Clinical trial results:
A Randomized, Double Blind, Multicenter, Parallel-Group, Phase III Study to Evaluate Efficacy and Safety of DCVAC/PCa Versus Placebo in Men with Metastatic Castration Resistant Prostate Cancer Eligible for 1st Line Chemotherapy

Summary

EudraCT number	2012-002814-38
Trial protocol	SE GB DE BE CZ IT NL ES HU PT BG SK PL HR AT LV LT DK FR
Global end of trial date	28 January 2020

Results information

Result version number	v1 (current)
This version publication date	07 February 2021
First version publication date	07 February 2021

Trial information

Trial identification

Sponsor protocol code	SP005

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02111577
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	SOTIO a.s.
Sponsor organisation address	Jankovcova 1518/2, Prague, Czechia,
Public contact	Clinical Trials Sotio, SOTIO a.s., +420 224175111, clinicaltrial@sotio.com
Scientific contact	Clinical Trials Sotio, SOTIO a.s., +420 224175111, clinicaltrial@sotio.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	03 July 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	04 December 2019
Global end of trial reached?	Yes
Global end of trial date	28 January 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Primary: The primary objective was to show superiority of treatment with DCVAC/PCa in addition to standard of care chemotherapy (docetaxel plus prednisone) over placebo in addition to standard of care chemotherapy (docetaxel plus prednisone) in men with metastatic castration resistant prostate cancer as measured by overall survival.
Key secondary: The key secondary objectives included assessments of safety, treatment group comparison with regard to radiographic progression-free survival, time to prostate-specific antigen progression, time to first occurrence of skeletal-related events.
Other secondary: To show clinical benefit of treatment with DCVAC/PCa plus standard of care over placebo in addition to standard of care with regard to time to radiographic progression or skeletal-related events, proportion of patients with skeletal-related events.

Protection of trial subjects:

Not applicable

Background therapy:

Docetaxel 75 mg/m2 intravenously every 3 weeks plus prednisone 5 mg orally twice daily or equivalent

Evidence for comparator: -

Actual start date of recruitment	26 May 2014
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Netherlands: 48
Country: Number of subjects enrolled	Poland: 130
Country: Number of subjects enrolled	Portugal: 30
Country: Number of subjects enrolled	Slovakia: 64
Country: Number of subjects enrolled	Spain: 32
Country: Number of subjects enrolled	Sweden: 5
Country: Number of subjects enrolled	United Kingdom: 96
Country: Number of subjects enrolled	Croatia: 24
Country: Number of subjects enrolled	Austria: 19
Country: Number of subjects enrolled	Belgium: 31
Country: Number of subjects enrolled	Bulgaria: 25
Country: Number of subjects enrolled	Czech Republic: 142
Country: Number of subjects enrolled	Denmark: 2
Country: Number of subjects enrolled	France: 30
Country: Number of subjects enrolled	Germany: 143

Country: Number of subjects enrolled	Hungary: 42
Country: Number of subjects enrolled	Italy: 22
Country: Number of subjects enrolled	Latvia: 2
Country: Number of subjects enrolled	Lithuania: 11
Country: Number of subjects enrolled	Belarus: 31
Country: Number of subjects enrolled	Serbia: 36
Country: Number of subjects enrolled	United States: 217
Worldwide total number of subjects	1182
EEA total number of subjects	898

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)	379
From 65 to 84 years	793
85 years and over	10

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

SP005 was conducted at 176 clinical sites. Recruitment (screening) started on 26-May-2014 and ended on 09-Oct-2017.
Patients:
- Screened: 1637
- Randomized: 1182
- Analyzed for efficacy: 1182
- Analyzed for safety: 1128

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	DCVAC/PCa

Arm description:

Patients randomized to receive DCVAC/PCa concurrently with docetaxel plus prednisone every 3 weeks (± 7 days). DCVAC/PCa was administered at least 7 days before or and at least 7 days after the nearest chemotherapy (days 8-15 of chemotherapy cycles). After discontinuation of chemotherapy for any reason, each following dose of DCVAC/PCa was given every 4 weeks (-7/+14 days) for up to a total of 15 doses.

Arm type	Experimental
Investigational medicinal product name	DCVAC/PCa
Investigational medicinal product code	Not applicable
Other name	Stapuldencel
Pharmaceutical forms	Dispersion for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Subcutaneous injection of approximately 1×10e7 autologous dendritic cells

Arm title	Placebo

Arm description:

Patients randomized to receive placebo concurrently with docetaxel plus prednisone every 3 weeks (± 7 days). Placebo was administered at least 7 days before or and at least 7 days after the nearest chemotherapy (days 8-15 of chemotherapy cycles). After discontinuation of chemotherapy for any reason, each following dose of placebo was given every 4 weeks (-7/+14 days) for up to a total of 15 doses.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	Not applicable
Other name	Not applicable
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Subcutaneous injection of aqueous, serum-free, animal protein-free balanced electrolyte solution

Number of subjects in period 1	DCVAC/PCa	Placebo
Started	787	395
Completed	188	106
Not completed	599	289
Consent withdrawn by subject	51	23
Medical monitor's decision (active hepatitis B)	1	-
Failure To produce study treatment	6	-
Disease progression	-	1
Adverse event, non-fatal	1	1
Death due to underlying disease	518	254
Lost to follow-up	19	10
Unable to tolerate leukapheresis	1	-
Protocol deviation	2	-

Baseline characteristics

Reporting groups	
Reporting group title	DCVAC/PCa

Reporting group description:

Patients randomized to receive DCVAC/PCa concurrently with docetaxel plus prednisone every 3 weeks (± 7 days). DCVAC/PCa was administered at least 7 days before or and at least 7 days after the nearest chemotherapy (days 8-15 of chemotherapy cycles). After discontinuation of chemotherapy for any reason, each following dose of DCVAC/PCa was given every 4 weeks (-7/+14 days) for up to a total of 15 doses.

Reporting group title	Placebo

Reporting group description:

Patients randomized to receive placebo concurrently with docetaxel plus prednisone every 3 weeks (± 7 days). Placebo was administered at least 7 days before or and at least 7 days after the nearest chemotherapy (days 8-15 of chemotherapy cycles). After discontinuation of chemotherapy for any reason, each following dose of placebo was given every 4 weeks (-7/+14 days) for up to a total of 15 doses.

Reporting group values	DCVAC/PCa	Placebo	Total
Number of subjects	787	395	1182
Age categorical Units: Subjects			
Adults (18-64 years)	272	107	379
From 65-84 years	509	284	793
85 years and over	6	4	10
Gender categorical Units: Subjects			
Female	0	0	0
Male	787	395	1182

End points

End points reporting groups

Reporting group title	DCVAC/PCa
Reporting group description:	
Patients randomized to receive DCVAC/PCa concurrently with docetaxel plus prednisone every 3 weeks (± 7 days). DCVAC/PCa was administered at least 7 days before or and at least 7 days after the nearest chemotherapy (days 8-15 of chemotherapy cycles). After discontinuation of chemotherapy for any reason, each following dose of DCVAC/PCa was given every 4 weeks (-7/+14 days) for up to a total of 15 doses.	
Reporting group title	Placebo
Reporting group description:	
Patients randomized to receive placebo concurrently with docetaxel plus prednisone every 3 weeks (± 7 days). Placebo was administered at least 7 days before or and at least 7 days after the nearest chemotherapy (days 8-15 of chemotherapy cycles). After discontinuation of chemotherapy for any reason, each following dose of placebo was given every 4 weeks (-7/+14 days) for up to a total of 15 doses.	

Primary: Overall survival, intention-to-treat population

End point title	Overall survival, intention-to-treat population
End point description:	
Intention-to-treat population definition: All randomized patients	
End point type	Primary
End point timeframe:	
From randomization to death due to any cause	

End point values	DCVAC/PCa	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	787	395		
Units: Months				
median (confidence interval 95%)	23.9 (21.6 to 25.3)	24.3 (22.6 to 26.0)		

Statistical analyses

Statistical analysis title	Stratified
Statistical analysis description:	
Stratified by region (US vs other), prior abiraterone (Yes vs No), prior enzalutamide (Yes vs No) and ECOG score (0, 1 vs 2)	
Comparison groups	DCVAC/PCa v Placebo

Number of subjects included in analysis	1182
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.596
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.042
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.895
upper limit	1.213

Statistical analysis title	Unstratified
Comparison groups	DCVAC/PCa v Placebo
Number of subjects included in analysis	1182
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.648
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.036
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.891
upper limit	1.204

Secondary: Overall survival, per protocol population	
End point title	Overall survival, per protocol population
End point description:	
Per protocol population definition: A subset of all randomized patients characterized by the following criteria: - had at least 1 post-baseline efficacy assessment - did not have any major protocol violation that would affect the endpoints being assessed - received at least 8 doses of DCVAC/PCa or placebo	
End point type	Secondary
End point timeframe:	
From randomization to death due to any cause	

End point values	DCVAC/PCa	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	438	284		
Units: Months				
median (confidence interval 95%)	29.7 (26.9 to 32.3)	26.7 (24.7 to 28.8)		

Statistical analyses

Statistical analysis title	Stratified
Statistical analysis description:	
Stratified by region (US vs other), prior abiraterone (Yes vs No), prior enzalutamide (Yes vs No) and ECOG score (0, 1 vs 2)	
Comparison groups	DCVAC/PCa v Placebo
Number of subjects included in analysis	722
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.335
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.908
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.746
upper limit	1.105

Statistical analysis title	Unstratified
Comparison groups	DCVAC/PCa v Placebo
Number of subjects included in analysis	722
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.192
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.879
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.725
upper limit	1.067

Secondary: Overall survival, intention-to-treat population, patients with abiraterone as prior therapy

End point title	Overall survival, intention-to-treat population, patients with

	abiraterone as prior therapy
End point description:	
Intention-to-treat population definition: All randomized patients with abiraterone as prior therapy	
End point type	Secondary
End point timeframe:	
From randomization to death due to any cause	

End point values	DCVAC/PCa	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	187	103		
Units: Months				
median (confidence interval 95%)	16.6 (14.9 to 19.7)	21.0 (16.6 to 24.1)		

Statistical analyses

Statistical analysis title	Stratified
Statistical analysis description:	
Stratified by region (US vs other), prior enzalutamide (Yes vs No) and ECOG score (0, 1 vs 2)	
Comparison groups	DCVAC/PCa v Placebo
Number of subjects included in analysis	290
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.071
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.312
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.976
upper limit	1.762

Statistical analysis title	Unstratified
Comparison groups	DCVAC/PCa v Placebo
Number of subjects included in analysis	290
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.09
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.283

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.961
upper limit	1.712

Secondary: Overall survival, intention-to-treat population, patients with enzalutamide as prior therapy

End point title	Overall survival, intention-to-treat population, patients with enzalutamide as prior therapy
End point description:	
Intention-to-treat population definition: All randomized patients with enzalutamide as prior therapy	
End point type	Secondary
End point timeframe:	
From randomization to death due to any cause	

End point values	DCVAC/PCa	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	137	60		
Units: Months				
median (confidence interval 95%)	15.2 (13.3 to 18.3)	21.4 (15.1 to 26.5)		

Statistical analyses

Statistical analysis title	Stratified
Statistical analysis description:	
Stratified by region (US vs other), prior abiraterone (Yes vs No) and ECOG score (0, 1 vs 2)	
Comparison groups	DCVAC/PCa v Placebo
Number of subjects included in analysis	197
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.049
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.461
Confidence interval	
level	95 %
sides	2-sided
lower limit	1
upper limit	2.134

Statistical analysis title	Unstratified
Comparison groups	DCVAC/PCa v Placebo
Number of subjects included in analysis	197
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.053
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.436
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.993
upper limit	2.077

Secondary: Overall survival, intention-to-treat population, patients with neither abiraterone nor enzalutamide as prior therapy

End point title	Overall survival, intention-to-treat population, patients with neither abiraterone nor enzalutamide as prior therapy

End point description:

Intention-to-treat population definition: All randomized patients with neither abiraterone nor enzalutamide as prior therapy

End point type	Secondary

End point timeframe:

From randomization to death due to any cause

End point values	DCVAC/PCa	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	546	271		
Units: Months				
median (confidence interval 95%)	26.7 (25.2 to 28.8)	25.7 (23.8 to 28.3)		

Statistical analyses

Statistical analysis title	Stratified

Statistical analysis description:

Stratified by region (US vs other) and ECOG score (0, 1 vs 2)

Comparison groups	DCVAC/PCa v Placebo

Number of subjects included in analysis	817
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.501
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.938
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.779
upper limit	1.13

Statistical analysis title	Unstratified
Comparison groups	DCVAC/PCa v Placebo
Number of subjects included in analysis	817
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.512
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.94
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.781
upper limit	1.131

Secondary: Radiological progression-free survival, intention-to-treat population

End point title	Radiological progression-free survival, intention-to-treat population

End point description:

Intention-to-treat population definition: All randomized patients

End point type	Secondary

End point timeframe:

Time from randomization to the date of the earliest objective evidence of either radiographic progression of bone lesions, radiographic progression of soft tissue lesions, or death due to any cause

End point values	DCVAC/PCa	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	787	395		
Units: Months				
median (confidence interval 95%)	11.1 (11.0 to 11.4)	11.1 (10.8 to 11.4)		

Statistical analyses

Statistical analysis title	Stratified
Statistical analysis description:	
Stratified by region (US vs other), prior abiraterone (Yes vs No), prior enzalutamide (Yes vs No) and ECOG score (0, 1 vs 2)	
Comparison groups	DCVAC/PCa v Placebo
Number of subjects included in analysis	1182
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.886
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.99
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.863
upper limit	1.136

Statistical analysis title	Unstratified
Comparison groups	DCVAC/PCa v Placebo
Number of subjects included in analysis	1182
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.992
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.001
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.875
upper limit	1.145

Secondary: Radiological progression-free survival, per protocol population

End point title	Radiological progression-free survival, per protocol population

End point description:

Per protocol population definition:
A subset of all randomized patients characterized by the following criteria:
- had at least 1 post-baseline efficacy assessment
- did not have any major protocol violation that would affect the endpoints being assessed
- received at least 8 doses of DCVAC/PCa or placebo

End point type	Secondary

End point timeframe:

Time from randomization to the date of the earliest objective evidence of either radiographic progression of bone lesions, radiographic progression of soft tissue lesions, or death due to any cause

End point values	DCVAC/PCa	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	438	284		
Units: Months				
median (confidence interval 95%)	11.2 (11.1 to 11.7)	11.2 (11.0 to 11.8)		

Statistical analyses

Statistical analysis title	Stratified

Statistical analysis description:

Stratified by region (US vs other), prior abiraterone (Yes vs No), prior enzalutamide (Yes vs No) and ECOG score (0, 1 vs 2)

Comparison groups	DCVAC/PCa v Placebo
Number of subjects included in analysis	722
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.994
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.001
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.847
upper limit	1.184

Statistical analysis title	Unstratified
Comparison groups	DCVAC/PCa v Placebo

Number of subjects included in analysis	722
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.982
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.002
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.851
upper limit	1.18

Secondary: Time to PSA progression, intention-to-treat population

End point title	Time to PSA progression, intention-to-treat population

End point description:

Intention-to-treat population definition: All randomized patients

End point type	Secondary

End point timeframe:

Time from randomization to the date of the earliest objective evidence of PSA progression (PSA absolute increase ≥ 2 ng/mL and ≥ 25% above nadir or baseline values providing confirmation by a second consecutive value obtained at least 3 weeks later)

End point values	DCVAC/PCa	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	787	395		
Units: Months				
median (confidence interval 95%)	10.5 (9.7 to 10.6)	10.6 (10.4 to 10.7)		

Statistical analyses

Statistical analysis title	Stratified

Statistical analysis description:

Stratified by region (US vs other), prior abiraterone (Yes vs No), prior enzalutamide (Yes vs No) and ECOG score (0, 1 vs 2)

Comparison groups	DCVAC/PCa v Placebo
Number of subjects included in analysis	1182
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.392
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.077

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.909
upper limit	1.277

Statistical analysis title	Unstratified
Comparison groups	DCVAC/PCa v Placebo
Number of subjects included in analysis	1182
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.439
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.068
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.905
upper limit	1.262

Secondary: Time to PSA progression, per protocol population

End point title	Time to PSA progression, per protocol population

End point description:

Per protocol population definition:
A subset of all randomized patients characterized by the following criteria:
- had at least 1 post-baseline efficacy assessment
- did not have any major protocol violation that would affect the endpoints being assessed
- received at least 8 doses of DCVAC/PCa or placebo

End point type	Secondary

End point timeframe:

Time from randomization to the date of the earliest objective evidence of PSA progression (PSA absolute increase ≥ 2 ng/mL and ≥ 25% above nadir or baseline values providing confirmation by a second consecutive value obtained at least 3 weeks later)

End point values	DCVAC/PCa	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	438	284		
Units: Months				
median (confidence interval 95%)	10.5 (10.4 to 10.7)	10.6 (10.4 to 10.7)		

Statistical analyses

Statistical analysis title	Stratified
Statistical analysis description:	
Stratified by region (US vs other), prior abiraterone (Yes vs No), prior enzalutamide (Yes vs No) and ECOG score (0, 1 vs 2)	
Comparison groups	DCVAC/PCa v Placebo
Number of subjects included in analysis	722
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.754
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.857
upper limit	1.238

Statistical analysis title	Unstratified
Comparison groups	DCVAC/PCa v Placebo
Number of subjects included in analysis	722
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.924
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.009
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.844
upper limit	1.207

Secondary: Time to first skeletal-related event, intention-to-treat population	
End point title	Time to first skeletal-related event, intention-to-treat population
End point description:	
Intention-to-treat population definition: All randomized patients; "1000000" means "not reached"	
End point type	Secondary
End point timeframe:	
Time from randomization to the date of the first skeletal-related event	

End point values	DCVAC/PCa	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	787	395		
Units: Months				
median (confidence interval 95%)	1000000 (1000000 to 1000000)	1000000 (1000000 to 1000000)		

Statistical analyses

Statistical analysis title	Stratified
Statistical analysis description:	
Stratified by region (US vs other), prior abiraterone (Yes vs No), prior enzalutamide (Yes vs No) and ECOG score (0, 1 vs 2)	
Comparison groups	DCVAC/PCa v Placebo
Number of subjects included in analysis	1182
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.732
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.918
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.563
upper limit	1.497

Statistical analysis title	Unstratified
Comparison groups	DCVAC/PCa v Placebo
Number of subjects included in analysis	1182
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.713
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.913
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.561
upper limit	1.485

Secondary: Time to first skeletal-related event, per protocol population

End point title	Time to first skeletal-related event, per protocol population

End point description:

Per protocol population definition:
A subset of all randomized patients characterized by the following criteria:
- had at least 1 post-baseline efficacy assessment
- did not have any major protocol violation that would affect the endpoints being assessed
- received at least 8 doses of DCVAC/PCa or placebo
"1000000" means "not reached"

End point type	Secondary

End point timeframe:

Time from randomization to the date of the first skeletal-related event

End point values	DCVAC/PCa	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	438	284		
Units: Months				
median (confidence interval 95%)	1000000 (1000000 to 1000000)	1000000 (1000000 to 1000000)		

Statistical analyses

Statistical analysis title	Stratified

Statistical analysis description:

Stratified by region (US vs other), prior abiraterone (Yes vs No), prior enzalutamide (Yes vs No) and ECOG score (0, 1 vs 2)

Comparison groups	DCVAC/PCa v Placebo
Number of subjects included in analysis	722
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.694
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.891
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.5
upper limit	1.587

Statistical analysis title	Unstratified
Comparison groups	DCVAC/PCa v Placebo

Number of subjects included in analysis	722
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.661
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.88
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.496
upper limit	1.562

Secondary: Time to radiological progression or skeletal-related event, intention-to-treat population

End point title	Time to radiological progression or skeletal-related event, intention-to-treat population

End point description:

Intention-to-treat population definition: All randomized patients

End point type	Secondary

End point timeframe:

Time from randomization to the date of the first radiological progression or skeletal-related event

End point values	DCVAC/PCa	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	787	395		
Units: Months				
median (confidence interval 95%)	11.1 (10.9 to 11.3)	10.9 (10.5 to 11.2)		

Statistical analyses

Statistical analysis title	Stratified

Statistical analysis description:

Stratified by region (US vs other), prior abiraterone (Yes vs No), prior enzalutamide (Yes vs No) and ECOG score (0, 1 vs 2)

Comparison groups	DCVAC/PCa v Placebo
Number of subjects included in analysis	1182
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.111
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.895

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.781
upper limit	1.027

Statistical analysis title	Unstratified
Comparison groups	DCVAC/PCa v Placebo
Number of subjects included in analysis	1182
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.184
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.913
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.798
upper limit	1.044

Secondary: Time to radiological progression or skeletal-related event, per protocol population

End point title	Time to radiological progression or skeletal-related event, per protocol population

End point description:

Per protocol population definition:
A subset of all randomized patients characterized by the following criteria:
- had at least 1 post-baseline efficacy assessment
- did not have any major protocol violation that would affect the endpoints being assessed
- received at least 8 doses of DCVAC/PCa or placebo

End point type	Secondary

End point timeframe:

Time from randomization to the date of the first radiological progression or skeletal-related event

End point values	DCVAC/PCa	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	438	284		
Units: Months				
median (confidence interval 95%)	11.1 (11.0 to 11.5)	11.1 (10.8 to 11.3)		

Statistical analyses

Statistical analysis title	Stratified
Statistical analysis description:	
Stratified by region (US vs other), prior abiraterone (Yes vs No), prior enzalutamide (Yes vs No) and ECOG score (0, 1 vs 2)	
Comparison groups	DCVAC/PCa v Placebo
Number of subjects included in analysis	722
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.46
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.939
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.795
upper limit	1.11

Statistical analysis title	Unstratified
Comparison groups	DCVAC/PCa v Placebo
Number of subjects included in analysis	722
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.534
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.95
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.807
upper limit	1.118

Secondary: Proportion of patients with skeletal-related events, intention-to-treat population

End point title	Proportion of patients with skeletal-related events, intention-to-treat population
End point description:	
Intention-to-treat population definition: All randomized patients	
End point type	Secondary
End point timeframe:	
From randomization to the end of the study	

End point values	DCVAC/PCa	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	787	395		
Units: Patients	43	26		

Statistical analyses

Statistical analysis title	Stratified

Statistical analysis description:

Adjusted by region (US vs other), prior abiraterone (Yes vs No), prior enzalutamide (Yes vs No) and ECOG score (0, 1 vs 2)

Comparison groups	DCVAC/PCa v Placebo
Number of subjects included in analysis	1182
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.485
Method	Log binomial model
Parameter estimate	Risk ratio (RR)
Point estimate	0.845
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.528
upper limit	1.355

Secondary: Proportion of patients with skeletal-related events, per protocol population

End point title	Proportion of patients with skeletal-related events, per protocol population

End point description:

Per protocol population definition:
A subset of all randomized patients characterized by the following criteria:
- had at least 1 post-baseline efficacy assessment
- did not have any major protocol violation that would affect the endpoints being assessed
- received at least 8 doses of DCVAC/PCa or placebo

End point type	Secondary

End point timeframe:

From randomization to the end of the study

End point values	DCVAC/PCa	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	438	284		
Units: Patients	28	20		

Statistical analyses

Statistical analysis title	Stratified
Statistical analysis description: Adjusted by region (US vs other), prior abiraterone (Yes vs No), prior enzalutamide (Yes vs No) and ECOG score (0, 1 vs 2)	
Comparison groups	DCVAC/PCa v Placebo
Number of subjects included in analysis	722
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.768
Method	Log binomial model
Parameter estimate	Risk ratio (RR)
Point estimate	0.92
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.529
upper limit	1.601

Adverse events

Adverse events information

Timeframe for reporting adverse events:

TEAEs: Start date on or after the earliest start of chemotherapy or study treatment or AE worsened (increased in severity) on or after the earliest start of chemotherapy or study treatment.
Deaths: From consent signature to study end.

Adverse event reporting additional description:

TEAE = treatment-emergent adverse events. Causal association of the event to the administration of DCVAC/PCa was assessed by investigators. Disease progression-related events (as evaluated by investigators) were excluded from SAE reporting.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	22.1

Reporting groups

Reporting group title	DCVAC/PCa

Reporting group description:

The safety population was comprised of all patients who received first-line chemotherapy and/or at least one dose of treatment with DCVAC/PCa and was based on the actual treatment received if this differs from that to which the patient was randomized.

Reporting group title	Placebo

Reporting group description:

The safety population was comprised of all patients who received first-line chemotherapy and/or at least one dose of treatment with placebo and was based on the actual treatment received if this differs from that to which the patient was randomized.

Serious adverse events	DCVAC/PCa	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	237 / 749 (31.64%)	150 / 379 (39.58%)	
number of deaths (all causes)	505	254	
number of deaths resulting from adverse events	39	30	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenocarcinoma of colon			
subjects affected / exposed	1 / 749 (0.13%)	0 / 379 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal squamous cell carcinoma			
subjects affected / exposed	1 / 749 (0.13%)	0 / 379 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Basal cell carcinoma			

subjects affected / exposed	2 / 749 (0.27%)	0 / 379 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cancer pain			
subjects affected / exposed	1 / 749 (0.13%)	3 / 379 (0.79%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Carcinoid tumour			
subjects affected / exposed	1 / 749 (0.13%)	0 / 379 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac myxoma			
subjects affected / exposed	1 / 749 (0.13%)	0 / 379 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chondrosarcoma			
subjects affected / exposed	0 / 749 (0.00%)	1 / 379 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic lymphocytic leukaemia			
subjects affected / exposed	1 / 749 (0.13%)	0 / 379 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant melanoma			
subjects affected / exposed	1 / 749 (0.13%)	1 / 379 (0.26%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant pleural effusion			
subjects affected / exposed	1 / 749 (0.13%)	0 / 379 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Aortic stenosis			

subjects affected / exposed	1 / 749 (0.13%)	0 / 379 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Deep vein thrombosis			
subjects affected / exposed	4 / 749 (0.53%)	1 / 379 (0.26%)	
occurrences causally related to treatment / all	0 / 5	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertension			
subjects affected / exposed	0 / 749 (0.00%)	1 / 379 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	2 / 749 (0.27%)	0 / 379 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypovolaemic shock			
subjects affected / exposed	1 / 749 (0.13%)	0 / 379 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Shock			
subjects affected / exposed	2 / 749 (0.27%)	0 / 379 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 2	0 / 0	
Temporal arteritis			
subjects affected / exposed	1 / 749 (0.13%)	0 / 379 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombophlebitis			
subjects affected / exposed	0 / 749 (0.00%)	1 / 379 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Venous thrombosis limb			

subjects affected / exposed	0 / 749 (0.00%)	1 / 379 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	3 / 749 (0.40%)	1 / 379 (0.26%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Catheter site inflammation			
subjects affected / exposed	1 / 749 (0.13%)	0 / 379 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Complication associated with device			
subjects affected / exposed	0 / 749 (0.00%)	1 / 379 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Death			
subjects affected / exposed	5 / 749 (0.67%)	5 / 379 (1.32%)	
occurrences causally related to treatment / all	0 / 5	0 / 5	
deaths causally related to treatment / all	0 / 5	0 / 5	
Fatigue			
subjects affected / exposed	5 / 749 (0.67%)	1 / 379 (0.26%)	
occurrences causally related to treatment / all	0 / 5	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical health deterioration			
subjects affected / exposed	6 / 749 (0.80%)	0 / 379 (0.00%)	
occurrences causally related to treatment / all	0 / 6	0 / 0	
deaths causally related to treatment / all	0 / 2	0 / 0	
Chest pain			
subjects affected / exposed	1 / 749 (0.13%)	0 / 379 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-cardiac chest pain			

subjects affected / exposed	1 / 749 (0.13%)	0 / 379 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oedema peripheral			
subjects affected / exposed	1 / 749 (0.13%)	1 / 379 (0.26%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	9 / 749 (1.20%)	6 / 379 (1.58%)	
occurrences causally related to treatment / all	2 / 13	0 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sudden death			
subjects affected / exposed	1 / 749 (0.13%)	0 / 379 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Systemic inflammatory response syndrome			
subjects affected / exposed	0 / 749 (0.00%)	3 / 379 (0.79%)	
occurrences causally related to treatment / all	0 / 0	2 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Allergy to arthropod sting			
subjects affected / exposed	1 / 749 (0.13%)	0 / 379 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaphylactic reaction			
subjects affected / exposed	1 / 749 (0.13%)	0 / 379 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypersensitivity			
subjects affected / exposed	0 / 749 (0.00%)	1 / 379 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			

Pelvic pain			
subjects affected / exposed	1 / 749 (0.13%)	0 / 379 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Scrotal oedema			
subjects affected / exposed	1 / 749 (0.13%)	0 / 379 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Acute respiratory distress syndrome			
subjects affected / exposed	1 / 749 (0.13%)	0 / 379 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Acute respiratory failure			
subjects affected / exposed	4 / 749 (0.53%)	2 / 379 (0.53%)	
occurrences causally related to treatment / all	0 / 4	0 / 2	
deaths causally related to treatment / all	0 / 3	0 / 1	
Dyspnoea			
subjects affected / exposed	0 / 749 (0.00%)	1 / 379 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea exertional			
subjects affected / exposed	1 / 749 (0.13%)	0 / 379 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hydrothorax			
subjects affected / exposed	1 / 749 (0.13%)	0 / 379 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Hypoxia			
subjects affected / exposed	1 / 749 (0.13%)	0 / 379 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Chronic obstructive pulmonary disease			
subjects affected / exposed	2 / 749 (0.27%)	0 / 379 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Interstitial lung disease			
subjects affected / exposed	2 / 749 (0.27%)	3 / 379 (0.79%)	
occurrences causally related to treatment / all	3 / 3	2 / 3	
deaths causally related to treatment / all	1 / 1	0 / 0	
Pleural effusion			
subjects affected / exposed	3 / 749 (0.40%)	0 / 379 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia aspiration			
subjects affected / exposed	2 / 749 (0.27%)	2 / 379 (0.53%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonitis			
subjects affected / exposed	3 / 749 (0.40%)	1 / 379 (0.26%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	18 / 749 (2.40%)	15 / 379 (3.96%)	
occurrences causally related to treatment / all	2 / 18	2 / 15	
deaths causally related to treatment / all	0 / 1	0 / 1	
Pulmonary fibrosis			
subjects affected / exposed	1 / 749 (0.13%)	0 / 379 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary oedema			
subjects affected / exposed	1 / 749 (0.13%)	0 / 379 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			

subjects affected / exposed	4 / 749 (0.53%)	0 / 379 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Psychiatric disorders			
Mental status changes			
subjects affected / exposed	1 / 749 (0.13%)	0 / 379 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nightmare			
subjects affected / exposed	1 / 749 (0.13%)	0 / 379 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Product issues			
Device occlusion			
subjects affected / exposed	1 / 749 (0.13%)	0 / 379 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Blood creatinine increased			
subjects affected / exposed	1 / 749 (0.13%)	0 / 379 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Computerised tomogram abnormal			
subjects affected / exposed	0 / 749 (0.00%)	1 / 379 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutrophil count decreased			
subjects affected / exposed	0 / 749 (0.00%)	1 / 379 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Ankle fracture			

subjects affected / exposed	0 / 749 (0.00%)	2 / 379 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cystitis radiation			
subjects affected / exposed	1 / 749 (0.13%)	0 / 379 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femoral neck fracture			
subjects affected / exposed	1 / 749 (0.13%)	0 / 379 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fibula fracture			
subjects affected / exposed	0 / 749 (0.00%)	1 / 379 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal stoma complication			
subjects affected / exposed	1 / 749 (0.13%)	0 / 379 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hip fracture			
subjects affected / exposed	2 / 749 (0.27%)	0 / 379 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Jaw fracture			
subjects affected / exposed	1 / 749 (0.13%)	0 / 379 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower limb fracture			
subjects affected / exposed	2 / 749 (0.27%)	0 / 379 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lumbar vertebral fracture			

subjects affected / exposed	1 / 749 (0.13%)	0 / 379 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postoperative wound complication			
subjects affected / exposed	1 / 749 (0.13%)	0 / 379 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Radiation proctitis			
subjects affected / exposed	1 / 749 (0.13%)	0 / 379 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skull fracture			
subjects affected / exposed	1 / 749 (0.13%)	0 / 379 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal compression fracture			
subjects affected / exposed	0 / 749 (0.00%)	2 / 379 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subdural haematoma			
subjects affected / exposed	2 / 749 (0.27%)	1 / 379 (0.26%)	
occurrences causally related to treatment / all	0 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Subdural haemorrhage			
subjects affected / exposed	1 / 749 (0.13%)	0 / 379 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	0 / 749 (0.00%)	2 / 379 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Angina pectoris			

subjects affected / exposed	1 / 749 (0.13%)	0 / 379 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aortic valve stenosis			
subjects affected / exposed	0 / 749 (0.00%)	1 / 379 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	7 / 749 (0.93%)	2 / 379 (0.53%)	
occurrences causally related to treatment / all	0 / 8	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial flutter			
subjects affected / exposed	1 / 749 (0.13%)	0 / 379 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial tachycardia			
subjects affected / exposed	0 / 749 (0.00%)	1 / 379 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrioventricular block			
subjects affected / exposed	2 / 749 (0.27%)	0 / 379 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	0 / 749 (0.00%)	1 / 379 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiac failure			
subjects affected / exposed	2 / 749 (0.27%)	2 / 379 (0.53%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure acute			

subjects affected / exposed	1 / 749 (0.13%)	0 / 379 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure congestive			
subjects affected / exposed	1 / 749 (0.13%)	2 / 379 (0.53%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure chronic			
subjects affected / exposed	0 / 749 (0.00%)	2 / 379 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiogenic shock			
subjects affected / exposed	1 / 749 (0.13%)	0 / 379 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiomyopathy			
subjects affected / exposed	0 / 749 (0.00%)	1 / 379 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Coronary artery disease			
subjects affected / exposed	1 / 749 (0.13%)	0 / 379 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	3 / 749 (0.40%)	1 / 379 (0.26%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 3	0 / 1	
Myocarditis			
subjects affected / exposed	0 / 749 (0.00%)	1 / 379 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tachycardia			

subjects affected / exposed	1 / 749 (0.13%)	0 / 379 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular extrasystoles			
subjects affected / exposed	1 / 749 (0.13%)	0 / 379 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Amnesia			
subjects affected / exposed	0 / 749 (0.00%)	1 / 379 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Brain injury			
subjects affected / exposed	1 / 749 (0.13%)	0 / 379 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cauda equina syndrome			
subjects affected / exposed	1 / 749 (0.13%)	0 / 379 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral haemorrhage			
subjects affected / exposed	2 / 749 (0.27%)	0 / 379 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cerebral infarction			
subjects affected / exposed	0 / 749 (0.00%)	1 / 379 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral venous thrombosis			
subjects affected / exposed	1 / 749 (0.13%)	0 / 379 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			

subjects affected / exposed	2 / 749 (0.27%)	0 / 379 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Diabetic coma			
subjects affected / exposed	0 / 749 (0.00%)	1 / 379 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Ischaemic cerebral infarction			
subjects affected / exposed	1 / 749 (0.13%)	0 / 379 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic stroke			
subjects affected / exposed	3 / 749 (0.40%)	2 / 379 (0.53%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Loss of consciousness			
subjects affected / exposed	1 / 749 (0.13%)	0 / 379 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Monoparesis			
subjects affected / exposed	1 / 749 (0.13%)	0 / 379 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neuropathy peripheral			
subjects affected / exposed	1 / 749 (0.13%)	2 / 379 (0.53%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paraparesis			
subjects affected / exposed	1 / 749 (0.13%)	0 / 379 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paraplegia			

subjects affected / exposed	0 / 749 (0.00%)	1 / 379 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral motor neuropathy			
subjects affected / exposed	0 / 749 (0.00%)	1 / 379 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral sensory neuropathy			
subjects affected / exposed	1 / 749 (0.13%)	0 / 379 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Polyneuropathy			
subjects affected / exposed	1 / 749 (0.13%)	0 / 379 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sciatica			
subjects affected / exposed	1 / 749 (0.13%)	0 / 379 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			
subjects affected / exposed	1 / 749 (0.13%)	0 / 379 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal cord compression			
subjects affected / exposed	2 / 749 (0.27%)	1 / 379 (0.26%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Superior sagittal sinus thrombosis			
subjects affected / exposed	1 / 749 (0.13%)	0 / 379 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			

subjects affected / exposed	7 / 749 (0.93%)	3 / 379 (0.79%)	
occurrences causally related to treatment / all	1 / 8	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	2 / 749 (0.27%)	0 / 379 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vertigo CNS origin			
subjects affected / exposed	1 / 749 (0.13%)	0 / 379 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Agranulocytosis			
subjects affected / exposed	0 / 749 (0.00%)	1 / 379 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaemia			
subjects affected / exposed	9 / 749 (1.20%)	3 / 379 (0.79%)	
occurrences causally related to treatment / all	0 / 14	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bicytopenia			
subjects affected / exposed	0 / 749 (0.00%)	1 / 379 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	25 / 749 (3.34%)	29 / 379 (7.65%)	
occurrences causally related to treatment / all	2 / 27	0 / 34	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukopenia			
subjects affected / exposed	2 / 749 (0.27%)	2 / 379 (0.53%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			

subjects affected / exposed	12 / 749 (1.60%)	5 / 379 (1.32%)	
occurrences causally related to treatment / all	0 / 12	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancytopenia			
subjects affected / exposed	4 / 749 (0.53%)	0 / 379 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	1 / 749 (0.13%)	0 / 379 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Diplopia			
subjects affected / exposed	1 / 749 (0.13%)	0 / 379 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retinal detachment			
subjects affected / exposed	1 / 749 (0.13%)	0 / 379 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uveitis			
subjects affected / exposed	1 / 749 (0.13%)	0 / 379 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 749 (0.13%)	1 / 379 (0.26%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain upper			
subjects affected / exposed	0 / 749 (0.00%)	1 / 379 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Colitis ischaemic			
subjects affected / exposed	1 / 749 (0.13%)	0 / 379 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	2 / 749 (0.27%)	1 / 379 (0.26%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	5 / 749 (0.67%)	5 / 379 (1.32%)	
occurrences causally related to treatment / all	0 / 5	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysphagia			
subjects affected / exposed	0 / 749 (0.00%)	1 / 379 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterocolitis haemorrhagic			
subjects affected / exposed	1 / 749 (0.13%)	0 / 379 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric antral vascular ectasia			
subjects affected / exposed	0 / 749 (0.00%)	1 / 379 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric haemorrhage			
subjects affected / exposed	1 / 749 (0.13%)	0 / 379 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric ulcer			
subjects affected / exposed	0 / 749 (0.00%)	1 / 379 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric ulcer haemorrhage			

subjects affected / exposed	0 / 749 (0.00%)	2 / 379 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric ulcer perforation			
subjects affected / exposed	1 / 749 (0.13%)	0 / 379 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis			
subjects affected / exposed	1 / 749 (0.13%)	0 / 379 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	1 / 749 (0.13%)	0 / 379 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Gastrointestinal inflammation			
subjects affected / exposed	0 / 749 (0.00%)	1 / 379 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematochezia			
subjects affected / exposed	1 / 749 (0.13%)	0 / 379 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhoidal haemorrhage			
subjects affected / exposed	1 / 749 (0.13%)	0 / 379 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus			
subjects affected / exposed	0 / 749 (0.00%)	1 / 379 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal obstruction			

subjects affected / exposed	2 / 749 (0.27%)	0 / 379 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestine perforation			
subjects affected / exposed	0 / 749 (0.00%)	2 / 379 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	1 / 749 (0.13%)	3 / 379 (0.79%)	
occurrences causally related to treatment / all	0 / 1	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Obstructive pancreatitis			
subjects affected / exposed	0 / 749 (0.00%)	1 / 379 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophagitis			
subjects affected / exposed	1 / 749 (0.13%)	1 / 379 (0.26%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			
subjects affected / exposed	1 / 749 (0.13%)	0 / 379 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis acute			
subjects affected / exposed	1 / 749 (0.13%)	1 / 379 (0.26%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peptic ulcer			
subjects affected / exposed	0 / 749 (0.00%)	1 / 379 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal haemorrhage			

subjects affected / exposed	1 / 749 (0.13%)	0 / 379 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal perforation			
subjects affected / exposed	0 / 749 (0.00%)	1 / 379 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal haemorrhage			
subjects affected / exposed	1 / 749 (0.13%)	0 / 379 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal obstruction			
subjects affected / exposed	1 / 749 (0.13%)	0 / 379 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal stenosis			
subjects affected / exposed	0 / 749 (0.00%)	1 / 379 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stomatitis			
subjects affected / exposed	0 / 749 (0.00%)	1 / 379 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	2 / 749 (0.27%)	4 / 379 (1.06%)	
occurrences causally related to treatment / all	0 / 2	1 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Hepatic cyst			
subjects affected / exposed	0 / 749 (0.00%)	1 / 379 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic failure			

subjects affected / exposed	1 / 749 (0.13%)	0 / 379 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Skin and subcutaneous tissue disorders			
Rash erythematous			
subjects affected / exposed	1 / 749 (0.13%)	0 / 379 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	5 / 749 (0.67%)	4 / 379 (1.06%)	
occurrences causally related to treatment / all	0 / 5	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Calculus bladder			
subjects affected / exposed	1 / 749 (0.13%)	0 / 379 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematuria			
subjects affected / exposed	6 / 749 (0.80%)	0 / 379 (0.00%)	
occurrences causally related to treatment / all	0 / 8	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hydronephrosis			
subjects affected / exposed	6 / 749 (0.80%)	2 / 379 (0.53%)	
occurrences causally related to treatment / all	0 / 6	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic kidney disease			
subjects affected / exposed	1 / 749 (0.13%)	0 / 379 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal atrophy			
subjects affected / exposed	0 / 749 (0.00%)	1 / 379 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			

subjects affected / exposed	3 / 749 (0.40%)	1 / 379 (0.26%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal impairment			
subjects affected / exposed	0 / 749 (0.00%)	1 / 379 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ureterolithiasis			
subjects affected / exposed	1 / 749 (0.13%)	0 / 379 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary retention			
subjects affected / exposed	7 / 749 (0.93%)	4 / 379 (1.06%)	
occurrences causally related to treatment / all	0 / 8	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract obstruction			
subjects affected / exposed	1 / 749 (0.13%)	1 / 379 (0.26%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 749 (0.13%)	1 / 379 (0.26%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthritis			
subjects affected / exposed	1 / 749 (0.13%)	0 / 379 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Back pain			
subjects affected / exposed	7 / 749 (0.93%)	1 / 379 (0.26%)	
occurrences causally related to treatment / all	0 / 7	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone pain			

subjects affected / exposed	1 / 749 (0.13%)	2 / 379 (0.53%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bursitis			
subjects affected / exposed	0 / 749 (0.00%)	1 / 379 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal pain			
subjects affected / exposed	1 / 749 (0.13%)	0 / 379 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neck pain			
subjects affected / exposed	0 / 749 (0.00%)	1 / 379 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteitis			
subjects affected / exposed	1 / 749 (0.13%)	0 / 379 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoarthritis			
subjects affected / exposed	1 / 749 (0.13%)	2 / 379 (0.53%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteonecrosis of jaw			
subjects affected / exposed	5 / 749 (0.67%)	1 / 379 (0.26%)	
occurrences causally related to treatment / all	0 / 5	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain in extremity			
subjects affected / exposed	1 / 749 (0.13%)	0 / 379 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pathological fracture			

subjects affected / exposed	0 / 749 (0.00%)	1 / 379 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Periarthritis			
subjects affected / exposed	0 / 749 (0.00%)	1 / 379 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal pain			
subjects affected / exposed	1 / 749 (0.13%)	0 / 379 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Abdominal infection			
subjects affected / exposed	0 / 749 (0.00%)	1 / 379 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abscess limb			
subjects affected / exposed	0 / 749 (0.00%)	1 / 379 (0.26%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abscess oral			
subjects affected / exposed	1 / 749 (0.13%)	0 / 379 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abscess soft tissue			
subjects affected / exposed	1 / 749 (0.13%)	0 / 379 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal abscess			
subjects affected / exposed	1 / 749 (0.13%)	1 / 379 (0.26%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis			

subjects affected / exposed	1 / 749 (0.13%)	0 / 379 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Biliary tract infection			
subjects affected / exposed	0 / 749 (0.00%)	1 / 379 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	2 / 749 (0.27%)	2 / 379 (0.53%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Catheter site cellulitis			
subjects affected / exposed	1 / 749 (0.13%)	0 / 379 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	3 / 749 (0.40%)	0 / 379 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis orbital			
subjects affected / exposed	1 / 749 (0.13%)	0 / 379 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile colitis			
subjects affected / exposed	2 / 749 (0.27%)	0 / 379 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile infection			
subjects affected / exposed	1 / 749 (0.13%)	1 / 379 (0.26%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Complicated appendicitis			

subjects affected / exposed	1 / 749 (0.13%)	0 / 379 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cytomegalovirus infection			
subjects affected / exposed	0 / 749 (0.00%)	1 / 379 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cytomegalovirus oesophagitis			
subjects affected / exposed	0 / 749 (0.00%)	1 / 379 (0.26%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dermo-hypodermitis			
subjects affected / exposed	0 / 749 (0.00%)	1 / 379 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related infection			
subjects affected / exposed	1 / 749 (0.13%)	1 / 379 (0.26%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related sepsis			
subjects affected / exposed	1 / 749 (0.13%)	0 / 379 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulitis			
subjects affected / exposed	1 / 749 (0.13%)	0 / 379 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterococcal bacteraemia			
subjects affected / exposed	0 / 749 (0.00%)	1 / 379 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterocolitis infectious			

subjects affected / exposed	1 / 749 (0.13%)	0 / 379 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erysipelas			
subjects affected / exposed	1 / 749 (0.13%)	0 / 379 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia sepsis			
subjects affected / exposed	1 / 749 (0.13%)	1 / 379 (0.26%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	2 / 749 (0.27%)	0 / 379 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis norovirus			
subjects affected / exposed	0 / 749 (0.00%)	1 / 379 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis viral			
subjects affected / exposed	0 / 749 (0.00%)	1 / 379 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes zoster			
subjects affected / exposed	0 / 749 (0.00%)	2 / 379 (0.53%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholangitis infective			
subjects affected / exposed	0 / 749 (0.00%)	1 / 379 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			

subjects affected / exposed	3 / 749 (0.40%)	1 / 379 (0.26%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
subjects affected / exposed	1 / 749 (0.13%)	1 / 379 (0.26%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	0 / 749 (0.00%)	2 / 379 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenic sepsis			
subjects affected / exposed	7 / 749 (0.93%)	5 / 379 (1.32%)	
occurrences causally related to treatment / all	0 / 7	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 1	
Osteomyelitis			
subjects affected / exposed	2 / 749 (0.27%)	0 / 379 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paraspinal abscess			
subjects affected / exposed	1 / 749 (0.13%)	0 / 379 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Perirectal abscess			
subjects affected / exposed	1 / 749 (0.13%)	0 / 379 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritonitis			
subjects affected / exposed	1 / 749 (0.13%)	1 / 379 (0.26%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			

subjects affected / exposed	18 / 749 (2.40%)	11 / 379 (2.90%)	
occurrences causally related to treatment / all	0 / 18	0 / 13	
deaths causally related to treatment / all	0 / 3	0 / 2	
Pneumonia mycoplasmal			
subjects affected / exposed	1 / 749 (0.13%)	0 / 379 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia viral			
subjects affected / exposed	0 / 749 (0.00%)	1 / 379 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis			
subjects affected / exposed	1 / 749 (0.13%)	1 / 379 (0.26%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Rectal abscess			
subjects affected / exposed	1 / 749 (0.13%)	0 / 379 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection			
subjects affected / exposed	1 / 749 (0.13%)	1 / 379 (0.26%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	8 / 749 (1.07%)	5 / 379 (1.32%)	
occurrences causally related to treatment / all	0 / 8	0 / 5	
deaths causally related to treatment / all	0 / 2	0 / 1	
Septic shock			
subjects affected / exposed	1 / 749 (0.13%)	0 / 379 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal abscess			

subjects affected / exposed	0 / 749 (0.00%)	1 / 379 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal bacteraemia			
subjects affected / exposed	2 / 749 (0.27%)	0 / 379 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal sepsis			
subjects affected / exposed	2 / 749 (0.27%)	0 / 379 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Streptococcal sepsis			
subjects affected / exposed	0 / 749 (0.00%)	1 / 379 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tracheobronchitis			
subjects affected / exposed	1 / 749 (0.13%)	0 / 379 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	10 / 749 (1.34%)	8 / 379 (2.11%)	
occurrences causally related to treatment / all	0 / 13	0 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection staphylococcal			
subjects affected / exposed	1 / 749 (0.13%)	0 / 379 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			
subjects affected / exposed	3 / 749 (0.40%)	0 / 379 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral sepsis			

subjects affected / exposed	1 / 749 (0.13%)	0 / 379 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	1 / 749 (0.13%)	0 / 379 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			
subjects affected / exposed	6 / 749 (0.80%)	4 / 379 (1.06%)	
occurrences causally related to treatment / all	1 / 6	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetes mellitus			
subjects affected / exposed	1 / 749 (0.13%)	0 / 379 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic metabolic decompensation			
subjects affected / exposed	1 / 749 (0.13%)	1 / 379 (0.26%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Failure to thrive			
subjects affected / exposed	0 / 749 (0.00%)	1 / 379 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			
subjects affected / exposed	0 / 749 (0.00%)	1 / 379 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycaemia			
subjects affected / exposed	1 / 749 (0.13%)	0 / 379 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			

subjects affected / exposed	4 / 749 (0.53%)	0 / 379 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	DCVAC/PCa	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	670 / 749 (89.45%)	365 / 379 (96.31%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	43 / 749 (5.74%)	34 / 379 (8.97%)	
occurrences (all)	56	44	
Hypotension			
subjects affected / exposed	40 / 749 (5.34%)	28 / 379 (7.39%)	
occurrences (all)	48	39	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	106 / 749 (14.15%)	69 / 379 (18.21%)	
occurrences (all)	156	107	
Fatigue			
subjects affected / exposed	268 / 749 (35.78%)	152 / 379 (40.11%)	
occurrences (all)	374	219	
Mucosal inflammation			
subjects affected / exposed	28 / 749 (3.74%)	22 / 379 (5.80%)	
occurrences (all)	33	37	
Oedema peripheral			
subjects affected / exposed	121 / 749 (16.15%)	87 / 379 (22.96%)	
occurrences (all)	146	107	
Pyrexia			
subjects affected / exposed	76 / 749 (10.15%)	42 / 379 (11.08%)	
occurrences (all)	104	64	
Respiratory, thoracic and mediastinal disorders			
Cough			

subjects affected / exposed	82 / 749 (10.95%)	47 / 379 (12.40%)	
occurrences (all)	95	54	
Dyspnoea			
subjects affected / exposed	82 / 749 (10.95%)	55 / 379 (14.51%)	
occurrences (all)	103	65	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	32 / 749 (4.27%)	24 / 379 (6.33%)	
occurrences (all)	33	25	
Investigations			
Weight decreased			
subjects affected / exposed	46 / 749 (6.14%)	24 / 379 (6.33%)	
occurrences (all)	48	25	
Nervous system disorders			
Dizziness			
subjects affected / exposed	41 / 749 (5.47%)	33 / 379 (8.71%)	
occurrences (all)	47	40	
Dysgeusia			
subjects affected / exposed	80 / 749 (10.68%)	59 / 379 (15.57%)	
occurrences (all)	105	91	
Headache			
subjects affected / exposed	35 / 749 (4.67%)	27 / 379 (7.12%)	
occurrences (all)	38	33	
Hypoaesthesia			
subjects affected / exposed	32 / 749 (4.27%)	20 / 379 (5.28%)	
occurrences (all)	41	25	
Neuropathy peripheral			
subjects affected / exposed	83 / 749 (11.08%)	54 / 379 (14.25%)	
occurrences (all)	110	59	
Paraesthesia			
subjects affected / exposed	76 / 749 (10.15%)	33 / 379 (8.71%)	
occurrences (all)	95	42	
Peripheral sensory neuropathy			
subjects affected / exposed	36 / 749 (4.81%)	28 / 379 (7.39%)	
occurrences (all)	39	31	
Polyneuropathy			

subjects affected / exposed	44 / 749 (5.87%)	24 / 379 (6.33%)	
occurrences (all)	47	28	
Taste disorder			
subjects affected / exposed	37 / 749 (4.94%)	21 / 379 (5.54%)	
occurrences (all)	39	23	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	123 / 749 (16.42%)	76 / 379 (20.05%)	
occurrences (all)	159	96	
Leukopenia			
subjects affected / exposed	63 / 749 (8.41%)	33 / 379 (8.71%)	
occurrences (all)	103	74	
Neutropenia			
subjects affected / exposed	103 / 749 (13.75%)	54 / 379 (14.25%)	
occurrences (all)	177	92	
Eye disorders			
Lacrimation increased			
subjects affected / exposed	29 / 749 (3.87%)	30 / 379 (7.92%)	
occurrences (all)	29	32	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	28 / 749 (3.74%)	23 / 379 (6.07%)	
occurrences (all)	31	26	
Constipation			
subjects affected / exposed	111 / 749 (14.82%)	71 / 379 (18.73%)	
occurrences (all)	133	94	
Diarrhoea			
subjects affected / exposed	204 / 749 (27.24%)	115 / 379 (30.34%)	
occurrences (all)	338	183	
Dyspepsia			
subjects affected / exposed	44 / 749 (5.87%)	22 / 379 (5.80%)	
occurrences (all)	47	26	
Nausea			
subjects affected / exposed	150 / 749 (20.03%)	96 / 379 (25.33%)	
occurrences (all)	196	142	
Stomatitis			

subjects affected / exposed	39 / 749 (5.21%)	24 / 379 (6.33%)	
occurrences (all)	54	35	
Vomiting			
subjects affected / exposed	78 / 749 (10.41%)	43 / 379 (11.35%)	
occurrences (all)	97	53	
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	222 / 749 (29.64%)	130 / 379 (34.30%)	
occurrences (all)	224	131	
Nail disorder			
subjects affected / exposed	38 / 749 (5.07%)	28 / 379 (7.39%)	
occurrences (all)	41	28	
Rash			
subjects affected / exposed	36 / 749 (4.81%)	22 / 379 (5.80%)	
occurrences (all)	40	25	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	114 / 749 (15.22%)	74 / 379 (19.53%)	
occurrences (all)	153	110	
Back pain			
subjects affected / exposed	113 / 749 (15.09%)	67 / 379 (17.68%)	
occurrences (all)	135	79	
Bone pain			
subjects affected / exposed	78 / 749 (10.41%)	26 / 379 (6.86%)	
occurrences (all)	91	29	
Muscular weakness			
subjects affected / exposed	32 / 749 (4.27%)	23 / 379 (6.07%)	
occurrences (all)	36	26	
Musculoskeletal pain			
subjects affected / exposed	46 / 749 (6.14%)	24 / 379 (6.33%)	
occurrences (all)	51	28	
Myalgia			
subjects affected / exposed	53 / 749 (7.08%)	32 / 379 (8.44%)	
occurrences (all)	74	47	
Pain in extremity			

subjects affected / exposed	87 / 749 (11.62%)	55 / 379 (14.51%)	
occurrences (all)	104	74	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	33 / 749 (4.41%)	22 / 379 (5.80%)	
occurrences (all)	39	26	
Upper respiratory tract infection			
subjects affected / exposed	34 / 749 (4.54%)	20 / 379 (5.28%)	
occurrences (all)	41	23	
Urinary tract infection			
subjects affected / exposed	53 / 749 (7.08%)	39 / 379 (10.29%)	
occurrences (all)	76	66	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	110 / 749 (14.69%)	79 / 379 (20.84%)	
occurrences (all)	137	102	
Hyperglycaemia			
subjects affected / exposed	56 / 749 (7.48%)	27 / 379 (7.12%)	
occurrences (all)	81	41	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
07 March 2013	For version 1.1 positive decision was received in VHP submission.
10 May 2013	Version 02 was based on v.1.1 and was modified for IND submission to FDA in USA. (Key changes included – specification of 1st line chemotherapy as docetaxel and prednisone and update of DCVAC/PCa safety information based on DSUR issued in February 2013; specification of exploratory studies on biomarkers; updated list of approved 2nd line chemotherapies).
01 August 2013	Version 03 was based on v.02 and was modified per feedback received from FDA. (Key changes included –Discontinuation of DCVAC/PCa or placebo with 2nd line chemotherapy; Treatment period divided into 2 periods - concurrent treatment of 1st line chemotherapy with DCVAC/PCa or placebo and Maintenance Boosting period post docetaxel-prednisone & prior 2nd line-chemotherapy; changes connected with this design change; updated list of approved 2nd line chemotherapies; Amendment of stratification criteria, updated statistical section)
05 December 2013	Version 04 is based on v.03 and mostly operational details have been adjusted to match properly the new design in v.03 (Study drug discontinuation, End of Treatment, Follow-up for survival); secondary endpoints were modified to better fulfill PCWG2 recommendations; inclusion and exclusion criteria were modified per PCWG2 guidelines; corrected statistical section and decreased number of stratification criteria)
16 October 2014	Version 05 includes updates based on current experience from the clinical trial - clarified inclusion/exclusion criteria; updated sections on patient follow-up for long term survival; sections related to safety were updated to improve understanding. Sections on interim analysis and statistical analyses were updated based on feedback received from FDA. Section on exploratory studies was updated to include possibility of pharmacogenomics research.
13 January 2015	Change in the exclusion criterion. It is possible to shorten the washout period for ADT.
03 August 2015	Version 05.2 introduces: clarification of follow-up procedures applicable to patients for whom leukapheresis or production failed, or who have not received DCVAC/PCa or placebo for other reasons; clarification that no further radiological examinations of a patient will be required for this trial after confirmation of radiological progression or introduction of 2nd line chemotherapy; changes related to transfer of pharmacovigilance responsibilities for safety monitoring and reporting from Chiltern to SOTIO; administrative changes in the Declaration of the Investigator
28 August 2015	Version 06.0 includes the same changes as US-specific versions 05.1 and 05.2 : change in wording of the exclusion criterion that shortens the ADT washout period; clarification of follow-up procedures applicable to patients for whom leukapheresis or production failed, or who have not received DCVAC/PCa or placebo for other reasons; clarification that no further radiological examinations of a patient will be required for this trial after confirmation of radiological progression or introduction of 2nd line chemotherapy; changes related to transfer of pharmacovigilance responsibilities for safety monitoring and reporting from Chiltern to SOTIO; administrative changes in the Declaration of the Investigator; Version 06.0 additionally includes the introduction of the EQ-5D questionnaire (only in Europe) and clarification that ECOG performance status is measured also at Randomization.

08 March 2018	• Deletion of information on third-party vendors • Deletion of information on interim analysis which will not be performed • Clarification that the date of randomization is Day 1 and not Day 0 • Update of the sections on statistics according to the updated draft SAP • Clarification that ECOG performance status is measured also at Randomization (already in European v. 06.0) • Introduction of the EQ-5D questionnaire (only in Europe) (already in European v. 06.0) • Safety reporting clarifications

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.

None reported

Notes: