Clinical trial results:
AFFIRM: A Multinational Phase 3, Randomized, Double-Blind, Placebo-Controlled Efficacy and Safety Study of Oral MDV3100 in Patients with Progressive Castration-Resistant Prostate Cancer Previously Treated with Docetaxel-Based Chemotherapy

Summary

EudraCT number	2009-013174-41
Trial protocol	BE GB FR ES DE AT IT
Global end of trial date	02 November 2017

Results information

Result version number	v2 (current)
This version publication date	03 November 2018
First version publication date	06 January 2017
Version creation reason	

Trial information

Trial identification

Sponsor protocol code	CRPC2 (C3431010)

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00974311
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Pfizer Inc.
Sponsor organisation address	235 E 42nd Street, New York, United States, 10017
Public contact	Pfizer ClinicalTrials.gov Call Center, Pfizer ClinicalTrials.gov Call Center, Pfizer Inc., 001 18007181021, ClinicalTrials.gov_Inquiries@pfizer.com
Scientific contact	Pfizer ClinicalTrials.gov Call Center, Pfizer Inc., 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	Final
Date of interim/final analysis	20 February 2018
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	02 November 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To determine the benefit of MDV3100 as compared to placebo as assessed by overall survival.

Protection of trial subjects:

The study was conducted 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	30 September 2009
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	5 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Argentina: 10
Country: Number of subjects enrolled	Australia: 93
Country: Number of subjects enrolled	Austria: 25
Country: Number of subjects enrolled	Belgium: 45
Country: Number of subjects enrolled	Canada: 107
Country: Number of subjects enrolled	Chile: 11
Country: Number of subjects enrolled	France: 273
Country: Number of subjects enrolled	Germany: 86
Country: Number of subjects enrolled	Italy: 30
Country: Number of subjects enrolled	Netherlands: 46
Country: Number of subjects enrolled	Poland: 11
Country: Number of subjects enrolled	South Africa: 6
Country: Number of subjects enrolled	Spain: 36
Country: Number of subjects enrolled	United Kingdom: 132
Country: Number of subjects enrolled	United States: 288
Worldwide total number of subjects	1199
EEA total number of subjects	684

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)	362
From 65 to 84 years	819
85 years and over	18

Subject disposition

Recruitment

Recruitment details:

A total of 1199 subjects were enrolled and randomized for double-blind (DB) phase. Out of which, 159 subjects entered the optional open-label extension (OLE) phase.

Pre-assignment

Screening details:

Subjects were randomized 2:1 to receive either Enzalutamide or Placebo in DB phase. All subjects who continued in OLE phase, received Enzalutamide.

Period 1

Period 1 title	DB Phase (up to 24 months)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Enzalutamide

Arm description:

In DB Phase, subjects received Enzalutamide capsules 160 mg orally per day. Subjects who completed DB Phase, entered in optional OLE Phase and received same treatment until unacceptable toxicity, confirmed disease progression and the subject was scheduled to initiate a new systemic anti-neoplastic therapy, death or withdrawal (median treatment duration was 8.3 months).

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

Dosage and administration details:

Enzalutamide was administered as oral capsules, once daily, up to a maximum of 36 months.

Arm title	Placebo

Arm description:

In DB Phase, subjects received placebo capsules (for Enzalutamide) orally per day. Subjects who completed DB Phase, entered in optional OLE Phase and received Enzalutamide 160 mg orally per day until unacceptable toxicity, confirmed disease progression and the subject was scheduled to initiate a new systemic anti-neoplastic therapy, death or withdrawal (median treatment duration was 3.0 months in DB Phase and 7.7 months in OLE Phase).

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 as oral capsules, once daily, up to a maximum of 36 months.

Number of subjects in period 1	Enzalutamide	Placebo
Started	800	399
Completed	109	50
Not completed	691	349
Consent withdrawn by subject	16	7
Death	561	298
Unspecified	1	-
Study Terminated by Sponsor	108	42
Lost to follow-up	5	2

Period 2

Period 2 title	OLE Phase (up to 77 months)
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Enzalutamide

Arm description:

In DB Phase, subjects received Enzalutamide capsules 160 mg orally per day. Subjects who completed DB Phase, entered in optional OLE Phase and received same treatment until unacceptable toxicity, confirmed disease progression and the subject was scheduled to initiate a new systemic anti-neoplastic therapy, death or withdrawal (median treatment duration was 8.3 months).

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

Dosage and administration details:

Enzalutamide was administered as oral capsules, once daily, up to a maximum of 88 months.

Arm title	Placebo

Arm description:

In DB Phase, subjects received placebo capsules (for Enzalutamide) orally per day. Subjects who completed DB Phase, entered in optional OLE Phase and received Enzalutamide 160 mg orally per day until unacceptable toxicity, confirmed disease progression and the subject was scheduled to initiate a new systemic anti-neoplastic therapy, death or withdrawal (median treatment duration was 3.0 months in DB Phase and 7.7 months in OLE Phase).

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 as oral capsules, once daily, up to a maximum of 88 months.

Number of subjects in period 2	Enzalutamide	Placebo
Started	109	50
Completed	0	0
Not completed	109	50
Consent withdrawn by subject	2	1
Death	14	21
Unspecified	15	2
Study Terminated by Sponsor	78	26

Baseline characteristics

Reporting groups	
Reporting group title	Enzalutamide
Reporting group description:	
In DB Phase, subjects received Enzalutamide capsules 160 mg orally per day. Subjects who completed DB Phase, entered in optional OLE Phase and received same treatment until unacceptable toxicity, confirmed disease progression and the subject was scheduled to initiate a new systemic anti-neoplastic therapy, death or withdrawal (median treatment duration was 8.3 months).	
Reporting group title	Placebo
Reporting group description:	
In DB Phase, subjects received placebo capsules (for Enzalutamide) orally per day. Subjects who completed DB Phase, entered in optional OLE Phase and received Enzalutamide 160 mg orally per day until unacceptable toxicity, confirmed disease progression and the subject was scheduled to initiate a new systemic anti-neoplastic therapy, death or withdrawal (median treatment duration was 3.0 months in DB Phase and 7.7 months in OLE Phase).	

Reporting group values	Enzalutamide	Placebo	Total
Number of subjects	800	399	1199
Age Categorical Units: Subjects			
<=18 years	0	0	0
Between 18 and 65 years	232	130	362
>=65 years	568	269	837
Age Continuous Units: years			
arithmetic mean	68.8	68.6	
standard deviation	± 7.96	± 8.39	-
Sex: Female, Male Units: Subjects			
Female	0	0	0
Male	800	399	1199
Region of Enrollment Units: Subjects			
United States	181	107	288
Spain	23	13	36
Austria	15	10	25
Chile	6	5	11
United Kingdom	82	50	132
Italy	20	10	30
France	193	80	273
Canada	82	25	107
Argentina	7	3	10
Belgium	27	18	45
Poland	7	4	11
Australia	60	33	93
South Africa	3	3	6
Germany	62	24	86
Netherlands	32	14	46
Ethnicity (NIH/OMB) Units: Subjects			

Hispanic or Latino	32	23	55
Not Hispanic or Latino	768	376	1144
Unknown or Not Reported	0	0	0
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	1	1	2
Asian	5	8	13
Native Hawaiian or Other Pacific Islander	1	0	1
Black or African American	27	20	47
White	745	366	1111
More than one race	0	0	0
Unknown or Not Reported	21	4	25

End points

End points reporting groups

Reporting group title	Enzalutamide

Reporting group description:

In DB Phase, subjects received Enzalutamide capsules 160 mg orally per day. Subjects who completed DB Phase, entered in optional OLE Phase and received same treatment until unacceptable toxicity, confirmed disease progression and the subject was scheduled to initiate a new systemic anti-neoplastic therapy, death or withdrawal (median treatment duration was 8.3 months).

Reporting group title	Placebo

Reporting group description:

In DB Phase, subjects received placebo capsules (for Enzalutamide) orally per day. Subjects who completed DB Phase, entered in optional OLE Phase and received Enzalutamide 160 mg orally per day until unacceptable toxicity, confirmed disease progression and the subject was scheduled to initiate a new systemic anti-neoplastic therapy, death or withdrawal (median treatment duration was 3.0 months in DB Phase and 7.7 months in OLE Phase).

Reporting group title	Enzalutamide

Reporting group description:

In DB Phase, subjects received Enzalutamide capsules 160 mg orally per day. Subjects who completed DB Phase, entered in optional OLE Phase and received same treatment until unacceptable toxicity, confirmed disease progression and the subject was scheduled to initiate a new systemic anti-neoplastic therapy, death or withdrawal (median treatment duration was 8.3 months).

Reporting group title	Placebo

Reporting group description:

In DB Phase, subjects received placebo capsules (for Enzalutamide) orally per day. Subjects who completed DB Phase, entered in optional OLE Phase and received Enzalutamide 160 mg orally per day until unacceptable toxicity, confirmed disease progression and the subject was scheduled to initiate a new systemic anti-neoplastic therapy, death or withdrawal (median treatment duration was 3.0 months in DB Phase and 7.7 months in OLE Phase).

Subject analysis set title	Enzalutamide: DB + OLE Phase
Subject analysis set type	Safety analysis

Subject analysis set description:

In DB Phase, subjects received Enzalutamide capsules 160 mg orally per day. Subjects who completed DB Phase, entered in optional OLE Phase and received same treatment until unacceptable toxicity, confirmed disease progression and the subject was scheduled to initiate a new systemic anti-neoplastic therapy, death or withdrawal (median treatment duration was 8.3 months).

Subject analysis set title	Placebo: DB Phase
Subject analysis set type	Safety analysis

Subject analysis set description:

In DB Phase, subjects received placebo capsules (for Enzalutamide) orally per day until unacceptable toxicity, confirmed disease progression and the subject was scheduled to initiate a new systemic anti-neoplastic therapy, death or withdrawal (median treatment duration was 3.0 months).

Subject analysis set title	Placebo (DB) /Enzalutamide 160 mg (OLE) Phase
Subject analysis set type	Safety analysis

Subject analysis set description:

Subjects who received placebo in DB phase, completed DB Phase and entered in optional OLE Phase, received Enzalutamide capsules 160 mg orally per day until unacceptable toxicity, confirmed disease progression and the subject was scheduled to initiate a new systemic anti-neoplastic therapy, death or withdrawal (median treatment duration was 7.7 months).

Primary: Overall Survival

End point title	Overall Survival

End point description:

Survival was defined as time from randomization to death due to any cause. The duration of overall survival was right-censored for subjects who were lost to follow-up since randomization or not known to have died at the data analysis cut-off date (this included subjects who were known to have died after the data analysis cut-off date). Intent to treat (ITT) population included all subjects who were randomized into the study. The upper limit of the 95% confidence interval was not calculable because an

insufficient number of subjects reached the event at the final time point for assessment, and has been denoted by '99999'.

End point type	Primary

End point timeframe:

During study period (up to 101 months)

End point values	Enzalutamide	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	800	399		
Units: months				
median (confidence interval 95%)	18.4 (17.3 to 99999)	13.6 (11.3 to 15.8)		

Statistical analyses

Statistical analysis title	Enzalutamide vs. Placebo
Comparison groups	Enzalutamide v Placebo
Number of subjects included in analysis	1199
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001 [1]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.63
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.53
upper limit	0.75

Notes:

[1] - Stratified by baseline Eastern Cooperative Oncology Group (ECOG) performance status and mean Brief Pain Inventory – Short Form score (Question #3).
Hazard Ratio and 95% confidence interval are from Cox regression model.

Secondary: Radiographic Progression-Free Survival

End point title	Radiographic Progression-Free Survival

End point description:

Radiographic progression-free survival was defined as time from randomization to the earliest objective evidence of radiographic progression or death due to any cause. Subjects were assessed for objective disease progression at regularly scheduled visits. The consensus guidelines of the Prostate Cancer Clinical Trials Working Group 2 were taken into consideration for the determination of disease progression. Radiographic disease progression was defined by Response Evaluation Criteria in Solid Tumours (RECIST) version (vs.) 1.1 for soft tissue disease, or the appearance of two or more new bone lesions on bone scan. Progression at the first scheduled reassessment at Week 13 required a confirmatory scan 6 or more weeks later. Subjects who did not reach the endpoint were right censored at their last assessment. ITT population included all subjects who were randomized into the study.

End point type	Secondary

End point timeframe:

During DB phase (up to 24 months)

End point values	Enzalutamide	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	800	399		
Units: months				
median (confidence interval 95%)	8.3 (8.2 to 9.4)	2.9 (2.8 to 3.4)		

Statistical analyses

Statistical analysis title	Enzalutamide vs. Placebo
Comparison groups	Enzalutamide v Placebo
Number of subjects included in analysis	1199
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001 [2]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.35
upper limit	0.47

Notes:

[2] - Stratified by baseline ECOG performance status and mean Brief Pain Inventory – Short Form score (Question #3).
Hazard Ratio and 95% confidence interval are from Cox regression model.

Secondary: Time to First Skeletal-Related Event

End point title	Time to First Skeletal-Related Event

End point description:

The time to first skeletal-related event was defined as time from randomization to the occurrence of the first skeletal-related event. Subjects were assessed for skeletal-related events at regularly scheduled visits. A skeletal-related event was defined as radiation therapy or surgery to bone, pathologic bone fracture, spinal cord compression, or change of antineoplastic therapy to treat bone pain. Subjects who did not reach the endpoint were right censored at their last assessment. ITT population included all subjects who were randomized into the study. The upper limit of the 95% confidence interval was not calculable because an insufficient number of subjects reached the event at the final time point for assessment, and has been denoted by '99999'.

End point type	Secondary

End point timeframe:

During DB Phase (up to 24 months)

End point values	Enzalutamide	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	800	399		
Units: months				
median (confidence interval 95%)	16.7 (14.6 to 19.1)	13.3 (9.9 to 99999)		

Statistical analyses

Statistical analysis title	Enzalutamide vs. Placebo
Comparison groups	Enzalutamide v Placebo
Number of subjects included in analysis	1199
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0001 [3]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.69
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.566
upper limit	0.835

Notes:

[3] - Stratified by baseline ECOG performance status and mean Brief Pain Inventory – Short Form score (Question #3).
Hazard Ratio and 95% confidence interval are from Cox regression model.

Secondary: Percentage of Subjects who Were Responders for Functional Assessment of Cancer Therapy-Prostate (FACT-P)

End point title	Percentage of Subjects who Were Responders for Functional Assessment of Cancer Therapy-Prostate (FACT-P)

End point description:

The FACT-P was a 39-item subject questionnaire which assessed physical well-being (7 items), social/family well-being (7 items), emotional well-being (6 items), functional well-being (7 items), and additional prostate cancer specific concerns (12 items). All items were scored from 0 (not at all) to 4 (very much). The sum of scores on all 5 domains constitutes the global FACT-P. The global/total FACT-P score ranged from 0 (worst) to 156 (best), higher scores indicate better health status. Responders were those subjects who had a 10-point improvement in their total FACT-P score, as compared with baseline, on two consecutive measurements obtained at least 3 weeks apart. Here, number of subjects analyzed signifies evaluable ITT that included all subjects who were part of the ITT population and had a global FACT-P score at baseline and at least 1 post-baseline assessment.

End point type	Secondary

End point timeframe:

Baseline up to 24 months

End point values	Enzalutamide	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	651	257		
Units: percentage of subjects				
number (confidence interval 95%)	43.2 (39.3 to 47.1)	18.3 (13.8 to 23.6)		

Statistical analyses

Statistical analysis title	Enzalutamide vs. Placebo
Comparison groups	Enzalutamide v Placebo
Number of subjects included in analysis	908
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001 [4]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in Percentage of Subjects
Point estimate	24.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	18.8
upper limit	30.9

Notes:

[4] - Stratified by baseline ECOG performance status and mean Brief Pain Inventory – Short Form score (Question #3).
Confidence Interval based on standard normal approximation.

Secondary: Time to Prostate-Specific Antigen (PSA) Progression

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

End point description:

Time to PSA progression was defined as time from randomization to PSA progression. Subjects who did not reach the endpoint were right censored at their last assessment. For subjects with PSA declines at Week 13, the PSA progression date was defined as the date that a greater than and equal to (>=)25 percent (%) increase and an absolute increase of >=2 nanogram per milliliter (ng/mL) above the nadir was documented, which was confirmed by a second consecutive value obtained 3 or more weeks later (required only if PSA progression did not occur at last PSA assessment). For subjects with no PSA declines at Week 13, PSA progression date was defined as the date that a >=25% increase and an absolute increase of >=2 ng/mL above the baseline was documented, which was confirmed by a second consecutive value 3 or more weeks later (required only if PSA progression did not occur at last PSA assessment). ITT population included all subjects who were randomized into the study.

End point type	Secondary

End point timeframe:

Baseline and at every study visit from Week 13 while on study drug (up to 24 months)

End point values	Enzalutamide	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	800	399		
Units: months				
median (confidence interval 95%)	8.3 (5.8 to 8.3)	3.0 (2.9 to 3.7)		

Statistical analyses

Statistical analysis title	Enzalutamide vs. Placebo
Comparison groups	Enzalutamide v Placebo
Number of subjects included in analysis	1199
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001 [5]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.248
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.204
upper limit	0.303

Notes:

[5] - Stratified by baseline ECOG performance
status and mean Brief Pain Inventory – Short Form score (Question #3).
Hazard Ratio and 95% confidence interval are from Cox regression model.

Secondary: Percentage of Subjects With Pain Palliation

End point title	Percentage of Subjects With Pain Palliation

End point description:

Proportion of subjects with pain palliation was assessed for subjects with a stable and sufficient pain burden at study entry. Pain burden was measured by question #3 of Brief Pain Inventory (short form). This scale measures pain on a 0 to 10 scale with 0 indicating no pain and 10 indicating pain as bad as you can imagine. Pain palliation at Week 13 was determined for proportion of men with baseline bone metastasis (es) who had baseline pain attributable to metastasis (es). Palliation was defined as >=30% reduction in average pain score at Week 13 compared to baseline without a >=30% increase in analgesic use. Here, number of subject analyzed signifies evaluable ITT that included subjects with metastatic bone disease at baseline; provided answers to Question #3 of Brief Pain Inventory - short form for a minimum of 4 out of 7 days in baseline run-in period; stable baseline pain; stable analgesic use; and had an average pain score during baseline run-in period of >=4.

End point type	Secondary

End point timeframe:

Baseline up to 24 months

End point values	Enzalutamide	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	49	15		
Units: percentage of subjects				
number (confidence interval 95%)	44.9 (30.7 to 59.8)	6.7 (0.2 to 31.9)		

Statistical analyses

Statistical analysis title	Enzalutamide vs. Placebo
Comparison groups	Enzalutamide v Placebo
Number of subjects included in analysis	64
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0079 [6]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in Rate of Pain Palliation
Point estimate	38.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	19.4
upper limit	57

Notes:

[6] - Stratified by baseline Eastern Cooperative Oncology Group performance status (0–1 vs. 2). Confidence Interval based on standard normal approximation.

Secondary: Percentage of Subjects With Prostate Specific Antigen (PSA) Response

End point title	Percentage of Subjects With Prostate Specific Antigen (PSA) Response

End point description:

Subjects were evaluable for PSA response rate if they had a PSA level measured at baseline and at least 1 post-baseline assessment. Both PSA responses of > 50% and > 90% were determined. PSA responses required confirmation with a subsequent assessment that was conducted at least 3 weeks later. Here, number of subject analyzed signifies evaluable ITT that included subjects who were part of the ITT Population and had a PSA level measured at baseline and at least 1 post-baseline assessment.

End point type	Secondary

End point timeframe:

During DB phase (up to 24 months)

End point values	Enzalutamide	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	731	330		
Units: percentage of subjects				
Decline >=50% from baseline	54	2		
Decline >=90% from baseline	25	1		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Soft-Tissue Objective Response

End point title	Percentage of Subjects With Soft-Tissue Objective Response

End point description:

Best overall soft tissue response as assessed using RECIST vs.1.1 during study was summarized using investigators' response assessments and also derived response assessments by treatment group. Only subjects with measurable soft tissue disease at screening were included in this analysis. Subjects with measurable disease at screening are subjects who had at least 1 target lesion identified per RECIST vs.1.1 at screening. Percentage of subjects summarizes number of subjects with complete or partial objective response (%). Soft Tissue assessment based on Eisenhauer EA, Therasse P, Bogaerts J et al. New response evaluation criteria in solid tumours: Revised RECIST guideline (vs.1.1). Eur J Cancer 2009; 45:228-247. Here, number of subject analyzed signifies evaluable ITT with measurable disease that included subjects who were part of ITT population and had measurable soft tissue disease at screening, defined by at least 1 target lesion according to RECIST vs.1.1.

End point type	Secondary

End point timeframe:

During DB phase (up to 24 months)

End point values	Enzalutamide	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	446	208		
Units: percentage of subjects	29	4		

Statistical analyses

No statistical analyses for this end point

Secondary: European Quality of Life Five-Domain (EQ-5D) Scale

End point title	European Quality of Life Five-Domain (EQ-5D) Scale

End point description:

EQ-5D: subject rated questionnaire to assess health-related quality of life in terms of a single utility or index score. Five parameters (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) were assessed on 3-point categorical scale (1= no problems, 2= some/moderate problems and 3= severe problem). Score were transformed and resulted in a total EQ-5D score range of 0 (worst imaginable health state) to 100 (best imaginable health state), with higher scores indicating better health and quality of life. Here, number of subject analyzed signifies evaluable ITT that included subjects who were part of the ITT population and who were evaluable for EQ-5D.

End point type	Secondary

End point timeframe:

Week 13

End point values	Enzalutamide	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	126	55		
Units: units on a scale				
arithmetic mean (standard deviation)	67.2 (± 19.29)	60.0 (± 19.26)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects with Circulating Tumor Cell (CTC) Conversion

End point title	Percentage of Subjects with Circulating Tumor Cell (CTC) Conversion

End point description:

CTC conversion was assessed for subjects with baseline CTC counts of >=5 cells per 7.5 milliliter (mL) of blood. A CTC conversion was defined as a decline in the CTC count to less than (<) 5 cells per 7.5 mL of blood. In this endpoint percentage of subjects with CTC conversion was reported. Here, number of subject analyzed signifies CTC evaluable population that included subjects with a baseline and at least 1 post baseline CTC assessment.

End point type	Secondary

End point timeframe:

Baseline up to 24 months

End point values	Enzalutamide	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	127	62		
Units: percentage of subjects				
number (confidence interval 95%)	48 (39.09 to 57.07)	9.7 (3.63 to 19.88)		

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

AE:any untoward medical occurrence in subject who received study drug without regard to possibility of causal relationship. SAE:AE resulting in any of following outcome/deemed significant and jeopardized subjects/required treatment to prevent other AE outcomes for any other reason:death;initial/prolonged

inpatient hospitalization;life-threatening experience(immediate risk of dying);persistent/significant disability/incapacity;congenital anomaly.TEAEs:events occurred between first dose of study drug and up to safety follow-up visit/initiation of another anti-neoplastic therapy, whichever occurred first(up to 101 months).AEs included both serious and non-serious AEs.Clinically significant physical examination abnormalities were reported as AEs.Safety population:all randomized subjects who received at least 1 dose of study drug.Unscheduled visit:performed at any time during study whenever necessary to assess for/follow-up on AEs, at subject's request/if deemed necessary by investigator.

End point type	Other pre-specified

End point timeframe:

Baseline, up to the safety follow-up visit or unscheduled visit or the initiation of another anti-neoplastic therapy whichever occurred first (up to 101 months)

End point values	Enzalutamide: DB + OLE Phase	Placebo: DB Phase	Placebo (DB) /Enzalutamide 160 mg (OLE) Phase	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	800	399	50	
Units: subjects				
AEs	789	390	48	
SAEs	319	155	25	

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Number of Subjects with Clinically Significant Changes in Vital Signs

End point title	Number of Subjects with Clinically Significant Changes in Vital Signs

End point description:

Criteria for abnormalities in vital signs included: sitting/supine systolic blood pressure (SBP) values: absolute result greater than (>) 180 millimeter of mercury (mmHg) and >40 mmHg increase from baseline (BL) and < 90 mmHg and >30 mmHg decrease from BL; diastolic blood pressure (DBP) values: absolute result >105 mmHg and >30 mmHg increase from BL and absolute result < 50 mmHg and >20 mmHg decrease from BL; any abnormalities in SBP or DBP; heart rate values: absolute result > 120 beats per minute (bpm) and >30 bpm increase from BL and absolute result < 50 bpm and >20 bpm decrease from BL or any abnormalities in heart rate. Safety population was defined as all randomized subjects who received at least 1 dose of study drug. Unscheduled visit was performed at any time during the study whenever necessary to assess for/follow-up on AEs, at the subject's request/if deemed necessary by the investigator.

End point type	Other pre-specified

End point timeframe:

Baseline, up to the safety follow-up visit or unscheduled visit or the initiation of another anti-neoplastic therapy whichever occurred first (up to 101 months)

End point values	Enzalutamide: DB + OLE Phase	Placebo: DB Phase	Placebo (DB) /Enzalutamide 160 mg (OLE) Phase	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	800	399	50	
Units: subjects				
SBP: >180 mmHg and >40 mmHg Increase from BL	28	7	1	
SBP: < 90 mmHg and >30 mmHg Decrease from BL	13	5	0	
DBP: >105 mmHg and >30 mmHg Increase from BL	5	2	0	
DBP: < 50 mmHg and >20 mmHg Decrease from BL	13	3	1	
Any abnormalities in SBP or DBP	52	16	2	
Heart Rate: > 120 bpm and >30 bpm Increase from BL	7	5	0	
Heart Rate: < 50 bpm and >20 bpm Decrease from BL	18	1	0	
Any abnormalities in Heart Rate	25	6	0	

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Number of Subjects With Any Newly Clinically Significant Abnormal Finding in Electrocardiogram (ECG)

End point title	Number of Subjects With Any Newly Clinically Significant Abnormal Finding in Electrocardiogram (ECG)[7]

End point description:

Any new post baseline abnormality was defined as any abnormal ECG finding that appeared after baseline assessment which was not seen at the screening or baseline ECG assessment. Where, criteria of abnormality was QTcF interval > 470 millisecond (msec). Subjects were counted once only for a specific abnormality. This endpoint was planned to be analysed in double blind phase only. Safety population was defined as all randomized subjects who received at least 1 dose of study drug. Unscheduled visit was performed at any time during the study whenever necessary to assess for or follow-up on AEs, at the subject's request or if deemed necessary by the investigator.

End point type	Other pre-specified

End point timeframe:

Baseline, up to the end of DB phase or unscheduled visit (up to 24 months)

Notes:

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

End point values	Enzalutamide	Placebo: DB Phase		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	800	399		
Units: subjects	28	13		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Number of Subjects With Grade 3/4 Post-Baseline Laboratory Toxicity (Hematology and Chemistry)

End point title	Number of Subjects With Grade 3/4 Post-Baseline Laboratory Toxicity (Hematology and Chemistry)

End point description:

Laboratory parameters included hematological and chemistry parameters. Chemistry parameters included alanine aminotransferase, albumin, alkaline phosphatase, aspartate aminotransferase, bilirubin, calcium, creatine kinase, creatinine, glucose, magnesium, phosphate, potassium and sodium. Hematology parameters included haemoglobin, leukocytes, lymphocytes, neutrophils and platelet. Test abnormalities were graded by NCI CTCAE version 4.03 as Grade 3= severe and Grade 4= life-threatening or disabling. Only categories with at least 1 subject with abnormality are reported in this endpoint. Safety population was defined as all randomized subjects who received at least 1 dose of study drug. Unscheduled visit was performed at any time during the study whenever necessary to assess for or follow-up on AEs, at the subject's request or if deemed necessary by the investigator.

End point type	Other pre-specified

End point timeframe:

Baseline, up to the safety follow-up visit or unscheduled visit or the initiation of another anti-neoplastic therapy whichever occurred first (up to 101 months)

End point values	Enzalutamide: DB + OLE Phase	Placebo: DB Phase	Placebo (DB) /Enzalutamide 160 mg (OLE) Phase	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	800	399	50	
Units: subjects				
Alanine Aminotransferase:High	2	2	1	
Albumin: Low	7	3	0	
Alkaline Phosphatase: High	102	74	3	
Aspartate Aminotransferase: High	3	4	1	
Bilirubin: High	2	0	0	
Calcium: Low	14	15	1	
Calcium: High	1	0	0	
Creatine Kinase: High	4	2	0	
Creatinine: High	0	2	0	
Glucose: High	17	10	1	
Magnesium: Low	0	1	0	
Magnesium: High	1	1	0	
Phosphate: Low	28	10	2	
Potassium: Low	7	4	1	
Potassium: High	2	3	0	
Sodium: Low	19	13	0	
Sodium: High	0	1	0	
Hemoglobin: Low	38	20	4	
Hemoglobin: High	1	0	0	
Leukocytes: Low	8	1	1	
Lymphocytes: Low	80	48	5	
Neutrophils: Low	10	0	1	
Platelet; Low	4	4	0	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Baseline, up to the safety follow-up visit or unscheduled visit or the initiation of another anti-neoplastic therapy whichever occurred first (up to 101 months)

Adverse event reporting additional description:

An event may be categorized as serious in 1 subject and non serious in another, or 1 subject may experience both serious and non serious event. All TEAEs and SAEs were collected and reported. The same event may appear as both AE and SAE. Analysis was done on safety population. Total number of deaths (all causes) included only grade 5 AEs.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	16.1

Reporting groups

Reporting group title	Enzalutamide: DB + OLE Phase

Reporting group description:

In DB Phase, subjects received Enzalutamide capsules 160 mg orally per day. Subjects who completed DB Phase, entered in optional OLE Phase and received same treatment until unacceptable toxicity, confirmed disease progression and the subject was scheduled to initiate a new systemic anti-neoplastic therapy, death or withdrawal (median treatment duration was 8.3 months).

Reporting group title	Placebo: DB Phase

Reporting group description:

In DB Phase, subjects received placebo capsules (for Enzalutamide) orally per day until unacceptable toxicity, confirmed disease progression and the subject was scheduled to initiate a new systemic anti-neoplastic therapy, death or withdrawal (median treatment duration was 3.0 months).

Reporting group title	Placebo (DB) /Enzalutamide 160 mg (OLE) Phase

Reporting group description:

Subjects who received placebo in DB phase, completed DB Phase and entered in optional OLE Phase, received Enzalutamide capsules 160 mg orally per day until unacceptable toxicity, confirmed disease progression and the subject was scheduled to initiate a new systemic anti-neoplastic therapy, death or withdrawal (median treatment duration was 7.7 months).

Serious adverse events	Enzalutamide: DB + OLE Phase	Placebo: DB Phase	Placebo (DB) /Enzalutamide 160 mg (OLE) Phase
Total subjects affected by serious adverse events			
subjects affected / exposed	319 / 800 (39.88%)	155 / 399 (38.85%)	25 / 50 (50.00%)
number of deaths (all causes)	578	321	21
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Metastatic pain			
subjects affected / exposed	18 / 800 (2.25%)	3 / 399 (0.75%)	3 / 50 (6.00%)
occurrences causally related to treatment / all	0 / 22	1 / 3	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cancer pain			

subjects affected / exposed	10 / 800 (1.25%)	5 / 399 (1.25%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	0 / 12	0 / 5	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metastases to central nervous system			
subjects affected / exposed	5 / 800 (0.63%)	1 / 399 (0.25%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 5	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Metastases to Bone			
subjects affected / exposed	1 / 800 (0.13%)	5 / 399 (1.25%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 5	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malignant pleural effusion			
subjects affected / exposed	2 / 800 (0.25%)	1 / 399 (0.25%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tumour pain			
subjects affected / exposed	0 / 800 (0.00%)	3 / 399 (0.75%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute leukaemia			
subjects affected / exposed	1 / 800 (0.13%)	0 / 399 (0.00%)	0 / 50 (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
Acute monocytic leukaemia			
subjects affected / exposed	1 / 800 (0.13%)	0 / 399 (0.00%)	0 / 50 (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
Bone marrow tumour cell infiltration			
subjects affected / exposed	1 / 800 (0.13%)	0 / 399 (0.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metastases to liver			

subjects affected / exposed	0 / 800 (0.00%)	1 / 399 (0.25%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metastases to meninges			
subjects affected / exposed	1 / 800 (0.13%)	0 / 399 (0.00%)	0 / 50 (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
Neoplasm progression			
subjects affected / exposed	0 / 800 (0.00%)	1 / 399 (0.25%)	0 / 50 (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
Small cell lung cancer			
subjects affected / exposed	1 / 800 (0.13%)	0 / 399 (0.00%)	0 / 50 (0.00%)
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	0 / 800 (0.00%)	1 / 399 (0.25%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal tract adenoma			
subjects affected / exposed	0 / 800 (0.00%)	1 / 399 (0.25%)	0 / 50 (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
Bronchial carcinoma			
subjects affected / exposed	1 / 800 (0.13%)	0 / 399 (0.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metastases to lung			
subjects affected / exposed	1 / 800 (0.13%)	0 / 399 (0.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute lymphocytic leukaemia			

subjects affected / exposed	1 / 800 (0.13%)	0 / 399 (0.00%)	0 / 50 (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
Colon cancer			
subjects affected / exposed	0 / 800 (0.00%)	0 / 399 (0.00%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intracranial tumour haemorrhage			
subjects affected / exposed	1 / 800 (0.13%)	0 / 399 (0.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myelodysplastic syndrome			
subjects affected / exposed	1 / 800 (0.13%)	0 / 399 (0.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Squamous cell carcinoma of head and neck			
subjects affected / exposed	1 / 800 (0.13%)	0 / 399 (0.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Squamous cell carcinoma of lung			
subjects affected / exposed	1 / 800 (0.13%)	0 / 399 (0.00%)	0 / 50 (0.00%)
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			
Deep vein thrombosis			
subjects affected / exposed	3 / 800 (0.38%)	3 / 399 (0.75%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	1 / 3	1 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematoma			
subjects affected / exposed	3 / 800 (0.38%)	0 / 399 (0.00%)	0 / 50 (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
Lymphoedema			

subjects affected / exposed	2 / 800 (0.25%)	0 / 399 (0.00%)	0 / 50 (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
Hypertensive crisis			
subjects affected / exposed	1 / 800 (0.13%)	1 / 399 (0.25%)	0 / 50 (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
Hypotension			
subjects affected / exposed	0 / 800 (0.00%)	1 / 399 (0.25%)	0 / 50 (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
Peripheral ischaemia			
subjects affected / exposed	1 / 800 (0.13%)	0 / 399 (0.00%)	0 / 50 (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
Orthostatic hypotension			
subjects affected / exposed	0 / 800 (0.00%)	1 / 399 (0.25%)	0 / 50 (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
Haemorrhage			
subjects affected / exposed	1 / 800 (0.13%)	0 / 399 (0.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertension			
subjects affected / exposed	1 / 800 (0.13%)	0 / 399 (0.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Surgical and medical procedures			
Bladder catheter removal			
subjects affected / exposed	1 / 800 (0.13%)	0 / 399 (0.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Limb operation			

subjects affected / exposed	1 / 800 (0.13%)	0 / 399 (0.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain management			
subjects affected / exposed	1 / 800 (0.13%)	0 / 399 (0.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cataract operation			
subjects affected / exposed	0 / 800 (0.00%)	1 / 399 (0.25%)	0 / 50 (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
Colon polypectomy			
subjects affected / exposed	1 / 800 (0.13%)	0 / 399 (0.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oesophageal dilation procedure			
subjects affected / exposed	1 / 800 (0.13%)	0 / 399 (0.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleurodesis			
subjects affected / exposed	1 / 800 (0.13%)	0 / 399 (0.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ureteral stent insertion			
subjects affected / exposed	1 / 800 (0.13%)	0 / 399 (0.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
General physical health deterioration			
subjects affected / exposed	22 / 800 (2.75%)	8 / 399 (2.01%)	3 / 50 (6.00%)
occurrences causally related to treatment / all	0 / 22	0 / 9	0 / 3
deaths causally related to treatment / all	0 / 7	0 / 5	0 / 1
Asthenia			

subjects affected / exposed	4 / 800 (0.50%)	2 / 399 (0.50%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	1 / 5	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain			
subjects affected / exposed	5 / 800 (0.63%)	1 / 399 (0.25%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	1 / 5	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fatigue			
subjects affected / exposed	3 / 800 (0.38%)	2 / 399 (0.50%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	0 / 3	0 / 2	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			
subjects affected / exposed	2 / 800 (0.25%)	5 / 399 (1.25%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	0 / 2	0 / 5	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oedema peripheral			
subjects affected / exposed	1 / 800 (0.13%)	2 / 399 (0.50%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malaise			
subjects affected / exposed	2 / 800 (0.25%)	2 / 399 (0.50%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 2	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chest pain			
subjects affected / exposed	1 / 800 (0.13%)	1 / 399 (0.25%)	0 / 50 (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
Death			
subjects affected / exposed	1 / 800 (0.13%)	0 / 399 (0.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Euthanasia			

subjects affected / exposed	0 / 800 (0.00%)	1 / 399 (0.25%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
General symptom			
subjects affected / exposed	1 / 800 (0.13%)	0 / 399 (0.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Device dislocation			
subjects affected / exposed	1 / 800 (0.13%)	0 / 399 (0.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Device occlusion			
subjects affected / exposed	0 / 800 (0.00%)	1 / 399 (0.25%)	0 / 50 (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
Disease progression			
subjects affected / exposed	1 / 800 (0.13%)	0 / 399 (0.00%)	2 / 50 (4.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 2
Local swelling			
subjects affected / exposed	0 / 800 (0.00%)	1 / 399 (0.25%)	0 / 50 (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
Immune system disorders			
Anaphylactic reaction			
subjects affected / exposed	1 / 800 (0.13%)	0 / 399 (0.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Pelvic pain			
subjects affected / exposed	1 / 800 (0.13%)	1 / 399 (0.25%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Respiratory, thoracic and mediastinal disorders			
Pulmonary embolism			
subjects affected / exposed	5 / 800 (0.63%)	4 / 399 (1.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	1 / 6	0 / 4	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0
Pleural effusion			
subjects affected / exposed	2 / 800 (0.25%)	3 / 399 (0.75%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	0 / 2	0 / 3	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic obstructive pulmonary disease			
subjects affected / exposed	4 / 800 (0.50%)	0 / 399 (0.00%)	0 / 50 (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
Pneumothorax			
subjects affected / exposed	2 / 800 (0.25%)	2 / 399 (0.50%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Epistaxis			
subjects affected / exposed	1 / 800 (0.13%)	1 / 399 (0.25%)	0 / 50 (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
Pulmonary oedema			
subjects affected / exposed	2 / 800 (0.25%)	0 / 399 (0.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Dyspnoea			
subjects affected / exposed	1 / 800 (0.13%)	1 / 399 (0.25%)	0 / 50 (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
Acute pulmonary oedema			
subjects affected / exposed	1 / 800 (0.13%)	0 / 399 (0.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Haemoptysis			
subjects affected / exposed	1 / 800 (0.13%)	0 / 399 (0.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory arrest			
subjects affected / exposed	0 / 800 (0.00%)	1 / 399 (0.25%)	0 / 50 (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
Hydropneumothorax			
subjects affected / exposed	1 / 800 (0.13%)	0 / 399 (0.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleuritic pain			
subjects affected / exposed	1 / 800 (0.13%)	0 / 399 (0.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoxia			
subjects affected / exposed	1 / 800 (0.13%)	0 / 399 (0.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Confusional state			
subjects affected / exposed	2 / 800 (0.25%)	2 / 399 (0.50%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 2	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Depressed mood			
subjects affected / exposed	1 / 800 (0.13%)	0 / 399 (0.00%)	0 / 50 (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
Hallucination			
subjects affected / exposed	1 / 800 (0.13%)	0 / 399 (0.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mental status changes			

subjects affected / exposed	2 / 800 (0.25%)	0 / 399 (0.00%)	0 / 50 (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
Depression			
subjects affected / exposed	1 / 800 (0.13%)	0 / 399 (0.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Disorientation			
subjects affected / exposed	0 / 800 (0.00%)	1 / 399 (0.25%)	0 / 50 (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
Investigations			
Liver function test abnormal			
subjects affected / exposed	0 / 800 (0.00%)	1 / 399 (0.25%)	0 / 50 (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
Weight decreased			
subjects affected / exposed	1 / 800 (0.13%)	0 / 399 (0.00%)	0 / 50 (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
Coagulation time prolonged			
subjects affected / exposed	1 / 800 (0.13%)	0 / 399 (0.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemoglobin decreased			
subjects affected / exposed	1 / 800 (0.13%)	0 / 399 (0.00%)	0 / 50 (0.00%)
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			
Subdural haematoma			
subjects affected / exposed	3 / 800 (0.38%)	1 / 399 (0.25%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0

Femur fracture			
subjects affected / exposed	3 / 800 (0.38%)	0 / 399 (0.00%)	0 / 50 (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
Fall			
subjects affected / exposed	1 / 800 (0.13%)	0 / 399 (0.00%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Femoral neck fracture			
subjects affected / exposed	2 / 800 (0.25%)	0 / 399 (0.00%)	0 / 50 (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
Fracture			
subjects affected / exposed	1 / 800 (0.13%)	0 / 399 (0.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hip fracture			
subjects affected / exposed	1 / 800 (0.13%)	0 / 399 (0.00%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lumbar vertebral fracture			
subjects affected / exposed	2 / 800 (0.25%)	0 / 399 (0.00%)	0 / 50 (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
Patella fracture			
subjects affected / exposed	1 / 800 (0.13%)	0 / 399 (0.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Post procedural haematuria			
subjects affected / exposed	1 / 800 (0.13%)	0 / 399 (0.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Post-traumatic pain			

subjects affected / exposed	0 / 800 (0.00%)	1 / 399 (0.25%)	0 / 50 (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
Radiation oesophagitis			
subjects affected / exposed	0 / 800 (0.00%)	1 / 399 (0.25%)	0 / 50 (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
Soft tissue injury			
subjects affected / exposed	0 / 800 (0.00%)	1 / 399 (0.25%)	0 / 50 (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	1 / 800 (0.13%)	1 / 399 (0.25%)	0 / 50 (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
Hand fracture			
subjects affected / exposed	1 / 800 (0.13%)	0 / 399 (0.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thoracic vertebral fracture			
subjects affected / exposed	1 / 800 (0.13%)	0 / 399 (0.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Facial bones fracture			
subjects affected / exposed	1 / 800 (0.13%)	0 / 399 (0.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis radiation			
subjects affected / exposed	1 / 800 (0.13%)	0 / 399 (0.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Head injury			

subjects affected / exposed	1 / 800 (0.13%)	0 / 399 (0.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Heat stroke			
subjects affected / exposed	1 / 800 (0.13%)	0 / 399 (0.00%)	0 / 50 (0.00%)
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 / 800 (0.13%)	0 / 399 (0.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pubis fracture			
subjects affected / exposed	1 / 800 (0.13%)	0 / 399 (0.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rib fracture			
subjects affected / exposed	1 / 800 (0.13%)	0 / 399 (0.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Congenital, familial and genetic disorders			
Adenomatous polyposis coli			
subjects affected / exposed	0 / 800 (0.00%)	1 / 399 (0.25%)	0 / 50 (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			
Cardiac failure			
subjects affected / exposed	3 / 800 (0.38%)	2 / 399 (0.50%)	2 / 50 (4.00%)
occurrences causally related to treatment / all	0 / 3	0 / 2	1 / 2
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Angina pectoris			
subjects affected / exposed	2 / 800 (0.25%)	1 / 399 (0.25%)	0 / 50 (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

Acute myocardial infarction			
subjects affected / exposed	3 / 800 (0.38%)	1 / 399 (0.25%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 2	0 / 0	0 / 0
Cardiac failure congestive			
subjects affected / exposed	2 / 800 (0.25%)	0 / 399 (0.00%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial flutter			
subjects affected / exposed	1 / 800 (0.13%)	1 / 399 (0.25%)	0 / 50 (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
Bradycardia			
subjects affected / exposed	0 / 800 (0.00%)	1 / 399 (0.25%)	0 / 50 (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
Cardiogenic shock			
subjects affected / exposed	0 / 800 (0.00%)	1 / 399 (0.25%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Left ventricular failure			
subjects affected / exposed	1 / 800 (0.13%)	0 / 399 (0.00%)	0 / 50 (0.00%)
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 incompetance			
subjects affected / exposed	1 / 800 (0.13%)	1 / 399 (0.25%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ventricular fibrillation			
subjects affected / exposed	0 / 800 (0.00%)	1 / 399 (0.25%)	0 / 50 (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
Arrhythmia supraventricular			

subjects affected / exposed	1 / 800 (0.13%)	0 / 399 (0.00%)	0 / 50 (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
Atrial fibrillation			
subjects affected / exposed	2 / 800 (0.25%)	0 / 399 (0.00%)	0 / 50 (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
Atrioventricular block complete			
subjects affected / exposed	2 / 800 (0.25%)	0 / 399 (0.00%)	0 / 50 (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
Myocardial ischaemia			
subjects affected / exposed	1 / 800 (0.13%)	0 / 399 (0.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial infarction			
subjects affected / exposed	0 / 800 (0.00%)	2 / 399 (0.50%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Acute coronary syndrome			
subjects affected / exposed	1 / 800 (0.13%)	0 / 399 (0.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aortic valve incompetence			
subjects affected / exposed	1 / 800 (0.13%)	0 / 399 (0.00%)	0 / 50 (0.00%)
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 / 800 (0.13%)	0 / 399 (0.00%)	0 / 50 (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
Nervous system disorders			
Spinal cord compression			

subjects affected / exposed	54 / 800 (6.75%)	15 / 399 (3.76%)	3 / 50 (6.00%)
occurrences causally related to treatment / all	0 / 56	0 / 16	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cauda equina syndrome			
subjects affected / exposed	6 / 800 (0.75%)	0 / 399 (0.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 6	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nerve root compression			
subjects affected / exposed	1 / 800 (0.13%)	4 / 399 (1.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			
subjects affected / exposed	5 / 800 (0.63%)	2 / 399 (0.50%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	1 / 5	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebrovascular accident			
subjects affected / exposed	4 / 800 (0.50%)	1 / 399 (0.25%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 4	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Hepatic encephalopathy			
subjects affected / exposed	1 / 800 (0.13%)	2 / 399 (0.50%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 2	0 / 0
Dizziness			
subjects affected / exposed	2 / 800 (0.25%)	1 / 399 (0.25%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transient ischemic attack			
subjects affected / exposed	3 / 800 (0.38%)	1 / 399 (0.25%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	1 / 3	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebral haemorrhage			

subjects affected / exposed	1 / 800 (0.13%)	1 / 399 (0.25%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Convulsion			
subjects affected / exposed	4 / 800 (0.50%)	0 / 399 (0.00%)	2 / 50 (4.00%)
occurrences causally related to treatment / all	2 / 4	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Epiduritis			
subjects affected / exposed	2 / 800 (0.25%)	0 / 399 (0.00%)	0 / 50 (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
Nerve compression			
subjects affected / exposed	1 / 800 (0.13%)	1 / 399 (0.25%)	0 / 50 (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
Partial seizures			
subjects affected / exposed	2 / 800 (0.25%)	0 / 399 (0.00%)	0 / 50 (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
Lethargy			
subjects affected / exposed	3 / 800 (0.38%)	0 / 399 (0.00%)	0 / 50 (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
Headache			
subjects affected / exposed	1 / 800 (0.13%)	1 / 399 (0.25%)	0 / 50 (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
Akathisia			
subjects affected / exposed	1 / 800 (0.13%)	0 / 399 (0.00%)	0 / 50 (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
Central nervous system lesion			

subjects affected / exposed	1 / 800 (0.13%)	0 / 399 (0.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cranial nerve palsies multiple			
subjects affected / exposed	1 / 800 (0.13%)	0 / 399 (0.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Embolic stroke			
subjects affected / exposed	0 / 800 (0.00%)	1 / 399 (0.25%)	0 / 50 (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
Haemorrhage intracranial			
subjects affected / exposed	1 / 800 (0.13%)	0 / 399 (0.00%)	0 / 50 (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
Haemorrhagic stroke			
subjects affected / exposed	1 / 800 (0.13%)	0 / 399 (0.00%)	0 / 50 (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
Ischaemic stroke			
subjects affected / exposed	0 / 800 (0.00%)	1 / 399 (0.25%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Lacunar infarction			
subjects affected / exposed	1 / 800 (0.13%)	0 / 399 (0.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Loss of consciousness			
subjects affected / exposed	0 / 800 (0.00%)	1 / 399 (0.25%)	0 / 50 (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
Lumbar radiculopathy			

subjects affected / exposed	1 / 800 (0.13%)	0 / 399 (0.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Motor dysfunction			
subjects affected / exposed	0 / 800 (0.00%)	1 / 399 (0.25%)	0 / 50 (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
Pachymeningitis			
subjects affected / exposed	1 / 800 (0.13%)	0 / 399 (0.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Presyncope			
subjects affected / exposed	1 / 800 (0.13%)	0 / 399 (0.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Status epilepticus			
subjects affected / exposed	1 / 800 (0.13%)	0 / 399 (0.00%)	0 / 50 (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
Hypoglossal nerve paresis			
subjects affected / exposed	1 / 800 (0.13%)	0 / 399 (0.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Normal pressure hydrocephalus			
subjects affected / exposed	1 / 800 (0.13%)	0 / 399 (0.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tremor			
subjects affected / exposed	1 / 800 (0.13%)	0 / 399 (0.00%)	0 / 50 (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
Trigeminal neuralgia			

subjects affected / exposed	1 / 800 (0.13%)	0 / 399 (0.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Visual field defect			
subjects affected / exposed	1 / 800 (0.13%)	0 / 399 (0.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ataxia			
subjects affected / exposed	0 / 800 (0.00%)	0 / 399 (0.00%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Carpal tunnel syndrome			
subjects affected / exposed	1 / 800 (0.13%)	0 / 399 (0.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Complex partial seizures			
subjects affected / exposed	1 / 800 (0.13%)	0 / 399 (0.00%)	0 / 50 (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
Cranial nerve disorder			
subjects affected / exposed	2 / 800 (0.25%)	0 / 399 (0.00%)	0 / 50 (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
Myoclonus			
subjects affected / exposed	0 / 800 (0.00%)	0 / 399 (0.00%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Paraplegia			
subjects affected / exposed	1 / 800 (0.13%)	0 / 399 (0.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sciatica			

subjects affected / exposed	1 / 800 (0.13%)	0 / 399 (0.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Senile dementia			
subjects affected / exposed	1 / 800 (0.13%)	0 / 399 (0.00%)	0 / 50 (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
Subarachnoid haemorrhage			
subjects affected / exposed	1 / 800 (0.13%)	0 / 399 (0.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thalamic infarction			
subjects affected / exposed	1 / 800 (0.13%)	0 / 399 (0.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
VIIth nerve paralysis			
subjects affected / exposed	0 / 800 (0.00%)	1 / 399 (0.25%)	0 / 50 (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
Neuropathy peripheral			
subjects affected / exposed	0 / 800 (0.00%)	0 / 399 (0.00%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	22 / 800 (2.75%)	12 / 399 (3.01%)	2 / 50 (4.00%)
occurrences causally related to treatment / all	1 / 29	2 / 15	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anaemia of malignant disease			
subjects affected / exposed	2 / 800 (0.25%)	1 / 399 (0.25%)	0 / 50 (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
Disseminated intravascular coagulation			

subjects affected / exposed	1 / 800 (0.13%)	0 / 399 (0.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancytopenia			
subjects affected / exposed	0 / 800 (0.00%)	1 / 399 (0.25%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombocytopenia			
subjects affected / exposed	1 / 800 (0.13%)	0 / 399 (0.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Leukocytosis			
subjects affected / exposed	0 / 800 (0.00%)	1 / 399 (0.25%)	0 / 50 (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
Ear and labyrinth disorders			
Ear pain			
subjects affected / exposed	0 / 800 (0.00%)	1 / 399 (0.25%)	0 / 50 (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
Vertigo			
subjects affected / exposed	0 / 800 (0.00%)	1 / 399 (0.25%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Retinal detachment			
subjects affected / exposed	0 / 800 (0.00%)	1 / 399 (0.25%)	0 / 50 (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
Papilloedema			
subjects affected / exposed	0 / 800 (0.00%)	1 / 399 (0.25%)	0 / 50 (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
Visual acuity reduced			

subjects affected / exposed	1 / 800 (0.13%)	0 / 399 (0.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Visual impairment			
subjects affected / exposed	1 / 800 (0.13%)	0 / 399 (0.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eyelid bleeding			
subjects affected / exposed	1 / 800 (0.13%)	0 / 399 (0.00%)	0 / 50 (0.00%)
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			
Vomiting			
subjects affected / exposed	3 / 800 (0.38%)	8 / 399 (2.01%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	2 / 3	4 / 9	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			
subjects affected / exposed	5 / 800 (0.63%)	3 / 399 (0.75%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	2 / 5	2 / 4	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Constipation			
subjects affected / exposed	5 / 800 (0.63%)	3 / 399 (0.75%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 5	0 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rectal haemorrhage			
subjects affected / exposed	3 / 800 (0.38%)	3 / 399 (0.75%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 4	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain			
subjects affected / exposed	2 / 800 (0.25%)	2 / 399 (0.50%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			

subjects affected / exposed	4 / 800 (0.50%)	0 / 399 (0.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 4	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Small intestinal obstruction			
subjects affected / exposed	3 / 800 (0.38%)	0 / 399 (0.00%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Faecaloma			
subjects affected / exposed	0 / 800 (0.00%)	2 / 399 (0.50%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal haemorrhage			
subjects affected / exposed	2 / 800 (0.25%)	1 / 399 (0.25%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal obstruction			
subjects affected / exposed	1 / 800 (0.13%)	1 / 399 (0.25%)	0 / 50 (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
Abdominal pain lower			
subjects affected / exposed	1 / 800 (0.13%)	0 / 399 (0.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colitis			
subjects affected / exposed	1 / 800 (0.13%)	0 / 399 (0.00%)	0 / 50 (0.00%)
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 haemorrhage			
subjects affected / exposed	1 / 800 (0.13%)	0 / 399 (0.00%)	0 / 50 (0.00%)
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 obstruction			

subjects affected / exposed	0 / 800 (0.00%)	1 / 399 (0.25%)	0 / 50 (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
Haematochezia			
subjects affected / exposed	0 / 800 (0.00%)	1 / 399 (0.25%)	0 / 50 (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
Intestinal perforation			
subjects affected / exposed	1 / 800 (0.13%)	0 / 399 (0.00%)	0 / 50 (0.00%)
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	0 / 800 (0.00%)	1 / 399 (0.25%)	0 / 50 (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
Pancreatitis			
subjects affected / exposed	1 / 800 (0.13%)	1 / 399 (0.25%)	0 / 50 (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
Proctalgia			
subjects affected / exposed	1 / 800 (0.13%)	0 / 399 (0.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Retroperitoneal haemorrhage			
subjects affected / exposed	1 / 800 (0.13%)	0 / 399 (0.00%)	0 / 50 (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
Intestinal mass			
subjects affected / exposed	0 / 800 (0.00%)	1 / 399 (0.25%)	0 / 50 (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
Pancreatitis acute			

subjects affected / exposed	0 / 800 (0.00%)	1 / 399 (0.25%)	0 / 50 (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
Peptic ulcer			
subjects affected / exposed	1 / 800 (0.13%)	0 / 399 (0.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diverticulum intestinal haemorrhagic			
subjects affected / exposed	1 / 800 (0.13%)	0 / 399 (0.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Duodenal ulcer haemorrhage			
subjects affected / exposed	0 / 800 (0.00%)	0 / 399 (0.00%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Inguinal hernia			
subjects affected / exposed	1 / 800 (0.13%)	0 / 399 (0.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Large intestinal obstruction			
subjects affected / exposed	2 / 800 (0.25%)	0 / 399 (0.00%)	0 / 50 (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
Lower gastrointestinal haemorrhage			
subjects affected / exposed	0 / 800 (0.00%)	0 / 399 (0.00%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Proctocolitis			
subjects affected / exposed	0 / 800 (0.00%)	0 / 399 (0.00%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Bile duct obstruction			

subjects affected / exposed	1 / 800 (0.13%)	0 / 399 (0.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholangitis			
subjects affected / exposed	1 / 800 (0.13%)	0 / 399 (0.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholelithiasis			
subjects affected / exposed	1 / 800 (0.13%)	0 / 399 (0.00%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Hyperhidrosis			
subjects affected / exposed	0 / 800 (0.00%)	1 / 399 (0.25%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular purpura			
subjects affected / exposed	0 / 800 (0.00%)	1 / 399 (0.25%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	18 / 800 (2.25%)	5 / 399 (1.25%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	0 / 27	0 / 5	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary retention			
subjects affected / exposed	7 / 800 (0.88%)	8 / 399 (2.01%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 10	0 / 9	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract obstruction			
subjects affected / exposed	8 / 800 (1.00%)	1 / 399 (0.25%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 8	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Post renal failure			

subjects affected / exposed	3 / 800 (0.38%)	3 / 399 (0.75%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 3	1 / 3	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Renal failure			
subjects affected / exposed	3 / 800 (0.38%)	3 / 399 (0.75%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 3	1 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal failure acute			
subjects affected / exposed	3 / 800 (0.38%)	3 / 399 (0.75%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 3	1 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bladder perforation			
subjects affected / exposed	1 / 800 (0.13%)	1 / 399 (0.25%)	0 / 50 (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
Hydronephrosis			
subjects affected / exposed	1 / 800 (0.13%)	1 / 399 (0.25%)	0 / 50 (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
Nephrolithiasis			
subjects affected / exposed	2 / 800 (0.25%)	0 / 399 (0.00%)	0 / 50 (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
Cystitis haemorrhagic			
subjects affected / exposed	2 / 800 (0.25%)	0 / 399 (0.00%)	0 / 50 (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
Renal colic			
subjects affected / exposed	2 / 800 (0.25%)	0 / 399 (0.00%)	0 / 50 (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
Bladder obstruction			

subjects affected / exposed	1 / 800 (0.13%)	0 / 399 (0.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dysuria			
subjects affected / exposed	1 / 800 (0.13%)	0 / 399 (0.00%)	0 / 50 (0.00%)
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	1 / 800 (0.13%)	0 / 399 (0.00%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ureteric obstruction			
subjects affected / exposed	1 / 800 (0.13%)	0 / 399 (0.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urethral obstruction			
subjects affected / exposed	1 / 800 (0.13%)	0 / 399 (0.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urethral stenosis			
subjects affected / exposed	0 / 800 (0.00%)	1 / 399 (0.25%)	0 / 50 (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
Endocrine disorders			
Adrenal insufficiency			
subjects affected / exposed	0 / 800 (0.00%)	1 / 399 (0.25%)	0 / 50 (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
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	11 / 800 (1.38%)	7 / 399 (1.75%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 13	0 / 8	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Bone pain			
subjects affected / exposed	12 / 800 (1.50%)	3 / 399 (0.75%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	0 / 12	0 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pathological fracture			
subjects affected / exposed	15 / 800 (1.88%)	2 / 399 (0.50%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	1 / 16	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain in extremity			
subjects affected / exposed	4 / 800 (0.50%)	2 / 399 (0.50%)	0 / 50 (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
Arthralgia			
subjects affected / exposed	3 / 800 (0.38%)	1 / 399 (0.25%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 4	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Muscular weakness			
subjects affected / exposed	2 / 800 (0.25%)	0 / 399 (0.00%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myalgia			
subjects affected / exposed	2 / 800 (0.25%)	0 / 399 (0.00%)	0 / 50 (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
Osteonecrosis of jaw			
subjects affected / exposed	2 / 800 (0.25%)	1 / 399 (0.25%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	0 / 3	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal chest pain			
subjects affected / exposed	2 / 800 (0.25%)	0 / 399 (0.00%)	0 / 50 (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
Chondrocalcinosis pyrophosphate			

subjects affected / exposed	1 / 800 (0.13%)	0 / 399 (0.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Flank pain			
subjects affected / exposed	1 / 800 (0.13%)	0 / 399 (0.00%)	0 / 50 (0.00%)
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	0 / 800 (0.00%)	1 / 399 (0.25%)	0 / 50 (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
Muscle haemorrhage			
subjects affected / exposed	1 / 800 (0.13%)	0 / 399 (0.00%)	0 / 50 (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
Osteoarthritis			
subjects affected / exposed	4 / 800 (0.50%)	0 / 399 (0.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 4	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rhabdomyolysis			
subjects affected / exposed	1 / 800 (0.13%)	0 / 399 (0.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal column stenosis			
subjects affected / exposed	1 / 800 (0.13%)	0 / 399 (0.00%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteitis			
subjects affected / exposed	1 / 800 (0.13%)	0 / 399 (0.00%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal pain			

subjects affected / exposed	2 / 800 (0.25%)	1 / 399 (0.25%)	0 / 50 (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
Bursitis			
subjects affected / exposed	1 / 800 (0.13%)	0 / 399 (0.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Pneumonia			
subjects affected / exposed	15 / 800 (1.88%)	5 / 399 (1.25%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	1 / 15	0 / 5	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	9 / 800 (1.13%)	5 / 399 (1.25%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	0 / 10	0 / 5	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urosepsis			
subjects affected / exposed	4 / 800 (0.50%)	1 / 399 (0.25%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 4	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	4 / 800 (0.50%)	1 / 399 (0.25%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 5	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 2	0 / 0	0 / 0
Gastroenteritis			
subjects affected / exposed	1 / 800 (0.13%)	2 / 399 (0.50%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchitis			
subjects affected / exposed	1 / 800 (0.13%)	1 / 399 (0.25%)	0 / 50 (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
Device related infection			

subjects affected / exposed	3 / 800 (0.38%)	0 / 399 (0.00%)	0 / 50 (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
Escherichia sepsis			
subjects affected / exposed	2 / 800 (0.25%)	0 / 399 (0.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Lobar pneumonia			
subjects affected / exposed	1 / 800 (0.13%)	1 / 399 (0.25%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	1 / 3	0 / 1	0 / 1
Staphylococcal sepsis			
subjects affected / exposed	1 / 800 (0.13%)	1 / 399 (0.25%)	0 / 50 (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
Cellulitis			
subjects affected / exposed	1 / 800 (0.13%)	1 / 399 (0.25%)	0 / 50 (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
Erysipelas			
subjects affected / exposed	1 / 800 (0.13%)	1 / 399 (0.25%)	0 / 50 (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
Lower respiratory tract infection			
subjects affected / exposed	2 / 800 (0.25%)	0 / 399 (0.00%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal abscess			
subjects affected / exposed	0 / 800 (0.00%)	1 / 399 (0.25%)	0 / 50 (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 wall abscess			

subjects affected / exposed	1 / 800 (0.13%)	0 / 399 (0.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Clostridium difficile colitis			
subjects affected / exposed	1 / 800 (0.13%)	0 / 399 (0.00%)	0 / 50 (0.00%)
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			
subjects affected / exposed	1 / 800 (0.13%)	0 / 399 (0.00%)	0 / 50 (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
Extradural abscess			
subjects affected / exposed	1 / 800 (0.13%)	0 / 399 (0.00%)	0 / 50 (0.00%)
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 / 800 (0.13%)	0 / 399 (0.00%)	0 / 50 (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
Infective exacerbation of chronic obstructive airways disease			
subjects affected / exposed	1 / 800 (0.13%)	0 / 399 (0.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Kidney infection			
subjects affected / exposed	1 / 800 (0.13%)	0 / 399 (0.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Klebsiella bacteraemia			
subjects affected / exposed	1 / 800 (0.13%)	0 / 399 (0.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Parotitis			

subjects affected / exposed	0 / 800 (0.00%)	1 / 399 (0.25%)	0 / 50 (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
Pneumonia bacterial			
subjects affected / exposed	1 / 800 (0.13%)	0 / 399 (0.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rectal abscess			
subjects affected / exposed	0 / 800 (0.00%)	1 / 399 (0.25%)	0 / 50 (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 tract infection			
subjects affected / exposed	0 / 800 (0.00%)	1 / 399 (0.25%)	0 / 50 (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
Septic Shock			
subjects affected / exposed	1 / 800 (0.13%)	1 / 399 (0.25%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Tooth Infection			
subjects affected / exposed	0 / 800 (0.00%)	1 / 399 (0.25%)	0 / 50 (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
Upper respiratory tract infection			
subjects affected / exposed	0 / 800 (0.00%)	1 / 399 (0.25%)	0 / 50 (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
Herpes zoster			
subjects affected / exposed	1 / 800 (0.13%)	0 / 399 (0.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Viral pericarditis			

subjects affected / exposed	1 / 800 (0.13%)	0 / 399 (0.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abscess jaw			
subjects affected / exposed	1 / 800 (0.13%)	0 / 399 (0.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anal abscess			
subjects affected / exposed	0 / 800 (0.00%)	0 / 399 (0.00%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atypical mycobacterial pneumonia			
subjects affected / exposed	1 / 800 (0.13%)	0 / 399 (0.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bacteraemia			
subjects affected / exposed	0 / 800 (0.00%)	0 / 399 (0.00%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diverticulitis			
subjects affected / exposed	1 / 800 (0.13%)	0 / 399 (0.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Febrile infection			
subjects affected / exposed	1 / 800 (0.13%)	0 / 399 (0.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gas gangrene			
subjects affected / exposed	1 / 800 (0.13%)	0 / 399 (0.00%)	0 / 50 (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
Pleural infection			

subjects affected / exposed	0 / 800 (0.00%)	0 / 399 (0.00%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia pneumococcal			
subjects affected / exposed	1 / 800 (0.13%)	0 / 399 (0.00%)	0 / 50 (0.00%)
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 sepsis			
subjects affected / exposed	1 / 800 (0.13%)	0 / 399 (0.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Pyelonephritis acute			
subjects affected / exposed	1 / 800 (0.13%)	0 / 399 (0.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	4 / 800 (0.50%)	3 / 399 (0.75%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	1 / 4	0 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyponatraemia			
subjects affected / exposed	2 / 800 (0.25%)	3 / 399 (0.75%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	0 / 3	0 / 3	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoglycaemia			
subjects affected / exposed	1 / 800 (0.13%)	2 / 399 (0.50%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypercalcaemia			
subjects affected / exposed	2 / 800 (0.25%)	0 / 399 (0.00%)	0 / 50 (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
Hyperuricaemia			

subjects affected / exposed	1 / 800 (0.13%)	0 / 399 (0.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypocalcaemia			
subjects affected / exposed	1 / 800 (0.13%)	0 / 399 (0.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypokalaemia			
subjects affected / exposed	1 / 800 (0.13%)	0 / 399 (0.00%)	0 / 50 (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
Hypophosphataemia			
subjects affected / exposed	1 / 800 (0.13%)	0 / 399 (0.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypovolaemia			
subjects affected / exposed	1 / 800 (0.13%)	0 / 399 (0.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cachexia			
subjects affected / exposed	0 / 800 (0.00%)	1 / 399 (0.25%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Decreased appetite			
subjects affected / exposed	1 / 800 (0.13%)	1 / 399 (0.25%)	0 / 50 (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
Diabetes mellitus			
subjects affected / exposed	1 / 800 (0.13%)	0 / 399 (0.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Failure to thrive			

subjects affected / exposed	0 / 800 (0.00%)	0 / 399 (0.00%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Malnutrition			
subjects affected / exposed	0 / 800 (0.00%)	0 / 399 (0.00%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoalbuminaemia			
subjects affected / exposed	0 / 800 (0.00%)	0 / 399 (0.00%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Enzalutamide: DB + OLE Phase	Placebo: DB Phase	Placebo (DB) /Enzalutamide 160 mg (OLE) Phase
Total subjects affected by non-serious adverse events			
subjects affected / exposed	784 / 800 (98.00%)	385 / 399 (96.49%)	47 / 50 (94.00%)
Vascular disorders			
Hot flush			
subjects affected / exposed	165 / 800 (20.63%)	41 / 399 (10.28%)	1 / 50 (2.00%)
occurrences (all)	186	46	1
Hypertension			
subjects affected / exposed	60 / 800 (7.50%)	11 / 399 (2.76%)	2 / 50 (4.00%)
occurrences (all)	88	12	2
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	280 / 800 (35.00%)	115 / 399 (28.82%)	14 / 50 (28.00%)
occurrences (all)	424	158	20
Asthenia			
subjects affected / exposed	148 / 800 (18.50%)	67 / 399 (16.79%)	9 / 50 (18.00%)
occurrences (all)	228	93	11
Oedema peripheral			
subjects affected / exposed	121 / 800 (15.13%)	46 / 399 (11.53%)	4 / 50 (8.00%)
occurrences (all)	145	57	6

Pyrexia			
subjects affected / exposed	59 / 800 (7.38%)	23 / 399 (5.76%)	4 / 50 (8.00%)
occurrences (all)	70	31	4
Pain			
subjects affected / exposed	27 / 800 (3.38%)	12 / 399 (3.01%)	3 / 50 (6.00%)
occurrences (all)	33	16	4
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	88 / 800 (11.00%)	39 / 399 (9.77%)	6 / 50 (12.00%)
occurrences (all)	108	45	6
Cough			
subjects affected / exposed	60 / 800 (7.50%)	25 / 399 (6.27%)	2 / 50 (4.00%)
occurrences (all)	64	27	2
Psychiatric disorders			
Insomnia			
subjects affected / exposed	71 / 800 (8.88%)	24 / 399 (6.02%)	2 / 50 (4.00%)
occurrences (all)	78	25	2
Anxiety			
subjects affected / exposed	55 / 800 (6.88%)	16 / 399 (4.01%)	6 / 50 (12.00%)
occurrences (all)	64	16	6
Depression			
subjects affected / exposed	51 / 800 (6.38%)	19 / 399 (4.76%)	4 / 50 (8.00%)
occurrences (all)	54	21	4
Confusional state			
subjects affected / exposed	23 / 800 (2.88%)	9 / 399 (2.26%)	3 / 50 (6.00%)
occurrences (all)	27	9	4
Investigations			
Weight decreased			
subjects affected / exposed	108 / 800 (13.50%)	42 / 399 (10.53%)	7 / 50 (14.00%)
occurrences (all)	138	49	8
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	44 / 800 (5.50%)	5 / 399 (1.25%)	5 / 50 (10.00%)
occurrences (all)	52	5	5
Nervous system disorders			

Headache			
subjects affected / exposed	101 / 800 (12.63%)	21 / 399 (5.26%)	1 / 50 (2.00%)
occurrences (all)	130	25	1
Dizziness			
subjects affected / exposed	59 / 800 (7.38%)	22 / 399 (5.51%)	4 / 50 (8.00%)
occurrences (all)	70	22	5
Paraesthesia			
subjects affected / exposed	53 / 800 (6.63%)	18 / 399 (4.51%)	1 / 50 (2.00%)
occurrences (all)	62	19	1
Hypoaesthesia			
subjects affected / exposed	33 / 800 (4.13%)	7 / 399 (1.75%)	4 / 50 (8.00%)
occurrences (all)	42	7	6
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	123 / 800 (15.38%)	70 / 399 (17.54%)	11 / 50 (22.00%)
occurrences (all)	211	117	41
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	276 / 800 (34.50%)	166 / 399 (41.60%)	16 / 50 (32.00%)
occurrences (all)	391	218	19
Constipation			
subjects affected / exposed	209 / 800 (26.13%)	109 / 399 (27.32%)	7 / 50 (14.00%)
occurrences (all)	249	249	8
Diarrhoea			
subjects affected / exposed	180 / 800 (22.50%)	70 / 399 (17.54%)	9 / 50 (18.00%)
occurrences (all)	251	82	11
Vomiting			
subjects affected / exposed	141 / 800 (17.63%)	84 / 399 (21.05%)	8 / 50 (16.00%)
occurrences (all)	214	112	8
Abdominal pain			
subjects affected / exposed	47 / 800 (5.88%)	21 / 399 (5.26%)	2 / 50 (4.00%)
occurrences (all)	51	23	2
Abdominal pain upper			
subjects affected / exposed	41 / 800 (5.13%)	13 / 399 (3.26%)	0 / 50 (0.00%)
occurrences (all)	50	16	0
Renal and urinary disorders			

Haematuria			
subjects affected / exposed	51 / 800 (6.38%)	14 / 399 (3.51%)	3 / 50 (6.00%)
occurrences (all)	75	19	3
Pollakiuria			
subjects affected / exposed	44 / 800 (5.50%)	10 / 399 (2.51%)	3 / 50 (6.00%)
occurrences (all)	48	11	3
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	225 / 800 (28.13%)	91 / 399 (22.81%)	9 / 50 (18.00%)
occurrences (all)	324	136	11
Arthralgia			
subjects affected / exposed	182 / 800 (22.75%)	71 / 399 (17.79%)	2 / 50 (4.00%)
occurrences (all)	276	112	2
Pain in extremity			
subjects affected / exposed	137 / 800 (17.13%)	62 / 399 (15.54%)	5 / 50 (10.00%)
occurrences (all)	198	97	6
Bone pain			
subjects affected / exposed	101 / 800 (12.63%)	61 / 399 (15.29%)	2 / 50 (4.00%)
occurrences (all)	132	75	2
Musculoskeletal pain			
subjects affected / exposed	121 / 800 (15.13%)	40 / 399 (10.03%)	3 / 50 (6.00%)
occurrences (all)	154	154	3
Musculoskeletal chest pain			
subjects affected / exposed	77 / 800 (9.63%)	34 / 399 (8.52%)	2 / 50 (4.00%)
occurrences (all)	101	44	2
Muscular weakness			
subjects affected / exposed	74 / 800 (9.25%)	27 / 399 (6.77%)	1 / 50 (2.00%)
occurrences (all)	95	34	1
Myalgia			
subjects affected / exposed	56 / 800 (7.00%)	26 / 399 (6.52%)	2 / 50 (4.00%)
occurrences (all)	61	34	6
Neck pain			
subjects affected / exposed	34 / 800 (4.25%)	17 / 399 (4.26%)	3 / 50 (6.00%)
occurrences (all)	35	19	3
Infections and infestations			

Urinary tract infection			
subjects affected / exposed	68 / 800 (8.50%)	24 / 399 (6.02%)	3 / 50 (6.00%)
occurrences (all)	90	27	3
Nasopharyngitis			
subjects affected / exposed	47 / 800 (5.88%)	12 / 399 (3.01%)	2 / 50 (4.00%)
occurrences (all)	58	18	2
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	246 / 800 (30.75%)	121 / 399 (30.33%)	9 / 50 (18.00%)
occurrences (all)	317	146	10
Hypokalaemia			
subjects affected / exposed	31 / 800 (3.88%)	14 / 399 (3.51%)	3 / 50 (6.00%)
occurrences (all)	37	16	3

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
30 July 2009	The dose for evaluation in this study was decreased from 240 mg/day to 160 mg/day to improve the risk/benefit profile of trial.
19 April 2011	The target number of deaths needed for the final analysis of overall survival reduced from 786 events to 650 events with an interim analysis at approximately 520 events.
05 January 2012	Access was provided to MDV3100 to patients who were either actively taking MDV3100 at the time of unblinding or were originally randomized to the placebo arm.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

The primary objectives (overall survival) of the study had been met and all subjecst who had remained on study treatment have discontinued and therefore the study has been considered as completed.

Notes: