nephrolithiasis			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Obstructive uropathy			
subjects affected / exposed	3 / 509 (0.59%)	0 / 125 (0.00%)	1 / 124 (0.81%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Prerenal failure			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
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 acute			

subjects affected / exposed	2 / 509 (0.39%)	0 / 125 (0.00%)	2 / 124 (1.61%)
occurrences causally related to treatment / all	0 / 2	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ureteric obstruction			
subjects affected / exposed	2 / 509 (0.39%)	1 / 125 (0.80%)	0 / 124 (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
Urinary incontinence			
subjects affected / exposed	1 / 509 (0.20%)	2 / 125 (1.60%)	1 / 124 (0.81%)
occurrences causally related to treatment / all	0 / 1	1 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary retention			
subjects affected / exposed	2 / 509 (0.39%)	2 / 125 (1.60%)	2 / 124 (1.61%)
occurrences causally related to treatment / all	0 / 2	0 / 4	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract obstruction			
subjects affected / exposed	1 / 509 (0.20%)	2 / 125 (1.60%)	1 / 124 (0.81%)
occurrences causally related to treatment / all	0 / 1	0 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	2 / 509 (0.39%)	0 / 125 (0.00%)	0 / 124 (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
Back pain			
subjects affected / exposed	4 / 509 (0.79%)	1 / 125 (0.80%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 5	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bone pain			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
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 spinal stenosis			

subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chondrocalcinosis pyrophosphate			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intervertebral disc protrusion			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mobility decreased			
subjects affected / exposed	0 / 509 (0.00%)	1 / 125 (0.80%)	0 / 124 (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
Muscular weakness			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
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 chest pain			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neck pain			
subjects affected / exposed	0 / 509 (0.00%)	1 / 125 (0.80%)	0 / 124 (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	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteonecrosis			

subjects affected / exposed	0 / 509 (0.00%)	0 / 125 (0.00%)	1 / 124 (0.81%)
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 / 509 (0.39%)	0 / 125 (0.00%)	0 / 124 (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
Osteoporosis			
subjects affected / exposed	0 / 509 (0.00%)	0 / 125 (0.00%)	1 / 124 (0.81%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteoporotic fracture			
subjects affected / exposed	1 / 509 (0.20%)	1 / 125 (0.80%)	1 / 124 (0.81%)
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	4 / 509 (0.79%)	0 / 125 (0.00%)	2 / 124 (1.61%)
occurrences causally related to treatment / all	0 / 4	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal osteoarthritis			
subjects affected / exposed	0 / 509 (0.00%)	1 / 125 (0.80%)	0 / 124 (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
Infections and infestations			
Abscess jaw			
subjects affected / exposed	0 / 509 (0.00%)	0 / 125 (0.00%)	1 / 124 (0.81%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abscess limb			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Appendicitis			

subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			
subjects affected / exposed	2 / 509 (0.39%)	0 / 125 (0.00%)	0 / 124 (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
Bronchitis			
subjects affected / exposed	1 / 509 (0.20%)	1 / 125 (0.80%)	0 / 124 (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
Enterococcal sepsis			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	1 / 124 (0.81%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infection			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower respiratory tract infection			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Meningitis tuberculous			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ophthalmic herpes zoster			

subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
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 / 509 (0.98%)	1 / 125 (0.80%)	3 / 124 (2.42%)
occurrences causally related to treatment / all	0 / 5	0 / 1	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Pneumonia respiratory syncytial viral			
subjects affected / exposed	0 / 509 (0.00%)	1 / 125 (0.80%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary sepsis			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	1 / 124 (0.81%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	2 / 509 (0.39%)	0 / 125 (0.00%)	0 / 124 (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
Septic shock			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	5 / 509 (0.98%)	1 / 125 (0.80%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 5	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection enterococcal			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urosepsis			

subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	1 / 124 (0.81%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	0 / 509 (0.00%)	1 / 125 (0.80%)	0 / 124 (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
Dehydration			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dystrophic calcification			
subjects affected / exposed	0 / 509 (0.00%)	0 / 125 (0.00%)	1 / 124 (0.81%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypercalcaemia			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	1 / 124 (0.81%)
occurrences causally related to treatment / all	0 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyponatraemia			
subjects affected / exposed	0 / 509 (0.00%)	0 / 125 (0.00%)	1 / 124 (0.81%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malnutrition			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
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: 0 %

Non-serious adverse events	Enzalutamide 160 mg	Enzalutamide 160mg+Abiraterone 1000mg+ Prednisone 10mg	Placebo+Abiraterone 1000mg+ Prednisone 10mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	473 / 509 (92.93%)	111 / 125 (88.80%)	111 / 124 (89.52%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
subjects affected / exposed	11 / 509 (2.16%)	1 / 125 (0.80%)	1 / 124 (0.81%)
occurrences (all)	15	1	1
Benign urinary tract neoplasm			
subjects affected / exposed	0 / 509 (0.00%)	1 / 125 (0.80%)	0 / 124 (0.00%)
occurrences (all)	0	1	0
Bowen's disease			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	1	0	0
Cancer pain			
subjects affected / exposed	2 / 509 (0.39%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	2	0	0
Choroidal haemangioma			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	1	0	0
Fibroma			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	1	0	0
Metastases to central nervous system			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	1	0	0
Renal neoplasm			
subjects affected / exposed	0 / 509 (0.00%)	0 / 125 (0.00%)	1 / 124 (0.81%)
occurrences (all)	0	0	1
Seborrhoeic keratosis			
subjects affected / exposed	2 / 509 (0.39%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	2	0	0
Skin cancer			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	1	0	0

Skin papilloma			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	1	0	0
Squamous cell carcinoma			
subjects affected / exposed	0 / 509 (0.00%)	1 / 125 (0.80%)	0 / 124 (0.00%)
occurrences (all)	0	1	0
Squamous cell carcinoma of skin			
subjects affected / exposed	5 / 509 (0.98%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	6	0	0
Tumour pain			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	1 / 124 (0.81%)
occurrences (all)	1	0	1
Vascular disorders			
Aortic aneurysm			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	1	0	0
Flushing			
subjects affected / exposed	3 / 509 (0.59%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	3	0	0
Deep vein thrombosis			
subjects affected / exposed	3 / 509 (0.59%)	1 / 125 (0.80%)	1 / 124 (0.81%)
occurrences (all)	3	1	1
Haematoma			
subjects affected / exposed	1 / 509 (0.20%)	1 / 125 (0.80%)	0 / 124 (0.00%)
occurrences (all)	1	1	0
Haemorrhage			
subjects affected / exposed	1 / 509 (0.20%)	1 / 125 (0.80%)	0 / 124 (0.00%)
occurrences (all)	1	1	0
Hot flush			
subjects affected / exposed	90 / 509 (17.68%)	6 / 125 (4.80%)	3 / 124 (2.42%)
occurrences (all)	100	7	3
Hypotension			
subjects affected / exposed	9 / 509 (1.77%)	0 / 125 (0.00%)	3 / 124 (2.42%)
occurrences (all)	9	0	3
Lymphoedema			

subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	1 / 124 (0.81%)
occurrences (all)	1	0	1
Orthostatic hypotension			
subjects affected / exposed	4 / 509 (0.79%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	4	0	0
Peripheral artery thrombosis			
subjects affected / exposed	0 / 509 (0.00%)	1 / 125 (0.80%)	0 / 124 (0.00%)
occurrences (all)	0	2	0
Phlebitis			
subjects affected / exposed	2 / 509 (0.39%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	2	0	0
Peripheral coldness			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	1	0	0
Thrombosis			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	1	0	0
Phlebitis superficial			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	1	0	0
Hypertension			
subjects affected / exposed	43 / 509 (8.45%)	24 / 125 (19.20%)	9 / 124 (7.26%)
occurrences (all)	53	36	10
Surgical and medical procedures			
Cataract operation			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	1	0	0
Dupuytren's contracture operation			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	1	0	0
Endodontic procedure			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	1	0	0
Glaucoma surgery			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	1	0	0

Nasal polypectomy			
subjects affected / exposed	0 / 509 (0.00%)	1 / 125 (0.80%)	0 / 124 (0.00%)
occurrences (all)	0	1	0
Mole excision			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	1	0	0
Peripheral nerve decompression			
subjects affected / exposed	0 / 509 (0.00%)	1 / 125 (0.80%)	0 / 124 (0.00%)
occurrences (all)	0	1	0
Pterygium operation			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	1	0	0
Skin neoplasm excision			
subjects affected / exposed	2 / 509 (0.39%)	0 / 125 (0.00%)	1 / 124 (0.81%)
occurrences (all)	3	0	1
Tendon sheath incision			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	1	0	0
Tooth extraction			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	1 / 124 (0.81%)
occurrences (all)	1	0	1
General disorders and administration site conditions			
Abasia			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	1	0	0
Asthenia			
subjects affected / exposed	25 / 509 (4.91%)	5 / 125 (4.00%)	3 / 124 (2.42%)
occurrences (all)	38	5	4
Catheter site haemorrhage			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	1	0	0
Chest pain			
subjects affected / exposed	2 / 509 (0.39%)	4 / 125 (3.20%)	3 / 124 (2.42%)
occurrences (all)	2	4	3
Chest discomfort			

subjects affected / exposed	3 / 509 (0.59%)	2 / 125 (1.60%)	0 / 124 (0.00%)
occurrences (all)	3	2	0
Chills			
subjects affected / exposed	5 / 509 (0.98%)	1 / 125 (0.80%)	2 / 124 (1.61%)
occurrences (all)	5	1	2
Cyst			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	1	0	0
Device failure			
subjects affected / exposed	2 / 509 (0.39%)	0 / 125 (0.00%)	1 / 124 (0.81%)
occurrences (all)	5	0	1
Device occlusion			
subjects affected / exposed	0 / 509 (0.00%)	1 / 125 (0.80%)	0 / 124 (0.00%)
occurrences (all)	0	1	0
Dysplasia			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	1	0	0
Face oedema			
subjects affected / exposed	0 / 509 (0.00%)	1 / 125 (0.80%)	1 / 124 (0.81%)
occurrences (all)	0	1	1
Facial pain			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	1 / 124 (0.81%)
occurrences (all)	1	0	1
Fatigue			
subjects affected / exposed	200 / 509 (39.29%)	17 / 125 (13.60%)	18 / 124 (14.52%)
occurrences (all)	284	24	20
Feeling abnormal			
subjects affected / exposed	4 / 509 (0.79%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	4	0	0
Feeling drunk			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	2	0	0
Feeling hot			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	1	0	0
Gait disturbance			

subjects affected / exposed	7 / 509 (1.38%)	1 / 125 (0.80%)	2 / 124 (1.61%)
occurrences (all)	7	1	2
General physical health deterioration			
subjects affected / exposed	5 / 509 (0.98%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	5	0	0
Hunger			
subjects affected / exposed	0 / 509 (0.00%)	1 / 125 (0.80%)	0 / 124 (0.00%)
occurrences (all)	0	1	0
Hyperpyrexia			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	1	0	0
Hypothermia			
subjects affected / exposed	0 / 509 (0.00%)	1 / 125 (0.80%)	0 / 124 (0.00%)
occurrences (all)	0	1	0
Inflammation			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	1	0	0
Influenza like illness			
subjects affected / exposed	6 / 509 (1.18%)	1 / 125 (0.80%)	1 / 124 (0.81%)
occurrences (all)	11	1	1
Infusion site extravasation			
subjects affected / exposed	0 / 509 (0.00%)	0 / 125 (0.00%)	1 / 124 (0.81%)
occurrences (all)	0	0	1
Injection site swelling			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	1	0	0
Irritability			
subjects affected / exposed	2 / 509 (0.39%)	1 / 125 (0.80%)	0 / 124 (0.00%)
occurrences (all)	2	1	0
Local swelling			
subjects affected / exposed	5 / 509 (0.98%)	4 / 125 (3.20%)	0 / 124 (0.00%)
occurrences (all)	5	5	0
Malaise			
subjects affected / exposed	5 / 509 (0.98%)	1 / 125 (0.80%)	0 / 124 (0.00%)
occurrences (all)	5	1	0
Medical device complication			

subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	8	0	0
Mucosal inflammation			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	1	0	0
Non-cardiac chest pain			
subjects affected / exposed	7 / 509 (1.38%)	3 / 125 (2.40%)	2 / 124 (1.61%)
occurrences (all)	8	4	3
Oedema			
subjects affected / exposed	3 / 509 (0.59%)	2 / 125 (1.60%)	0 / 124 (0.00%)
occurrences (all)	4	2	0
Oedema peripheral			
subjects affected / exposed	49 / 509 (9.63%)	7 / 125 (5.60%)	16 / 124 (12.90%)
occurrences (all)	51	8	18
Pain			
subjects affected / exposed	7 / 509 (1.38%)	6 / 125 (4.80%)	2 / 124 (1.61%)
occurrences (all)	8	6	2
Performance status decreased			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	1	0	0
Pyrexia			
subjects affected / exposed	11 / 509 (2.16%)	4 / 125 (3.20%)	3 / 124 (2.42%)
occurrences (all)	13	4	4
Immune system disorders			
Contrast media allergy			
subjects affected / exposed	0 / 509 (0.00%)	0 / 125 (0.00%)	1 / 124 (0.81%)
occurrences (all)	0	0	1
Drug hypersensitivity			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	1 / 124 (0.81%)
occurrences (all)	1	0	1
Hypersensitivity			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	1	0	0
Hypogammaglobulinaemia			
subjects affected / exposed	0 / 509 (0.00%)	1 / 125 (0.80%)	0 / 124 (0.00%)
occurrences (all)	0	1	0

Milk allergy			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	1	0	0
Seasonal allergy			
subjects affected / exposed	3 / 509 (0.59%)	0 / 125 (0.00%)	1 / 124 (0.81%)
occurrences (all)	4	0	1
Social circumstances			
Physical assault			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	2	0	0
Reproductive system and breast disorders			
Balanitis			
subjects affected / exposed	0 / 509 (0.00%)	1 / 125 (0.80%)	0 / 124 (0.00%)
occurrences (all)	0	1	0
Breast pain			
subjects affected / exposed	3 / 509 (0.59%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	3	0	0
Breast tenderness			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	1	0	0
Genital rash			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	1	0	0
Gynaecomastia			
subjects affected / exposed	9 / 509 (1.77%)	0 / 125 (0.00%)	1 / 124 (0.81%)
occurrences (all)	10	0	1
Pelvic pain			
subjects affected / exposed	8 / 509 (1.57%)	2 / 125 (1.60%)	3 / 124 (2.42%)
occurrences (all)	8	2	3
Perineal pain			
subjects affected / exposed	2 / 509 (0.39%)	0 / 125 (0.00%)	1 / 124 (0.81%)
occurrences (all)	2	0	1
Prostatitis			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	1	0	0
Prostatic pain			

subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	1	0	0
Pruritus genital			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	1	0	0
Scrotal pain			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	1	0	0
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	1	0	0
Allergic sinusitis			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	1	0	0
Alveolitis			
subjects affected / exposed	0 / 509 (0.00%)	0 / 125 (0.00%)	1 / 124 (0.81%)
occurrences (all)	0	0	1
Atelectasis			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	1	0	0
Asthma			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	1	0	0
Dysphonia			
subjects affected / exposed	3 / 509 (0.59%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	3	0	0
Cough			
subjects affected / exposed	27 / 509 (5.30%)	5 / 125 (4.00%)	8 / 124 (6.45%)
occurrences (all)	29	5	8
Dyspnoea			
subjects affected / exposed	36 / 509 (7.07%)	5 / 125 (4.00%)	5 / 124 (4.03%)
occurrences (all)	43	5	8
Dyspnoea exertional			

subjects affected / exposed	7 / 509 (1.38%)	1 / 125 (0.80%)	0 / 124 (0.00%)
occurrences (all)	8	1	0
Emphysema			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	1	0	0
Dyspnoea paroxysmal nocturnal			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	1	0	0
Epistaxis			
subjects affected / exposed	9 / 509 (1.77%)	3 / 125 (2.40%)	2 / 124 (1.61%)
occurrences (all)	9	3	3
Haemoptysis			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	1	0	0
Hiccups			
subjects affected / exposed	0 / 509 (0.00%)	1 / 125 (0.80%)	0 / 124 (0.00%)
occurrences (all)	0	1	0
Interstitial lung disease			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	1	0	0
Laryngeal disorder			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	1	0	0
Laryngeal erythema			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	1	0	0
Laryngeal oedema			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	1	0	0
Lung infiltration			
subjects affected / exposed	0 / 509 (0.00%)	0 / 125 (0.00%)	1 / 124 (0.81%)
occurrences (all)	0	0	1
Nasal obstruction			
subjects affected / exposed	2 / 509 (0.39%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	2	0	0
Nasal congestion			

subjects affected / exposed	4 / 509 (0.79%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	4	0	0
Pleural effusion			
subjects affected / exposed	3 / 509 (0.59%)	0 / 125 (0.00%)	1 / 124 (0.81%)
occurrences (all)	3	0	1
Oropharyngeal pain			
subjects affected / exposed	8 / 509 (1.57%)	1 / 125 (0.80%)	1 / 124 (0.81%)
occurrences (all)	8	1	1
Pleuritic pain			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	1	0	0
Pneumonia aspiration			
subjects affected / exposed	0 / 509 (0.00%)	0 / 125 (0.00%)	1 / 124 (0.81%)
occurrences (all)	0	0	1
Pneumothorax			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	1	0	0
Productive cough			
subjects affected / exposed	3 / 509 (0.59%)	0 / 125 (0.00%)	1 / 124 (0.81%)
occurrences (all)	3	0	1
Pulmonary embolism			
subjects affected / exposed	3 / 509 (0.59%)	0 / 125 (0.00%)	2 / 124 (1.61%)
occurrences (all)	3	0	2
Pulmonary fibrosis			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	1	0	0
Pulmonary mass			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	1	0	0
Respiration abnormal			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	1	0	0
Rales			
subjects affected / exposed	0 / 509 (0.00%)	0 / 125 (0.00%)	1 / 124 (0.81%)
occurrences (all)	0	0	1
Respiratory failure			

subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	1	0	0
Rhinorrhoea			
subjects affected / exposed	2 / 509 (0.39%)	2 / 125 (1.60%)	0 / 124 (0.00%)
occurrences (all)	2	2	0
Rhonchi			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	1	0	0
Sinus disorder			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	1	0	0
Sleep apnoea syndrome			
subjects affected / exposed	3 / 509 (0.59%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	3	0	0
Sneezing			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	1	0	0
Wheezing			
subjects affected / exposed	2 / 509 (0.39%)	0 / 125 (0.00%)	1 / 124 (0.81%)
occurrences (all)	2	0	1
Psychiatric disorders			
Abnormal dreams			
subjects affected / exposed	7 / 509 (1.38%)	0 / 125 (0.00%)	1 / 124 (0.81%)
occurrences (all)	11	0	1
Agitation			
subjects affected / exposed	3 / 509 (0.59%)	1 / 125 (0.80%)	0 / 124 (0.00%)
occurrences (all)	3	1	0
Anxiety			
subjects affected / exposed	16 / 509 (3.14%)	1 / 125 (0.80%)	1 / 124 (0.81%)
occurrences (all)	17	1	1
Apathy			
subjects affected / exposed	3 / 509 (0.59%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	3	0	0
Bruxism			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	1	0	0

Confusional state			
subjects affected / exposed	10 / 509 (1.96%)	4 / 125 (3.20%)	1 / 124 (0.81%)
occurrences (all)	12	4	1
Delirium			
subjects affected / exposed	3 / 509 (0.59%)	1 / 125 (0.80%)	1 / 124 (0.81%)
occurrences (all)	3	1	1
Depressed mood			
subjects affected / exposed	3 / 509 (0.59%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	3	0	0
Disorientation			
subjects affected / exposed	4 / 509 (0.79%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	4	0	0
Depression			
subjects affected / exposed	11 / 509 (2.16%)	1 / 125 (0.80%)	5 / 124 (4.03%)
occurrences (all)	11	1	5
Emotional disorder			
subjects affected / exposed	3 / 509 (0.59%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	3	0	0
Flat affect			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	1	0	0
Hallucination			
subjects affected / exposed	2 / 509 (0.39%)	1 / 125 (0.80%)	0 / 124 (0.00%)
occurrences (all)	2	1	0
Initial insomnia			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	1	0	0
Insomnia			
subjects affected / exposed	37 / 509 (7.27%)	6 / 125 (4.80%)	5 / 124 (4.03%)
occurrences (all)	40	6	5
Mood altered			
subjects affected / exposed	3 / 509 (0.59%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	3	0	0
Mood swings			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	1	0	0

Nightmare			
subjects affected / exposed	3 / 509 (0.59%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	3	0	0
Stress			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	2	0	0
Sleep disorder			
subjects affected / exposed	2 / 509 (0.39%)	0 / 125 (0.00%)	1 / 124 (0.81%)
occurrences (all)	2	0	1
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	1	0	0
Hepatic lesion			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	1	0	0
Hepatic steatosis			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	1	0	0
Hepatomegaly			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	1	0	0
Hepatotoxicity			
subjects affected / exposed	0 / 509 (0.00%)	2 / 125 (1.60%)	2 / 124 (1.61%)
occurrences (all)	0	4	4
Hyperbilirubinaemia			
subjects affected / exposed	2 / 509 (0.39%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	2	0	0
Hypertransaminasaemia			
subjects affected / exposed	0 / 509 (0.00%)	1 / 125 (0.80%)	1 / 124 (0.81%)
occurrences (all)	0	1	6
Jaundice			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	1 / 124 (0.81%)
occurrences (all)	1	0	1
Non-alcoholic steatohepatitis			

subjects affected / exposed	0 / 509 (0.00%)	1 / 125 (0.80%)	0 / 124 (0.00%)
occurrences (all)	0	1	0
Pneumobilia			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	1	0	0
Investigations			
Activated partial thromboplastin time prolonged			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	1	0	0
Alanine aminotransferase increased			
subjects affected / exposed	1 / 509 (0.20%)	8 / 125 (6.40%)	6 / 124 (4.84%)
occurrences (all)	1	14	10
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 509 (0.00%)	4 / 125 (3.20%)	2 / 124 (1.61%)
occurrences (all)	0	6	2
Bacterial test positive			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	1	0	0
Blood albumin increased			
subjects affected / exposed	0 / 509 (0.00%)	0 / 125 (0.00%)	1 / 124 (0.81%)
occurrences (all)	0	0	1
Blood alkaline phosphatase increased			
subjects affected / exposed	3 / 509 (0.59%)	1 / 125 (0.80%)	2 / 124 (1.61%)
occurrences (all)	4	1	2
Blood bilirubin increased			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	1 / 124 (0.81%)
occurrences (all)	1	0	1
Blood calcium decreased			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	1	0	0
Blood calcium increased			
subjects affected / exposed	1 / 509 (0.20%)	1 / 125 (0.80%)	0 / 124 (0.00%)
occurrences (all)	1	1	0
Blood cholesterol increased			

subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	1	0	0
Blood creatine phosphokinase increased			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	1	0	0
Blood creatinine increased			
subjects affected / exposed	6 / 509 (1.18%)	3 / 125 (2.40%)	2 / 124 (1.61%)
occurrences (all)	7	3	2
Blood glucose increased			
subjects affected / exposed	2 / 509 (0.39%)	1 / 125 (0.80%)	0 / 124 (0.00%)
occurrences (all)	5	1	0
Blood iron decreased			
subjects affected / exposed	0 / 509 (0.00%)	1 / 125 (0.80%)	0 / 124 (0.00%)
occurrences (all)	0	1	0
Blood lactate dehydrogenase increased			
subjects affected / exposed	2 / 509 (0.39%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	2	0	0
Blood potassium decreased			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	1 / 124 (0.81%)
occurrences (all)	1	0	1
Blood potassium increased			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	1	0	0
Blood pressure increased			
subjects affected / exposed	2 / 509 (0.39%)	2 / 125 (1.60%)	1 / 124 (0.81%)
occurrences (all)	2	3	1
Blood pressure orthostatic decreased			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	1	0	0
Blood urine present			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	1	0	0
Cardiac murmur			

subjects affected / exposed	2 / 509 (0.39%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	2	0	0
Cardioactive drug level increased			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	1	0	0
Cystoscopy			
subjects affected / exposed	0 / 509 (0.00%)	0 / 125 (0.00%)	1 / 124 (0.81%)
occurrences (all)	0	0	1
Ejection fraction decreased			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	1	0	0
Electrocardiogram QT prolonged			
subjects affected / exposed	0 / 509 (0.00%)	1 / 125 (0.80%)	1 / 124 (0.81%)
occurrences (all)	0	1	1
Gamma-glutamyltransferase abnormal			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	1	0	0
Haemoglobin decreased			
subjects affected / exposed	5 / 509 (0.98%)	0 / 125 (0.00%)	2 / 124 (1.61%)
occurrences (all)	6	0	2
Heart rate increased			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	1	0	0
Heart rate irregular			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	1	0	0
Heart sounds abnormal			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	1	0	0
Hepatic enzyme increased			
subjects affected / exposed	0 / 509 (0.00%)	1 / 125 (0.80%)	0 / 124 (0.00%)
occurrences (all)	0	1	0
International normalised ratio increased			

subjects affected / exposed	2 / 509 (0.39%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	2	0	0
Liver function test abnormal			
subjects affected / exposed	0 / 509 (0.00%)	3 / 125 (2.40%)	1 / 124 (0.81%)
occurrences (all)	0	5	1
Lymph node palpable			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	1	0	0
Lymphocyte count decreased			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	1 / 124 (0.81%)
occurrences (all)	1	0	1
Norovirus test positive			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	1	0	0
Respiratory rate increased			
subjects affected / exposed	0 / 509 (0.00%)	1 / 125 (0.80%)	0 / 124 (0.00%)
occurrences (all)	0	1	0
Transaminases increased			
subjects affected / exposed	0 / 509 (0.00%)	2 / 125 (1.60%)	0 / 124 (0.00%)
occurrences (all)	0	2	0
Troponin increased			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	2	0	0
Urine output decreased			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	1	0	0
Vitamin B12 decreased			
subjects affected / exposed	0 / 509 (0.00%)	1 / 125 (0.80%)	1 / 124 (0.81%)
occurrences (all)	0	1	1
Weight decreased			
subjects affected / exposed	22 / 509 (4.32%)	2 / 125 (1.60%)	3 / 124 (2.42%)
occurrences (all)	27	3	3
Weight increased			
subjects affected / exposed	2 / 509 (0.39%)	1 / 125 (0.80%)	0 / 124 (0.00%)
occurrences (all)	2	1	0
White blood cell count decreased			

subjects affected / exposed	1 / 509 (0.20%)	1 / 125 (0.80%)	0 / 124 (0.00%)
occurrences (all)	1	1	0
White blood cell count increased			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	1	0	0
Injury, poisoning and procedural complications			
Accident			
subjects affected / exposed	0 / 509 (0.00%)	1 / 125 (0.80%)	0 / 124 (0.00%)
occurrences (all)	0	1	0
Accidental overdose			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	1	0	0
Ankle fracture			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	1	0	0
Arthropod bite			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	1 / 124 (0.81%)
occurrences (all)	1	0	1
Bone contusion			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	1 / 124 (0.81%)
occurrences (all)	1	0	1
Chest injury			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	1	0	0
Contusion			
subjects affected / exposed	7 / 509 (1.38%)	2 / 125 (1.60%)	3 / 124 (2.42%)
occurrences (all)	10	2	3
Excoriation			
subjects affected / exposed	4 / 509 (0.79%)	1 / 125 (0.80%)	2 / 124 (1.61%)
occurrences (all)	4	1	3
Eye contusion			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	1	0	0
Face injury			

subjects affected / exposed	0 / 509 (0.00%)	1 / 125 (0.80%)	0 / 124 (0.00%)
occurrences (all)	0	1	0
Fall			
subjects affected / exposed	45 / 509 (8.84%)	11 / 125 (8.80%)	8 / 124 (6.45%)
occurrences (all)	68	13	8
Femur fracture			
subjects affected / exposed	2 / 509 (0.39%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	2	0	0
Foreign body in eye			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	2	0	0
Fractured coccyx			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	1	0	0
Gastroenteritis radiation			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	1	0	0
Hand fracture			
subjects affected / exposed	2 / 509 (0.39%)	1 / 125 (0.80%)	0 / 124 (0.00%)
occurrences (all)	2	1	0
Head injury			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	1 / 124 (0.81%)
occurrences (all)	1	0	1
Humerus fracture			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	1	0	0
Injection related reaction			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	1	0	0
Joint injury			
subjects affected / exposed	2 / 509 (0.39%)	1 / 125 (0.80%)	0 / 124 (0.00%)
occurrences (all)	2	1	0
Laceration			
subjects affected / exposed	9 / 509 (1.77%)	2 / 125 (1.60%)	1 / 124 (0.81%)
occurrences (all)	11	3	1
Ligament sprain			

subjects affected / exposed	1 / 509 (0.20%)	1 / 125 (0.80%)	0 / 124 (0.00%)
occurrences (all)	1	1	0
Limb injury			
subjects affected / exposed	1 / 509 (0.20%)	1 / 125 (0.80%)	0 / 124 (0.00%)
occurrences (all)	1	1	0
Lumbar vertebral fracture			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	1	0	0
Multiple injuries			
subjects affected / exposed	0 / 509 (0.00%)	1 / 125 (0.80%)	0 / 124 (0.00%)
occurrences (all)	0	1	0
Muscle injury			
subjects affected / exposed	0 / 509 (0.00%)	1 / 125 (0.80%)	0 / 124 (0.00%)
occurrences (all)	0	1	0
Muscle strain			
subjects affected / exposed	4 / 509 (0.79%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	7	0	0
Overdose			
subjects affected / exposed	2 / 509 (0.39%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	2	0	0
Pelvic fracture			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	1	0	0
Periorbital contusion			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	1	0	0
Post procedural haematuria			
subjects affected / exposed	0 / 509 (0.00%)	1 / 125 (0.80%)	0 / 124 (0.00%)
occurrences (all)	0	1	0
Post-traumatic pain			
subjects affected / exposed	2 / 509 (0.39%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	2	0	0
Procedural hypotension			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	1	0	0
Procedural nausea			

subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	2	0	0
Procedural pain			
subjects affected / exposed	2 / 509 (0.39%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	2	0	0
Procedural vomiting			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	1	0	0
Radius fracture			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	1	0	0
Rib fracture			
subjects affected / exposed	4 / 509 (0.79%)	1 / 125 (0.80%)	1 / 124 (0.81%)
occurrences (all)	4	1	1
Skeletal injury			
subjects affected / exposed	1 / 509 (0.20%)	1 / 125 (0.80%)	1 / 124 (0.81%)
occurrences (all)	1	1	1
Skin wound			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	1	0	0
Spinal compression fracture			
subjects affected / exposed	3 / 509 (0.59%)	1 / 125 (0.80%)	1 / 124 (0.81%)
occurrences (all)	3	1	1
Thoracic vertebral fracture			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	1	0	0
Toxicity to various agents			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	1	0	0
Traumatic fracture			
subjects affected / exposed	0 / 509 (0.00%)	1 / 125 (0.80%)	2 / 124 (1.61%)
occurrences (all)	0	1	3
Urethral injury			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	1	0	0
Wound			

subjects affected / exposed	3 / 509 (0.59%)	0 / 125 (0.00%)	1 / 124 (0.81%)
occurrences (all)	4	0	1
Wound dehiscence			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	1	0	0
Wound secretion			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	1	0	0
Wrist fracture			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	1	0	0
Congenital, familial and genetic disorders			
Phimosis			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	1	0	0
Cardiac disorders			
Aortic valve stenosis			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	1	0	0
Angina pectoris			
subjects affected / exposed	3 / 509 (0.59%)	1 / 125 (0.80%)	0 / 124 (0.00%)
occurrences (all)	3	1	0
Arrhythmia			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	1	0	0
Atrial fibrillation			
subjects affected / exposed	4 / 509 (0.79%)	3 / 125 (2.40%)	4 / 124 (3.23%)
occurrences (all)	4	3	4
Atrial flutter			
subjects affected / exposed	5 / 509 (0.98%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	5	0	0
Bradycardia			
subjects affected / exposed	5 / 509 (0.98%)	0 / 125 (0.00%)	1 / 124 (0.81%)
occurrences (all)	5	0	1
Bundle branch block right			

subjects affected / exposed	1 / 509 (0.20%)	1 / 125 (0.80%)	1 / 124 (0.81%)
occurrences (all)	1	1	1
Cardiac failure			
subjects affected / exposed	2 / 509 (0.39%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	2	0	0
Cardiac failure congestive			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	1 / 124 (0.81%)
occurrences (all)	1	0	1
Chordae tendinae rupture			
subjects affected / exposed	0 / 509 (0.00%)	0 / 125 (0.00%)	1 / 124 (0.81%)
occurrences (all)	0	0	1
Coronary artery stenosis			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	1 / 124 (0.81%)
occurrences (all)	1	0	1
Diastolic dysfunction			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	1	0	0
Extrasystoles			
subjects affected / exposed	3 / 509 (0.59%)	0 / 125 (0.00%)	1 / 124 (0.81%)
occurrences (all)	3	0	1
Left ventricular dysfunction			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	1	0	0
Mitral valve disease			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	1	0	0
Mitral valve prolapse			
subjects affected / exposed	0 / 509 (0.00%)	0 / 125 (0.00%)	1 / 124 (0.81%)
occurrences (all)	0	0	1
Myocardial infarction			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	1	0	0
Myocardial ischaemia			
subjects affected / exposed	0 / 509 (0.00%)	1 / 125 (0.80%)	0 / 124 (0.00%)
occurrences (all)	0	1	0
Palpitations			

subjects affected / exposed	2 / 509 (0.39%)	1 / 125 (0.80%)	1 / 124 (0.81%)
occurrences (all)	2	1	1
Right ventricular dysfunction			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	1	0	0
Sinus bradycardia			
subjects affected / exposed	2 / 509 (0.39%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	2	0	0
Sinus tachycardia			
subjects affected / exposed	0 / 509 (0.00%)	0 / 125 (0.00%)	1 / 124 (0.81%)
occurrences (all)	0	0	1
Supraventricular extrasystoles			
subjects affected / exposed	0 / 509 (0.00%)	1 / 125 (0.80%)	0 / 124 (0.00%)
occurrences (all)	0	1	0
Tachycardia			
subjects affected / exposed	7 / 509 (1.38%)	0 / 125 (0.00%)	2 / 124 (1.61%)
occurrences (all)	7	0	2
Ventricular extrasystoles			
subjects affected / exposed	2 / 509 (0.39%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	2	0	0
Nervous system disorders			
Ageusia			
subjects affected / exposed	1 / 509 (0.20%)	1 / 125 (0.80%)	0 / 124 (0.00%)
occurrences (all)	1	1	0
Amnesia			
subjects affected / exposed	9 / 509 (1.77%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	9	0	0
Ataxia			
subjects affected / exposed	5 / 509 (0.98%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	5	0	0
Balance disorder			
subjects affected / exposed	8 / 509 (1.57%)	1 / 125 (0.80%)	0 / 124 (0.00%)
occurrences (all)	8	1	0
Burning sensation			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	1	0	0

Carpal tunnel syndrome			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	1	0	0
Cauda equina syndrome			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	1 / 124 (0.81%)
occurrences (all)	1	0	1
Cognitive disorder			
subjects affected / exposed	11 / 509 (2.16%)	1 / 125 (0.80%)	0 / 124 (0.00%)
occurrences (all)	18	1	0
Dementia			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	1	0	0
Dementia Alzheimer's type			
subjects affected / exposed	0 / 509 (0.00%)	1 / 125 (0.80%)	0 / 124 (0.00%)
occurrences (all)	0	1	0
Disturbance in attention			
subjects affected / exposed	7 / 509 (1.38%)	1 / 125 (0.80%)	1 / 124 (0.81%)
occurrences (all)	8	1	1
Dizziness postural			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	1	0	0
Dizziness			
subjects affected / exposed	41 / 509 (8.06%)	6 / 125 (4.80%)	4 / 124 (3.23%)
occurrences (all)	49	6	5
Dysaesthesia			
subjects affected / exposed	2 / 509 (0.39%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	2	0	0
Dysarthria			
subjects affected / exposed	2 / 509 (0.39%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	2	0	0
Dysgeusia			
subjects affected / exposed	24 / 509 (4.72%)	3 / 125 (2.40%)	1 / 124 (0.81%)
occurrences (all)	26	4	1
Dyskinesia			
subjects affected / exposed	1 / 509 (0.20%)	1 / 125 (0.80%)	0 / 124 (0.00%)
occurrences (all)	1	1	0

Head discomfort			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	1	0	0
Headache			
subjects affected / exposed	49 / 509 (9.63%)	5 / 125 (4.00%)	2 / 124 (1.61%)
occurrences (all)	53	5	2
Hemiparesis			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	1	0	0
Hyperreflexia			
subjects affected / exposed	0 / 509 (0.00%)	0 / 125 (0.00%)	1 / 124 (0.81%)
occurrences (all)	0	0	1
Hypoaesthesia			
subjects affected / exposed	10 / 509 (1.96%)	4 / 125 (3.20%)	3 / 124 (2.42%)
occurrences (all)	10	4	3
Hypoglossal nerve paralysis			
subjects affected / exposed	0 / 509 (0.00%)	1 / 125 (0.80%)	0 / 124 (0.00%)
occurrences (all)	0	1	0
Hypokinesia			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	1	0	0
Lethargy			
subjects affected / exposed	34 / 509 (6.68%)	3 / 125 (2.40%)	1 / 124 (0.81%)
occurrences (all)	37	5	1
Loss of consciousness			
subjects affected / exposed	3 / 509 (0.59%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	3	0	0
Memory impairment			
subjects affected / exposed	16 / 509 (3.14%)	2 / 125 (1.60%)	2 / 124 (1.61%)
occurrences (all)	19	2	2
Nerve compression			
subjects affected / exposed	0 / 509 (0.00%)	1 / 125 (0.80%)	0 / 124 (0.00%)
occurrences (all)	0	1	0
Migraine			
subjects affected / exposed	3 / 509 (0.59%)	1 / 125 (0.80%)	0 / 124 (0.00%)
occurrences (all)	3	1	0

Neuralgia			
subjects affected / exposed	5 / 509 (0.98%)	0 / 125 (0.00%)	1 / 124 (0.81%)
occurrences (all)	6	0	1
Neuropathy peripheral			
subjects affected / exposed	2 / 509 (0.39%)	0 / 125 (0.00%)	1 / 124 (0.81%)
occurrences (all)	2	0	1
Paraesthesia			
subjects affected / exposed	21 / 509 (4.13%)	1 / 125 (0.80%)	0 / 124 (0.00%)
occurrences (all)	23	1	0
Parkinsonian gait			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	1	0	0
Parkinson's disease			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	1	0	0
Parosmia			
subjects affected / exposed	0 / 509 (0.00%)	1 / 125 (0.80%)	0 / 124 (0.00%)
occurrences (all)	0	1	0
Peripheral sensory neuropathy			
subjects affected / exposed	2 / 509 (0.39%)	1 / 125 (0.80%)	0 / 124 (0.00%)
occurrences (all)	2	1	0
Poor quality sleep			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	1	0	0
Post herpetic neuralgia			
subjects affected / exposed	2 / 509 (0.39%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	2	0	0
Presyncope			
subjects affected / exposed	4 / 509 (0.79%)	1 / 125 (0.80%)	1 / 124 (0.81%)
occurrences (all)	5	1	1
Radicular pain			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	1	0	0
Restless legs syndrome			
subjects affected / exposed	9 / 509 (1.77%)	0 / 125 (0.00%)	1 / 124 (0.81%)
occurrences (all)	9	0	1

Sciatica			
subjects affected / exposed	4 / 509 (0.79%)	0 / 125 (0.00%)	1 / 124 (0.81%)
occurrences (all)	6	0	2
Somnolence			
subjects affected / exposed	7 / 509 (1.38%)	1 / 125 (0.80%)	1 / 124 (0.81%)
occurrences (all)	7	1	1
Syncope			
subjects affected / exposed	4 / 509 (0.79%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	4	0	0
Tension headache			
subjects affected / exposed	0 / 509 (0.00%)	1 / 125 (0.80%)	0 / 124 (0.00%)
occurrences (all)	0	1	0
Tongue paralysis			
subjects affected / exposed	0 / 509 (0.00%)	0 / 125 (0.00%)	1 / 124 (0.81%)
occurrences (all)	0	0	1
Transient ischaemic attack			
subjects affected / exposed	2 / 509 (0.39%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	2	0	0
Tremor			
subjects affected / exposed	5 / 509 (0.98%)	0 / 125 (0.00%)	2 / 124 (1.61%)
occurrences (all)	5	0	2
Trigeminal neuralgia			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	1	0	0
Seventh nerve paralysis			
subjects affected / exposed	0 / 509 (0.00%)	1 / 125 (0.80%)	0 / 124 (0.00%)
occurrences (all)	0	2	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	30 / 509 (5.89%)	5 / 125 (4.00%)	5 / 124 (4.03%)
occurrences (all)	36	10	7
Bone marrow failure			
subjects affected / exposed	0 / 509 (0.00%)	0 / 125 (0.00%)	1 / 124 (0.81%)
occurrences (all)	0	0	1
Haemorrhagic anaemia			

subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	1	0	0
Iron deficiency anaemia			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	1	0	0
Leukocytosis			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	1	0	0
Lymphadenopathy			
subjects affected / exposed	2 / 509 (0.39%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	2	0	0
Lymphopenia			
subjects affected / exposed	0 / 509 (0.00%)	1 / 125 (0.80%)	0 / 124 (0.00%)
occurrences (all)	0	1	0
Pancytopenia			
subjects affected / exposed	0 / 509 (0.00%)	1 / 125 (0.80%)	0 / 124 (0.00%)
occurrences (all)	0	1	0
Pernicious anaemia			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	1	0	0
Thrombocytopenia			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	1 / 124 (0.81%)
occurrences (all)	2	0	3
Ear and labyrinth disorders			
Cerumen impaction			
subjects affected / exposed	2 / 509 (0.39%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	2	0	0
Deafness bilateral			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	1	0	0
Deafness neurosensory			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	1	0	0
Hearing impaired			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	1	0	0

Motion sickness			
subjects affected / exposed	2 / 509 (0.39%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	2	0	0
Tinnitus			
subjects affected / exposed	2 / 509 (0.39%)	1 / 125 (0.80%)	0 / 124 (0.00%)
occurrences (all)	2	1	0
Vertigo			
subjects affected / exposed	13 / 509 (2.55%)	0 / 125 (0.00%)	1 / 124 (0.81%)
occurrences (all)	17	0	1
Vertigo positional			
subjects affected / exposed	1 / 509 (0.20%)	1 / 125 (0.80%)	0 / 124 (0.00%)
occurrences (all)	1	1	0
Eye disorders			
Amaurosis			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	1	0	0
Cataract			
subjects affected / exposed	6 / 509 (1.18%)	1 / 125 (0.80%)	1 / 124 (0.81%)
occurrences (all)	10	1	2
Conjunctival haemorrhage			
subjects affected / exposed	0 / 509 (0.00%)	0 / 125 (0.00%)	1 / 124 (0.81%)
occurrences (all)	0	0	1
Conjunctivitis			
subjects affected / exposed	9 / 509 (1.77%)	2 / 125 (1.60%)	1 / 124 (0.81%)
occurrences (all)	10	2	1
Diplopia			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	1	0	0
Dry eye			
subjects affected / exposed	5 / 509 (0.98%)	1 / 125 (0.80%)	0 / 124 (0.00%)
occurrences (all)	5	1	0
Exophthalmos			
subjects affected / exposed	2 / 509 (0.39%)	0 / 125 (0.00%)	1 / 124 (0.81%)
occurrences (all)	2	0	1
Eye disorder			

subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	1	0	0
Eye inflammation			
subjects affected / exposed	0 / 509 (0.00%)	1 / 125 (0.80%)	0 / 124 (0.00%)
occurrences (all)	0	1	0
Eye irritation			
subjects affected / exposed	3 / 509 (0.59%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	3	0	0
Eye pain			
subjects affected / exposed	2 / 509 (0.39%)	1 / 125 (0.80%)	0 / 124 (0.00%)
occurrences (all)	2	1	0
Eyelid margin crusting			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	1	0	0
Iritis			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	1	0	0
Glaucoma			
subjects affected / exposed	2 / 509 (0.39%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	2	0	0
Lacrimation increased			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	1	0	0
Macular fibrosis			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	1	0	0
Ocular icterus			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	1	0	0
Night blindness			
subjects affected / exposed	0 / 509 (0.00%)	1 / 125 (0.80%)	0 / 124 (0.00%)
occurrences (all)	0	1	0
Optic ischaemic neuropathy			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	1	0	0
Retinal artery occlusion			

subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	1	0	0
Photophobia			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	1	0	0
Strabismus			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	1	0	0
Trichiasis			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	1	0	0
Vision blurred			
subjects affected / exposed	3 / 509 (0.59%)	0 / 125 (0.00%)	1 / 124 (0.81%)
occurrences (all)	3	0	1
Visual acuity reduced			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	1	0	0
Visual impairment			
subjects affected / exposed	2 / 509 (0.39%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	2	0	0
Vitreous floaters			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	1	0	0
Vitreous haemorrhage			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	1	0	0
Eye swelling			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	1	0	0
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	5 / 509 (0.98%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	6	0	0
Abdominal distension			
subjects affected / exposed	8 / 509 (1.57%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	9	0	0

Abdominal pain			
subjects affected / exposed	14 / 509 (2.75%)	7 / 125 (5.60%)	7 / 124 (5.65%)
occurrences (all)	14	7	7
Abdominal pain lower			
subjects affected / exposed	5 / 509 (0.98%)	2 / 125 (1.60%)	1 / 124 (0.81%)
occurrences (all)	5	3	1
Abdominal pain upper			
subjects affected / exposed	19 / 509 (3.73%)	0 / 125 (0.00%)	2 / 124 (1.61%)
occurrences (all)	21	0	2
Anal haemorrhage			
subjects affected / exposed	3 / 509 (0.59%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	4	0	0
Apical granuloma			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	1	0	0
Barrett's oesophagus			
subjects affected / exposed	0 / 509 (0.00%)	0 / 125 (0.00%)	1 / 124 (0.81%)
occurrences (all)	0	0	1
Breath odour			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	1	0	0
Cheilitis			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	1	0	0
Colitis microscopic			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	1	0	0
Constipation			
subjects affected / exposed	78 / 509 (15.32%)	17 / 125 (13.60%)	12 / 124 (9.68%)
occurrences (all)	89	21	13
Dental caries			
subjects affected / exposed	3 / 509 (0.59%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	4	0	0
Diarrhoea			
subjects affected / exposed	66 / 509 (12.97%)	7 / 125 (5.60%)	12 / 124 (9.68%)
occurrences (all)	77	9	12

Diverticulum intestinal			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	1	0	0
Dry mouth			
subjects affected / exposed	4 / 509 (0.79%)	2 / 125 (1.60%)	1 / 124 (0.81%)
occurrences (all)	4	2	1
Dyspepsia			
subjects affected / exposed	16 / 509 (3.14%)	3 / 125 (2.40%)	4 / 124 (3.23%)
occurrences (all)	19	3	4
Dysphagia			
subjects affected / exposed	3 / 509 (0.59%)	2 / 125 (1.60%)	1 / 124 (0.81%)
occurrences (all)	3	2	1
Epigastric discomfort			
subjects affected / exposed	0 / 509 (0.00%)	0 / 125 (0.00%)	1 / 124 (0.81%)
occurrences (all)	0	0	1
Erosive oesophagitis			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	1	0	0
Eructation			
subjects affected / exposed	2 / 509 (0.39%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	2	0	0
Faecal incontinence			
subjects affected / exposed	3 / 509 (0.59%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	3	0	0
Faecaloma			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	1	0	0
Faeces hard			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	1	0	0
Flatulence			
subjects affected / exposed	12 / 509 (2.36%)	3 / 125 (2.40%)	1 / 124 (0.81%)
occurrences (all)	12	3	1
Food poisoning			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	1	0	0

Frequent bowel movements			
subjects affected / exposed	2 / 509 (0.39%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	2	0	0
Gastric mucosa erythema			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	1	0	0
Gastric ulcer			
subjects affected / exposed	3 / 509 (0.59%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	4	0	0
Gastritis			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	2 / 124 (1.61%)
occurrences (all)	1	0	2
Gastrooesophageal reflux disease			
subjects affected / exposed	13 / 509 (2.55%)	4 / 125 (3.20%)	5 / 124 (4.03%)
occurrences (all)	13	4	5
Gingival bleeding			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	1	0	0
Gingival inflammation			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	1	0	0
Gingival pain			
subjects affected / exposed	2 / 509 (0.39%)	1 / 125 (0.80%)	0 / 124 (0.00%)
occurrences (all)	2	1	0
Haematochezia			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	2	0	0
Haemorrhoids			
subjects affected / exposed	4 / 509 (0.79%)	0 / 125 (0.00%)	1 / 124 (0.81%)
occurrences (all)	4	0	1
Hiatus hernia			
subjects affected / exposed	2 / 509 (0.39%)	0 / 125 (0.00%)	2 / 124 (1.61%)
occurrences (all)	2	0	2
Inguinal hernia			
subjects affected / exposed	3 / 509 (0.59%)	0 / 125 (0.00%)	2 / 124 (1.61%)
occurrences (all)	3	0	2

Large intestine polyp			
subjects affected / exposed	3 / 509 (0.59%)	0 / 125 (0.00%)	1 / 124 (0.81%)
occurrences (all)	3	0	1
Lip dry			
subjects affected / exposed	0 / 509 (0.00%)	0 / 125 (0.00%)	1 / 124 (0.81%)
occurrences (all)	0	0	1
Lip oedema			
subjects affected / exposed	0 / 509 (0.00%)	0 / 125 (0.00%)	1 / 124 (0.81%)
occurrences (all)	0	0	1
Localised intraabdominal fluid collection			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	1	0	0
Melaena			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	1	0	0
Mouth ulceration			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	1	0	0
Nausea			
subjects affected / exposed	97 / 509 (19.06%)	21 / 125 (16.80%)	11 / 124 (8.87%)
occurrences (all)	123	27	11
Odynophagia			
subjects affected / exposed	2 / 509 (0.39%)	1 / 125 (0.80%)	0 / 124 (0.00%)
occurrences (all)	2	1	0
Oesophageal pain			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	1	0	0
Oesophagitis			
subjects affected / exposed	2 / 509 (0.39%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	2	0	0
Pancreatic disorder			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	1	0	0
Pancreatitis			

subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	1	0	0
Paraesthesia oral			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	1	0	0
Periodontal disease			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	1	0	0
Proctalgia			
subjects affected / exposed	2 / 509 (0.39%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	2	0	0
Rectal haemorrhage			
subjects affected / exposed	2 / 509 (0.39%)	2 / 125 (1.60%)	0 / 124 (0.00%)
occurrences (all)	2	2	0
Retching			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	1	0	0
Salivary hypersecretion			
subjects affected / exposed	2 / 509 (0.39%)	1 / 125 (0.80%)	0 / 124 (0.00%)
occurrences (all)	2	1	0
Tongue disorder			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	1	0	0
Toothache			
subjects affected / exposed	7 / 509 (1.38%)	0 / 125 (0.00%)	1 / 124 (0.81%)
occurrences (all)	7	0	1
Umbilical hernia			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	1	0	0
Vomiting			
subjects affected / exposed	28 / 509 (5.50%)	7 / 125 (5.60%)	2 / 124 (1.61%)
occurrences (all)	32	9	3
Skin and subcutaneous tissue disorders			
Actinic keratosis			
subjects affected / exposed	1 / 509 (0.20%)	1 / 125 (0.80%)	0 / 124 (0.00%)
occurrences (all)	2	1	0

Actinic prurigo			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	1	0	0
Alopecia			
subjects affected / exposed	11 / 509 (2.16%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	11	0	0
Blister			
subjects affected / exposed	0 / 509 (0.00%)	1 / 125 (0.80%)	0 / 124 (0.00%)
occurrences (all)	0	1	0
Cold sweat			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	1	0	0
Cutaneous lupus erythematosus			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	1	0	0
Decubitus ulcer			
subjects affected / exposed	3 / 509 (0.59%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	3	0	0
Dermal cyst			
subjects affected / exposed	2 / 509 (0.39%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	2	0	0
Dermatitis			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	1	0	0
Dermatitis acneiform			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	1	0	0
Dermatitis contact			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	1	0	0
Diabetic foot			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	1	0	0
Dry skin			
subjects affected / exposed	5 / 509 (0.98%)	0 / 125 (0.00%)	2 / 124 (1.61%)
occurrences (all)	5	0	2

Eczema			
subjects affected / exposed	5 / 509 (0.98%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	5	0	0
Granuloma annulare			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	1	0	0
Hair growth abnormal			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	1	0	0
Haemorrhage subcutaneous			
subjects affected / exposed	0 / 509 (0.00%)	0 / 125 (0.00%)	1 / 124 (0.81%)
occurrences (all)	0	0	1
Hyperhidrosis			
subjects affected / exposed	11 / 509 (2.16%)	2 / 125 (1.60%)	0 / 124 (0.00%)
occurrences (all)	11	2	0
Hypertrichosis			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	1	0	0
Intertrigo			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	1	0	0
Miliaria			
subjects affected / exposed	0 / 509 (0.00%)	1 / 125 (0.80%)	0 / 124 (0.00%)
occurrences (all)	0	1	0
Erythema			
subjects affected / exposed	3 / 509 (0.59%)	1 / 125 (0.80%)	0 / 124 (0.00%)
occurrences (all)	3	1	0
Night sweats			
subjects affected / exposed	2 / 509 (0.39%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	3	0	0
Nail disorder			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	2	0	0
Onychoclasis			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	1	0	0

Panniculitis			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	1	0	0
Pain of skin			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	1	0	0
Penile ulceration			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	1	0	0
Petechiae			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	3	0	0
Photodermatosis			
subjects affected / exposed	2 / 509 (0.39%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	2	0	0
Pruritus			
subjects affected / exposed	8 / 509 (1.57%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	11	0	0
Psoriasis			
subjects affected / exposed	2 / 509 (0.39%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	2	0	0
Rash			
subjects affected / exposed	14 / 509 (2.75%)	6 / 125 (4.80%)	4 / 124 (3.23%)
occurrences (all)	20	7	4
Rash macular			
subjects affected / exposed	2 / 509 (0.39%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	2	0	0
Rash erythematous			
subjects affected / exposed	0 / 509 (0.00%)	1 / 125 (0.80%)	0 / 124 (0.00%)
occurrences (all)	0	1	0
Rash maculo-papular			
subjects affected / exposed	2 / 509 (0.39%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	2	0	0
Rash pruritic			
subjects affected / exposed	2 / 509 (0.39%)	0 / 125 (0.00%)	1 / 124 (0.81%)
occurrences (all)	3	0	1

Rash papular			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	1	0	0
Skin lesion			
subjects affected / exposed	4 / 509 (0.79%)	1 / 125 (0.80%)	1 / 124 (0.81%)
occurrences (all)	6	1	1
Skin exfoliation			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	1	0	0
Skin ulcer			
subjects affected / exposed	2 / 509 (0.39%)	2 / 125 (1.60%)	0 / 124 (0.00%)
occurrences (all)	2	2	0
Sticky skin			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	1	0	0
Swelling face			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	1	0	0
Urticaria			
subjects affected / exposed	3 / 509 (0.59%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	3	0	0
Renal and urinary disorders			
Bladder pain			
subjects affected / exposed	0 / 509 (0.00%)	1 / 125 (0.80%)	0 / 124 (0.00%)
occurrences (all)	0	1	0
Bladder dysfunction			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	1	0	0
Bladder spasm			
subjects affected / exposed	1 / 509 (0.20%)	1 / 125 (0.80%)	0 / 124 (0.00%)
occurrences (all)	1	1	0
Calculus bladder			
subjects affected / exposed	4 / 509 (0.79%)	1 / 125 (0.80%)	0 / 124 (0.00%)
occurrences (all)	4	1	0
Calculus ureteric			

subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	1	0	0
Haematuria			
subjects affected / exposed	18 / 509 (3.54%)	6 / 125 (4.80%)	11 / 124 (8.87%)
occurrences (all)	31	6	14
Dysuria			
subjects affected / exposed	12 / 509 (2.36%)	1 / 125 (0.80%)	5 / 124 (4.03%)
occurrences (all)	13	1	5
Haemorrhage urinary tract			
subjects affected / exposed	1 / 509 (0.20%)	1 / 125 (0.80%)	0 / 124 (0.00%)
occurrences (all)	1	1	0
Hydronephrosis			
subjects affected / exposed	3 / 509 (0.59%)	1 / 125 (0.80%)	1 / 124 (0.81%)
occurrences (all)	3	3	1
Incontinence			
subjects affected / exposed	7 / 509 (1.38%)	2 / 125 (1.60%)	1 / 124 (0.81%)
occurrences (all)	8	2	1
Lower urinary tract symptoms			
subjects affected / exposed	0 / 509 (0.00%)	0 / 125 (0.00%)	1 / 124 (0.81%)
occurrences (all)	0	0	1
Micturition urgency			
subjects affected / exposed	6 / 509 (1.18%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	6	0	0
Nephrolithiasis			
subjects affected / exposed	3 / 509 (0.59%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	3	0	0
Nocturia			
subjects affected / exposed	18 / 509 (3.54%)	1 / 125 (0.80%)	4 / 124 (3.23%)
occurrences (all)	18	1	4
Pollakiuria			
subjects affected / exposed	12 / 509 (2.36%)	2 / 125 (1.60%)	4 / 124 (3.23%)
occurrences (all)	12	2	4
Polyuria			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	1 / 124 (0.81%)
occurrences (all)	1	0	1
Prerenal failure			

subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	1	0	0
Renal colic			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	1	0	0
Renal failure			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	1	0	0
Renal impairment			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	1	0	0
Strangury			
subjects affected / exposed	1 / 509 (0.20%)	1 / 125 (0.80%)	2 / 124 (1.61%)
occurrences (all)	1	1	2
Ureteric obstruction			
subjects affected / exposed	3 / 509 (0.59%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	3	0	0
Urethral dilatation			
subjects affected / exposed	0 / 509 (0.00%)	0 / 125 (0.00%)	1 / 124 (0.81%)
occurrences (all)	0	0	1
Urethral stenosis			
subjects affected / exposed	0 / 509 (0.00%)	0 / 125 (0.00%)	1 / 124 (0.81%)
occurrences (all)	0	0	1
Urethral pain			
subjects affected / exposed	1 / 509 (0.20%)	2 / 125 (1.60%)	0 / 124 (0.00%)
occurrences (all)	1	2	0
Urge incontinence			
subjects affected / exposed	1 / 509 (0.20%)	1 / 125 (0.80%)	0 / 124 (0.00%)
occurrences (all)	1	1	0
Urethritis noninfective			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	1 / 124 (0.81%)
occurrences (all)	2	0	1
Urinary incontinence			
subjects affected / exposed	16 / 509 (3.14%)	2 / 125 (1.60%)	1 / 124 (0.81%)
occurrences (all)	16	2	1
Urinary hesitation			

subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	1 / 124 (0.81%)
occurrences (all)	2	0	1
Urinary retention			
subjects affected / exposed	8 / 509 (1.57%)	2 / 125 (1.60%)	2 / 124 (1.61%)
occurrences (all)	9	2	2
Urine odour abnormal			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	1	0	0
Urinary tract obstruction			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	1 / 124 (0.81%)
occurrences (all)	2	0	1
Endocrine disorders			
Adrenal insufficiency			
subjects affected / exposed	0 / 509 (0.00%)	0 / 125 (0.00%)	1 / 124 (0.81%)
occurrences (all)	0	0	1
Cushingoid			
subjects affected / exposed	0 / 509 (0.00%)	1 / 125 (0.80%)	1 / 124 (0.81%)
occurrences (all)	0	1	1
Goitre			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	1	0	0
Hyperthyroidism			
subjects affected / exposed	0 / 509 (0.00%)	0 / 125 (0.00%)	1 / 124 (0.81%)
occurrences (all)	0	0	1
Hypothyroidism			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	1	0	0
Thyroid mass			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	1	0	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	74 / 509 (14.54%)	18 / 125 (14.40%)	14 / 124 (11.29%)
occurrences (all)	90	30	18
Arthritis			

subjects affected / exposed	3 / 509 (0.59%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	3	0	0
Arthropathy			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	1	0	0
Back pain			
subjects affected / exposed	104 / 509 (20.43%)	25 / 125 (20.00%)	28 / 124 (22.58%)
occurrences (all)	133	32	33
Bone fistula			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	1	0	0
Bone pain			
subjects affected / exposed	21 / 509 (4.13%)	3 / 125 (2.40%)	4 / 124 (3.23%)
occurrences (all)	23	3	6
Bursitis			
subjects affected / exposed	3 / 509 (0.59%)	0 / 125 (0.00%)	1 / 124 (0.81%)
occurrences (all)	3	0	1
Coccydynia			
subjects affected / exposed	3 / 509 (0.59%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	3	0	0
Flank pain			
subjects affected / exposed	5 / 509 (0.98%)	2 / 125 (1.60%)	0 / 124 (0.00%)
occurrences (all)	5	2	0
Groin pain			
subjects affected / exposed	12 / 509 (2.36%)	1 / 125 (0.80%)	5 / 124 (4.03%)
occurrences (all)	12	2	5
Inguinal mass			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	1	0	0
Intervertebral disc protrusion			
subjects affected / exposed	1 / 509 (0.20%)	1 / 125 (0.80%)	0 / 124 (0.00%)
occurrences (all)	1	1	0
Joint range of motion decreased			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	1	0	0
Joint stiffness			

subjects affected / exposed	2 / 509 (0.39%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	2	0	0
Joint swelling			
subjects affected / exposed	4 / 509 (0.79%)	2 / 125 (1.60%)	1 / 124 (0.81%)
occurrences (all)	4	2	1
Mobility decreased			
subjects affected / exposed	2 / 509 (0.39%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	2	0	0
Muscle atrophy			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	1	0	0
Muscle fatigue			
subjects affected / exposed	2 / 509 (0.39%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	2	0	0
Muscle tightness			
subjects affected / exposed	2 / 509 (0.39%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	2	0	0
Muscle spasms			
subjects affected / exposed	7 / 509 (1.38%)	4 / 125 (3.20%)	9 / 124 (7.26%)
occurrences (all)	7	9	10
Muscular weakness			
subjects affected / exposed	21 / 509 (4.13%)	6 / 125 (4.80%)	4 / 124 (3.23%)
occurrences (all)	26	6	7
Musculoskeletal chest pain			
subjects affected / exposed	23 / 509 (4.52%)	13 / 125 (10.40%)	7 / 124 (5.65%)
occurrences (all)	26	17	9
Musculoskeletal discomfort			
subjects affected / exposed	1 / 509 (0.20%)	1 / 125 (0.80%)	0 / 124 (0.00%)
occurrences (all)	1	1	0
Musculoskeletal pain			
subjects affected / exposed	33 / 509 (6.48%)	11 / 125 (8.80%)	8 / 124 (6.45%)
occurrences (all)	34	14	9
Myalgia			
subjects affected / exposed	23 / 509 (4.52%)	1 / 125 (0.80%)	2 / 124 (1.61%)
occurrences (all)	25	1	2
Musculoskeletal stiffness			

subjects affected / exposed	4 / 509 (0.79%)	3 / 125 (2.40%)	0 / 124 (0.00%)
occurrences (all)	4	3	0
Myopathy			
subjects affected / exposed	2 / 509 (0.39%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	2	0	0
Myositis			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	1	0	0
Neck pain			
subjects affected / exposed	23 / 509 (4.52%)	2 / 125 (1.60%)	3 / 124 (2.42%)
occurrences (all)	26	3	3
Osteoarthritis			
subjects affected / exposed	6 / 509 (1.18%)	0 / 125 (0.00%)	1 / 124 (0.81%)
occurrences (all)	8	0	1
Osteonecrosis			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	1	0	0
Osteonecrosis of jaw			
subjects affected / exposed	2 / 509 (0.39%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	2	0	0
Osteopenia			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	1	0	0
Osteoporosis			
subjects affected / exposed	0 / 509 (0.00%)	2 / 125 (1.60%)	0 / 124 (0.00%)
occurrences (all)	0	2	0
Pain in extremity			
subjects affected / exposed	33 / 509 (6.48%)	9 / 125 (7.20%)	6 / 124 (4.84%)
occurrences (all)	39	11	7
Pain in jaw			
subjects affected / exposed	0 / 509 (0.00%)	0 / 125 (0.00%)	1 / 124 (0.81%)
occurrences (all)	0	0	1
Pathological fracture			
subjects affected / exposed	1 / 509 (0.20%)	1 / 125 (0.80%)	0 / 124 (0.00%)
occurrences (all)	1	1	0
Plantar fasciitis			

subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	1	0	0
Scoliosis			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	1	0	0
Spinal column stenosis			
subjects affected / exposed	2 / 509 (0.39%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	2	0	0
Spinal osteoarthritis			
subjects affected / exposed	2 / 509 (0.39%)	1 / 125 (0.80%)	0 / 124 (0.00%)
occurrences (all)	2	1	0
Spinal pain			
subjects affected / exposed	4 / 509 (0.79%)	0 / 125 (0.00%)	1 / 124 (0.81%)
occurrences (all)	5	0	1
Synovial cyst			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	1	0	0
Synovitis			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	1	0	0
Tendonitis			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	1 / 124 (0.81%)
occurrences (all)	2	0	1
Trismus			
subjects affected / exposed	0 / 509 (0.00%)	1 / 125 (0.80%)	0 / 124 (0.00%)
occurrences (all)	0	1	0
Infections and infestations			
Abdominal abscess			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	1	0	0
Abscess			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	1	0	0
Abscess neck			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	1	0	0

Atypical mycobacterial infection			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	1	0	0
Bronchitis			
subjects affected / exposed	4 / 509 (0.79%)	1 / 125 (0.80%)	1 / 124 (0.81%)
occurrences (all)	6	1	1
Bronchopneumonia			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	1	0	0
Carbuncle			
subjects affected / exposed	0 / 509 (0.00%)	1 / 125 (0.80%)	0 / 124 (0.00%)
occurrences (all)	0	2	0
Catheter site infection			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	1	0	0
Cellulitis			
subjects affected / exposed	2 / 509 (0.39%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	2	0	0
Conjunctivitis infective			
subjects affected / exposed	0 / 509 (0.00%)	0 / 125 (0.00%)	1 / 124 (0.81%)
occurrences (all)	0	0	1
Cystitis			
subjects affected / exposed	4 / 509 (0.79%)	1 / 125 (0.80%)	2 / 124 (1.61%)
occurrences (all)	4	1	3
Diverticulitis			
subjects affected / exposed	2 / 509 (0.39%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	2	0	0
Ear infection			
subjects affected / exposed	2 / 509 (0.39%)	2 / 125 (1.60%)	1 / 124 (0.81%)
occurrences (all)	2	2	1
Erysipelas			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	1	0	0
Eye infection			
subjects affected / exposed	4 / 509 (0.79%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	4	0	0

Escherichia urinary tract infection			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	1	0	0
Eyelid infection			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	1	0	0
Fungal skin infection			
subjects affected / exposed	1 / 509 (0.20%)	1 / 125 (0.80%)	0 / 124 (0.00%)
occurrences (all)	1	1	0
Folliculitis			
subjects affected / exposed	3 / 509 (0.59%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	4	0	0
Furuncle			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	1	0	0
Gastroenteritis			
subjects affected / exposed	4 / 509 (0.79%)	1 / 125 (0.80%)	0 / 124 (0.00%)
occurrences (all)	5	1	0
Genital candidiasis			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	1	0	0
Gingival infection			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	1	0	0
Gingivitis			
subjects affected / exposed	0 / 509 (0.00%)	0 / 125 (0.00%)	1 / 124 (0.81%)
occurrences (all)	0	0	1
Helicobacter infection			
subjects affected / exposed	1 / 509 (0.20%)	1 / 125 (0.80%)	0 / 124 (0.00%)
occurrences (all)	1	1	0
Herpes simplex			
subjects affected / exposed	0 / 509 (0.00%)	0 / 125 (0.00%)	1 / 124 (0.81%)
occurrences (all)	0	0	1
Herpes zoster			
subjects affected / exposed	5 / 509 (0.98%)	4 / 125 (3.20%)	2 / 124 (1.61%)
occurrences (all)	5	4	2

Herpes zoster oticus			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	1	0	0
Infected cyst			
subjects affected / exposed	0 / 509 (0.00%)	1 / 125 (0.80%)	0 / 124 (0.00%)
occurrences (all)	0	1	0
Infected dermal cyst			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	1	0	0
Infection			
subjects affected / exposed	2 / 509 (0.39%)	0 / 125 (0.00%)	1 / 124 (0.81%)
occurrences (all)	2	0	1
Infection parasitic			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	1	0	0
Influenza			
subjects affected / exposed	20 / 509 (3.93%)	4 / 125 (3.20%)	5 / 124 (4.03%)
occurrences (all)	22	4	5
Injection site infection			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	1	0	0
Labyrinthitis			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	1	0	0
Laryngitis			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	1	0	0
Lip infection			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	1	0	0
Lobar pneumonia			
subjects affected / exposed	0 / 509 (0.00%)	0 / 125 (0.00%)	1 / 124 (0.81%)
occurrences (all)	0	0	1
Localised infection			
subjects affected / exposed	3 / 509 (0.59%)	1 / 125 (0.80%)	0 / 124 (0.00%)
occurrences (all)	3	1	0

Lower respiratory tract infection			
subjects affected / exposed	16 / 509 (3.14%)	2 / 125 (1.60%)	4 / 124 (3.23%)
occurrences (all)	19	2	5
Lung infection			
subjects affected / exposed	0 / 509 (0.00%)	1 / 125 (0.80%)	0 / 124 (0.00%)
occurrences (all)	0	1	0
Mediastinitis			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	1	0	0
Nail infection			
subjects affected / exposed	0 / 509 (0.00%)	1 / 125 (0.80%)	0 / 124 (0.00%)
occurrences (all)	0	1	0
Nasopharyngitis			
subjects affected / exposed	31 / 509 (6.09%)	0 / 125 (0.00%)	7 / 124 (5.65%)
occurrences (all)	43	0	8
Onychomycosis			
subjects affected / exposed	2 / 509 (0.39%)	1 / 125 (0.80%)	1 / 124 (0.81%)
occurrences (all)	2	1	1
Oral candidiasis			
subjects affected / exposed	9 / 509 (1.77%)	1 / 125 (0.80%)	1 / 124 (0.81%)
occurrences (all)	9	1	1
Oral herpes			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	1	0	0
Otitis media			
subjects affected / exposed	2 / 509 (0.39%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	2	0	0
Peritonitis			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	1	0	0
Pharyngitis			
subjects affected / exposed	3 / 509 (0.59%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	3	0	0
Pneumonia			
subjects affected / exposed	3 / 509 (0.59%)	1 / 125 (0.80%)	0 / 124 (0.00%)
occurrences (all)	3	1	0

Pulpitis dental			
subjects affected / exposed	0 / 509 (0.00%)	0 / 125 (0.00%)	1 / 124 (0.81%)
occurrences (all)	0	0	1
Rash pustular			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	1	0	0
Respiratory tract infection			
subjects affected / exposed	4 / 509 (0.79%)	0 / 125 (0.00%)	1 / 124 (0.81%)
occurrences (all)	4	0	1
Respiratory tract infection viral			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	1	0	0
Rhinitis			
subjects affected / exposed	5 / 509 (0.98%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	5	0	0
Scrotal abscess			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	1	0	0
Sialoadenitis			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	1	0	0
Sinusitis			
subjects affected / exposed	4 / 509 (0.79%)	0 / 125 (0.00%)	3 / 124 (2.42%)
occurrences (all)	6	0	3
Skin candida			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	1	0	0
Skin infection			
subjects affected / exposed	0 / 509 (0.00%)	1 / 125 (0.80%)	0 / 124 (0.00%)
occurrences (all)	0	1	0
Soft tissue infection			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	1	0	0
Tinea cruris			
subjects affected / exposed	0 / 509 (0.00%)	1 / 125 (0.80%)	0 / 124 (0.00%)
occurrences (all)	0	1	0

Tooth abscess			
subjects affected / exposed	0 / 509 (0.00%)	2 / 125 (1.60%)	0 / 124 (0.00%)
occurrences (all)	0	2	0
Tooth infection			
subjects affected / exposed	3 / 509 (0.59%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	3	0	0
Tracheitis			
subjects affected / exposed	0 / 509 (0.00%)	1 / 125 (0.80%)	0 / 124 (0.00%)
occurrences (all)	0	1	0
Upper respiratory tract infection			
subjects affected / exposed	25 / 509 (4.91%)	9 / 125 (7.20%)	5 / 124 (4.03%)
occurrences (all)	26	12	5
Urethritis			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	1 / 124 (0.81%)
occurrences (all)	1	0	1
Urinary tract infection			
subjects affected / exposed	29 / 509 (5.70%)	9 / 125 (7.20%)	6 / 124 (4.84%)
occurrences (all)	41	11	6
Urosepsis			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	1	0	0
Viral infection			
subjects affected / exposed	3 / 509 (0.59%)	1 / 125 (0.80%)	1 / 124 (0.81%)
occurrences (all)	5	2	1
Metabolism and nutrition disorders			
Abnormal loss of weight			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	1	0	0
Decreased appetite			
subjects affected / exposed	82 / 509 (16.11%)	13 / 125 (10.40%)	10 / 124 (8.06%)
occurrences (all)	97	15	10
Dehydration			
subjects affected / exposed	4 / 509 (0.79%)	2 / 125 (1.60%)	1 / 124 (0.81%)
occurrences (all)	4	2	1
Diabetes mellitus			

subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	2 / 124 (1.61%)
occurrences (all)	1	0	2
Dyslipidaemia			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	1	0	0
Fluid overload			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	1	0	0
Fluid retention			
subjects affected / exposed	0 / 509 (0.00%)	2 / 125 (1.60%)	0 / 124 (0.00%)
occurrences (all)	0	2	0
Gout			
subjects affected / exposed	0 / 509 (0.00%)	0 / 125 (0.00%)	1 / 124 (0.81%)
occurrences (all)	0	0	1
Hypercalcaemia			
subjects affected / exposed	5 / 509 (0.98%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	5	0	0
Hypercholesterolaemia			
subjects affected / exposed	4 / 509 (0.79%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	4	0	0
Hyperglycaemia			
subjects affected / exposed	8 / 509 (1.57%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	8	0	0
Hyperkalaemia			
subjects affected / exposed	4 / 509 (0.79%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	6	0	0
Hyperlipidaemia			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	1	0	0
Hypernatraemia			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	1	0	0
Hypoalbuminaemia			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	1	0	0
Hypocalcaemia			

subjects affected / exposed	6 / 509 (1.18%)	2 / 125 (1.60%)	0 / 124 (0.00%)
occurrences (all)	6	2	0
Hypoglycaemia			
subjects affected / exposed	1 / 509 (0.20%)	1 / 125 (0.80%)	3 / 124 (2.42%)
occurrences (all)	1	1	4
Hypokalaemia			
subjects affected / exposed	7 / 509 (1.38%)	9 / 125 (7.20%)	7 / 124 (5.65%)
occurrences (all)	8	11	9
Hypomagnesaemia			
subjects affected / exposed	3 / 509 (0.59%)	1 / 125 (0.80%)	2 / 124 (1.61%)
occurrences (all)	4	3	2
Hyponatraemia			
subjects affected / exposed	5 / 509 (0.98%)	0 / 125 (0.00%)	1 / 124 (0.81%)
occurrences (all)	6	0	5
Increased appetite			
subjects affected / exposed	0 / 509 (0.00%)	1 / 125 (0.80%)	0 / 124 (0.00%)
occurrences (all)	0	1	0
Iron deficiency			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	1	0	0
Lactic acidosis			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	1	0	0
Malnutrition			
subjects affected / exposed	3 / 509 (0.59%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	3	0	0
Type 2 diabetes mellitus			
subjects affected / exposed	3 / 509 (0.59%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	3	0	0
Vitamin B complex deficiency			
subjects affected / exposed	1 / 509 (0.20%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	1	0	0
Vitamin B12 deficiency			
subjects affected / exposed	2 / 509 (0.39%)	0 / 125 (0.00%)	0 / 124 (0.00%)
occurrences (all)	2	0	0
Vitamin D deficiency			

subjects affected / exposed occurrences (all)	2 / 509 (0.39%) 2	0 / 125 (0.00%) 0	0 / 124 (0.00%) 0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
20 June 2014	The main purpose was to add an exploratory objective to analyze candidate biomarkers in circulation for association with disease response or progression and to evaluate mechanisms of resistance to identify future subjects who may benefit most from these androgen receptor targeting treatment strategies.The purpose was also to define and clarify the requirements for PSA assessments to determine eligibility, the possible outcomes for responders and nonresponders based on the initial PSA assessment at week 13, the timing of unconfirmed and confirmed PSA assessments for the transition from period 1 and period 2, and the new PSA assessment at safety follow-up. there
07 July 2016	The purpose was to include a second open-label period after randomization closed in period 2 to offer qualifying subjects participating in period 1 the opportunity to continue receiving enzalutamide or to receive abiraterone and prednisone after confirmed PSA progression.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported