Clinical trial results:
A Randomised, Double-blind, Placebo-controlled, Phase I/II Trial of RNActive®-derived Cancer Vaccine (CV9104) in Asymptomatic or Minimally Symptomatic Patients with Metastatic Castrate-refractory Prostate Cancer

Summary

EudraCT number	2011-006314-14
Trial protocol	DE GB ES SE CZ
Global end of trial date	20 March 2017

Results information

Result version number	v1 (current)
This version publication date	01 February 2018
First version publication date	01 February 2018

Trial information

Trial identification

Sponsor protocol code	CV-9104-004

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01817738
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	CureVac AG
Sponsor organisation address	Paul-Ehrlich-Strasse 15, Tübingen, Germany, 72076
Public contact	Clinical Trials Information, CureVac AG, +49 7071-9883-0, clinicaltrials@curevac.com
Scientific contact	Clinical Trials Information, CureVac AG, +49 7071-9883-0, clinicaltrials@curevac.com

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	20 March 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	20 March 2017
Global end of trial reached?	Yes
Global end of trial date	20 March 2017
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

Phase I (safety lead-in):
The primary objective of the safety lead-in portion of the study was to assess the safety and tolerability of CV9104 and to determine the dose for the randomised portion.

Phase II (randomised portion):
The primary objective of the randomised portion of the study was the comparison of overall survival (OS) in the CV9104 and placebo groups.

Protection of trial subjects:

Additional measures for monitoring and minimizing potential risks were undertaken by involving an Independent Data Monitoring Committee (IDMC) to closely monitor all safety-related procedures and review safety data during the study conduct. The IDMC reviewed safety data during the safety lead-in and randomised portions of the study and also assessed interim data related to the primary efficacy endpoint of the randomised part of the study.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	27 August 2012
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	Poland: 40
Country: Number of subjects enrolled	Spain: 16
Country: Number of subjects enrolled	Sweden: 12
Country: Number of subjects enrolled	United Kingdom: 21
Country: Number of subjects enrolled	Czech Republic: 20
Country: Number of subjects enrolled	France: 5
Country: Number of subjects enrolled	Germany: 79
Country: Number of subjects enrolled	Switzerland: 11
Worldwide total number of subjects	204
EEA total number of subjects	193

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)	58
From 65 to 84 years	142
85 years and over	4

Subject disposition

Recruitment

Recruitment details:

Overall, 204 patients were enrolled in the study. A total of 7 patients were included in the safety lead-in period (Phase I). A total of 197 patients were randomised in the Phase II period at 48 sites in 8 countries (Czech Republic, France, Germany, Poland, Spain, Sweden, Switzerland, and United Kingdom); 5 of which were not treated.

Pre-assignment

Screening details:

For Phase I, patients with asymptomatic or minimally symptomatic disease progressing after surgical castration or GNRH analogue therapy and after at least one second-line antihormonal manipulation. For Phase II, also previous chemotherapies and other malignancies were prohibited.

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, Assessor

Blinding implementation details:

Phase I was open label to determine safety and tolerability of CV9104 and to determine dosage for Phase II.
Phase II: After a patient had given informed consent, the interactive web response system (IWRS) assigned a subject identification number. Before the first vaccination, eligible patients were randomly assigned to either active vaccine or placebo by the IWRS based on a permuted block randomisation list. Vials containing active vaccine (CV9104) or placebo were identical in appearance.

Arms

Are arms mutually exclusive?	Yes
Arm title	CV9104

Arm description:

Phase I:
At Weeks 1, 2, and 3, each patient received open-label vaccinations of CV9104 at a starting total dose of 1920 µg (320 µg of each of the 6 components administered in 12 intradermal (ID) injections) using a standard 3 + 3 design. Patients were offered to continue treatment, and were included in the safety analysis for the phase II part of the trial.

Phase II:
Patients received CV9104 at 1920 µg at weeks 1, 2, 3, 5, 7, 9, 12, 15, 18 and 24, then every 6 weeks for up to 12 months (Week 54) after the first vaccination and then every 3 months thereafter until one of the criteria for study treatment discontinuation were met. After discontinuation of study treatment, patients were to be followed-up for survival every 3 months until death or loss to follow-up.

Arm type	Experimental
Investigational medicinal product name	CV9104
Investigational medicinal product code	CV9104
Other name	messenger ribonucleic acid (mRNA)
Pharmaceutical forms	Solution for injection
Routes of administration	Intradermal use

Dosage and administration details:

CV9104 consists of 6 drug product components (320 µg each, 1920 µg total dose), each component stored as a sterile lyophilizate, for reconstitution with ringer lactate solution. At each vaccination timepoint, each of the 6 drug components was to be administered individually as 2 ID injections for a total of 12 injections distributed over 4 limbs. CV9104 was to be applied stricly intradermally into the thigh and upper arm of either side (4 sites total).

Arm title	Placebo

Arm description:

Patients received placebo on Day 1 of weeks 1, 2, 3, 5, 7, 9, 12, 15, 18 and 24, then every 6 weeks for up to 12 months following the first vaccination and then every 3 months until one of the criteria for study treatment discontinuation were met. After discontinuation of study treatment, patients were to be followed-up for survival every 3 months until death or loss to follow-up.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intradermal use

Dosage and administration details:

At each vaccination timepoint, the placebo was to be administered individually as 2 intradermal injections for a total of 12 injections distributed over 4 limbs.

Number of subjects in period 1[1]	CV9104	Placebo
Started	137	63
Completed	132	60
Not completed	5	3
Consent withdrawn by subject	4	2
Lost to follow-up	1	1

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: Of the 204 patients enrolled, 5 did not receive any IMP and were therefore excluded from any further analysis.

Baseline characteristics

Reporting groups	
Reporting group title	CV9104

Reporting group description:

Phase I:
At Weeks 1, 2, and 3, each patient received open-label vaccinations of CV9104 at a starting total dose of 1920 µg (320 µg of each of the 6 components administered in 12 intradermal (ID) injections) using a standard 3 + 3 design. Patients were offered to continue treatment, and were included in the safety analysis for the phase II part of the trial.

Phase II:
Patients received CV9104 at 1920 µg at weeks 1, 2, 3, 5, 7, 9, 12, 15, 18 and 24, then every 6 weeks for up to 12 months (Week 54) after the first vaccination and then every 3 months thereafter until one of the criteria for study treatment discontinuation were met. After discontinuation of study treatment, patients were to be followed-up for survival every 3 months until death or loss to follow-up.

Reporting group title	Placebo

Reporting group description:

Patients received placebo on Day 1 of weeks 1, 2, 3, 5, 7, 9, 12, 15, 18 and 24, then every 6 weeks for up to 12 months following the first vaccination and then every 3 months until one of the criteria for study treatment discontinuation were met. After discontinuation of study treatment, patients were to be followed-up for survival every 3 months until death or loss to follow-up.

Reporting group values	CV9104	Placebo	Total
Number of subjects	137	63	200
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	38	19	57
From 65-84 years	96	43	139
85 years and over	3	1	4
Age continuous Units: years			
arithmetic mean	70.1	68.8	
standard deviation	± 8.28	± 8.34	-
Gender categorical Units: Subjects			
Female	0	0	0
Male	137	63	200
ECOG score			
ECOG (Eastern Cooperative Oncology Group) score			
Units: Subjects			
ECOG 0	107	45	152
ECOG 1	30	18	48
ECOG 2	0	0	0
ECOG 3	0	0	0

ECOG 4	0	0	0

End points

End points reporting groups

Reporting group title	CV9104

Reporting group description:

Phase I:
At Weeks 1, 2, and 3, each patient received open-label vaccinations of CV9104 at a starting total dose of 1920 µg (320 µg of each of the 6 components administered in 12 intradermal (ID) injections) using a standard 3 + 3 design. Patients were offered to continue treatment, and were included in the safety analysis for the phase II part of the trial.

Phase II:
Patients received CV9104 at 1920 µg at weeks 1, 2, 3, 5, 7, 9, 12, 15, 18 and 24, then every 6 weeks for up to 12 months (Week 54) after the first vaccination and then every 3 months thereafter until one of the criteria for study treatment discontinuation were met. After discontinuation of study treatment, patients were to be followed-up for survival every 3 months until death or loss to follow-up.

Reporting group title	Placebo

Reporting group description:

Patients received placebo on Day 1 of weeks 1, 2, 3, 5, 7, 9, 12, 15, 18 and 24, then every 6 weeks for up to 12 months following the first vaccination and then every 3 months until one of the criteria for study treatment discontinuation were met. After discontinuation of study treatment, patients were to be followed-up for survival every 3 months until death or loss to follow-up.

Subject analysis set title	ITT
Subject analysis set type	Intention-to-treat

Subject analysis set description:

The term 'intention-to-treat (ITT) analysis set' refers to all randomised patients. Patients were assigned to the randomised treatment groups, also in case a different treatment was actually given.

Subject analysis set title	Safety Analysis
Subject analysis set type	Safety analysis

Subject analysis set description:

The term 'safety analysis set' refers to patients who received at least 1 administration of study drug, including patients from safety lead-in phase. Patients without any post-baseline safety data were excluded from this analysis set.

Primary: Overall survival

End point title	Overall survival

End point description:

patients were censored at last date known alive

End point type	Primary

End point timeframe:

from randomization to death or end of study

End point values	CV9104	Placebo	ITT	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	134	63	197	
Units: months				
median (confidence interval 95%)	36.21 (28.39 to 43.01)	33.94 (28.65 to 40.25)	34.96 (30.72 to 39.49)	

Statistical analyses

Statistical analysis title	Adjusted Cox PH model

Statistical analysis description:

Cox proportional-hazards regression model

Comparison groups	CV9104 v Placebo
Number of subjects included in analysis	197
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	< 0.0985 [2]
Method	Wald test
Parameter estimate	Cox proportional hazard
Point estimate	0.942
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.623
upper limit	1.427
Variability estimate	Standard deviation

Notes:

[1] - The alternative hypothesis states that the treatment with CV9104 results in longer survival compared to treatment with placebo. The primary efficacy endpoint was analysed by a Cox proportional-hazards regression model with treatment and further explanatory variables.
[2] - The 1 sided significance level for the primary analysis was 0.0985 according to the specified group sequential design (one interim and one primary analysis). This ensured an overall type-I error of 0.1.

Secondary: Number of patients with TEAEs leading to discontinuation of study treatment

End point title	Number of patients with TEAEs leading to discontinuation of study treatment

End point description:

Number of patients with treatment-emergent adverse events (TEAEs) leading to discontinuation of study treatment

End point type	Secondary

End point timeframe:

from informed consent up to 30 days after last IMP administration

End point values	CV9104	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	137	62		
Units: patients	16	6		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of patients with TEAE of NCI-CTCAE Grade => 3

End point title	Number of patients with TEAE of NCI-CTCAE Grade => 3

End point description:

End point type	Secondary

End point timeframe:

from informed consent up to 30 days after last IMP administration

End point values	CV9104	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	137	62		
Units: patients	72	37		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of patients with serious related TEAEs

End point title	Number of patients with serious related TEAEs

End point description:

End point type	Secondary

End point timeframe:

from informed consent up to 30 days after last IMP administration

End point values	CV9104	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	137	62		
Units: patients	2	3		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of patients with adverse events of special interest (AESI)

End point title	Number of patients with adverse events of special interest (AESI)

End point description:

End point type	Secondary

End point timeframe:

from informed consent up to 30 days after last IMP administration

End point values	CV9104	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	137	62		
Units: patients				
Vaccine-Associated Flu-like Symptoms	93	25		
Injection Site Reactions	114	30		
Urinary Retention	15	5		
Urinary Infections	16	6		
Cardiac Events	16	9		
Bone-related Events	33	21		
Anaphylaxis/hypersensitivity incl. local reactions	20	9		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of patients with TEAEs leading to death

End point title	Number of patients with TEAEs leading to death

End point description:

End point type	Secondary

End point timeframe:

from informed consent up to 30 days after last IMP administration

End point values	CV9104	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	137	62		
Units: patients	10	5		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

from informed consent up to 30 days after last IMP administration

Adverse event reporting additional description:

Frequency tables show treatment emergent adverse events (TEAE), i.e. events that emerge during treatment, having been absent pre-treatment, or worsen relative to the pre-treatment state occurring within the specified timeframe.
Patients with more than one TEAE within the same PT are only counted once.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	15.1

Reporting groups

Reporting group title	Placebo

Reporting group description:

Placebo administered on Day 1 of weeks 1, 2, 3, 5, 7, 9, 12, 15, 18 and 24, then every 6 weeks for up to 12 months following the first vaccination and then every 3 months until one of the criteria for study treatment discontinuation is met.

Reporting group title	CV9104

Reporting group description:

CV9104 at 1920 µg (recommended dose determined by the IDMC based on safety lead-in) at weeks 1, 2, 3, 5, 7, 9, 12, 15, 18 and 24, then every 6 weeks for up to 12 months (Week 54) after the first vaccination and then every 3 months thereafter until one of the criteria for study treatment discontinuation are met

Serious adverse events	Placebo	CV9104	
Total subjects affected by serious adverse events			
subjects affected / exposed	27 / 62 (43.55%)	64 / 137 (46.72%)	
number of deaths (all causes)	41	75	
number of deaths resulting from adverse events	5	10	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
subjects affected / exposed	0 / 62 (0.00%)	2 / 137 (1.46%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bladder transitional cell carcinoma			
subjects affected / exposed	0 / 62 (0.00%)	1 / 137 (0.73%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant melanoma			

subjects affected / exposed	0 / 62 (0.00%)	1 / 137 (0.73%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to bone			
subjects affected / exposed	1 / 62 (1.61%)	1 / 137 (0.73%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mantle cell lymphoma			
subjects affected / exposed	1 / 62 (1.61%)	0 / 137 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostate cancer			
subjects affected / exposed	1 / 62 (1.61%)	3 / 137 (2.19%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 3	
Oesophageal carcinoma			
subjects affected / exposed	1 / 62 (1.61%)	0 / 137 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostate cancer metastatic			
subjects affected / exposed	1 / 62 (1.61%)	1 / 137 (0.73%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous cell carcinoma			
subjects affected / exposed	0 / 62 (0.00%)	1 / 137 (0.73%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour necrosis			
subjects affected / exposed	1 / 62 (1.61%)	0 / 137 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant pleural effusion			

subjects affected / exposed	1 / 62 (1.61%)	0 / 137 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	1 / 62 (1.61%)	0 / 137 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertension			
subjects affected / exposed	0 / 62 (0.00%)	1 / 137 (0.73%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Embolism			
subjects affected / exposed	0 / 62 (0.00%)	1 / 137 (0.73%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	0 / 62 (0.00%)	1 / 137 (0.73%)	
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	1 / 62 (1.61%)	0 / 137 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device occlusion			
subjects affected / exposed	0 / 62 (0.00%)	1 / 137 (0.73%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Disease progression			
subjects affected / exposed	1 / 62 (1.61%)	0 / 137 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	

Non-cardiac chest pain			
subjects affected / exposed	0 / 62 (0.00%)	1 / 137 (0.73%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical health deterioration			
subjects affected / exposed	1 / 62 (1.61%)	1 / 137 (0.73%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pain			
subjects affected / exposed	1 / 62 (1.61%)	0 / 137 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pyrexia			
subjects affected / exposed	1 / 62 (1.61%)	0 / 137 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sudden death			
subjects affected / exposed	0 / 62 (0.00%)	1 / 137 (0.73%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Death			
subjects affected / exposed	0 / 62 (0.00%)	1 / 137 (0.73%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Reproductive system and breast disorders			
Prostatic pain			
subjects affected / exposed	1 / 62 (1.61%)	0 / 137 (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			
Pulmonary embolism			

subjects affected / exposed	1 / 62 (1.61%)	1 / 137 (0.73%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	0 / 62 (0.00%)	1 / 137 (0.73%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Eastern Cooperative Oncology Group performance status worsened			
subjects affected / exposed	1 / 62 (1.61%)	0 / 137 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Arthropod sting			
subjects affected / exposed	1 / 62 (1.61%)	0 / 137 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone fissure			
subjects affected / exposed	0 / 62 (0.00%)	1 / 137 (0.73%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cervical vertebral fracture			
subjects affected / exposed	0 / 62 (0.00%)	2 / 137 (1.46%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Concussion			
subjects affected / exposed	0 / 62 (0.00%)	1 / 137 (0.73%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Contusion			
subjects affected / exposed	1 / 62 (1.61%)	0 / 137 (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	0 / 62 (0.00%)	1 / 137 (0.73%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Forearm fracture			
subjects affected / exposed	0 / 62 (0.00%)	1 / 137 (0.73%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pelvic fracture			
subjects affected / exposed	0 / 62 (0.00%)	1 / 137 (0.73%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural haemorrhage			
subjects affected / exposed	1 / 62 (1.61%)	0 / 137 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Radius fracture			
subjects affected / exposed	0 / 62 (0.00%)	1 / 137 (0.73%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tibia fracture			
subjects affected / exposed	0 / 62 (0.00%)	1 / 137 (0.73%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper limb fracture			
subjects affected / exposed	1 / 62 (1.61%)	0 / 137 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thoracic vertebral fracture			
subjects affected / exposed	1 / 62 (1.61%)	0 / 137 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Craniocerebral injury			

subjects affected / exposed	0 / 62 (0.00%)	1 / 137 (0.73%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Congenital, familial and genetic disorders			
Congenital spinal fusion			
subjects affected / exposed	0 / 62 (0.00%)	1 / 137 (0.73%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Cardiac arrest			
subjects affected / exposed	0 / 62 (0.00%)	1 / 137 (0.73%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Atrial fibrillation			
subjects affected / exposed	2 / 62 (3.23%)	0 / 137 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure acute			
subjects affected / exposed	1 / 62 (1.61%)	0 / 137 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			
subjects affected / exposed	1 / 62 (1.61%)	3 / 137 (2.19%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
Myocardial infarction			
subjects affected / exposed	1 / 62 (1.61%)	1 / 137 (0.73%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiovascular insufficiency			
subjects affected / exposed	0 / 62 (0.00%)	1 / 137 (0.73%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	

Tachyarrhythmia			
subjects affected / exposed	0 / 62 (0.00%)	1 / 137 (0.73%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Embolic stroke			
subjects affected / exposed	0 / 62 (0.00%)	1 / 137 (0.73%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Convulsion			
subjects affected / exposed	0 / 62 (0.00%)	1 / 137 (0.73%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paraparesis			
subjects affected / exposed	1 / 62 (1.61%)	0 / 137 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Quadriparesis			
subjects affected / exposed	0 / 62 (0.00%)	1 / 137 (0.73%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sciatica			
subjects affected / exposed	0 / 62 (0.00%)	1 / 137 (0.73%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	2 / 62 (3.23%)	3 / 137 (2.19%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal cord compression			
subjects affected / exposed	1 / 62 (1.61%)	1 / 137 (0.73%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Trigeminal neuralgia			

subjects affected / exposed	1 / 62 (1.61%)	0 / 137 (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			
Anaemia			
subjects affected / exposed	1 / 62 (1.61%)	4 / 137 (2.92%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 1	
Agranulocytosis			
subjects affected / exposed	1 / 62 (1.61%)	0 / 137 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhagic diathesis			
subjects affected / exposed	0 / 62 (0.00%)	1 / 137 (0.73%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Febrile neutropenia			
subjects affected / exposed	1 / 62 (1.61%)	1 / 137 (0.73%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukopenia			
subjects affected / exposed	0 / 62 (0.00%)	1 / 137 (0.73%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	1 / 62 (1.61%)	1 / 137 (0.73%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 62 (0.00%)	1 / 137 (0.73%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			

Cataract			
subjects affected / exposed	0 / 62 (0.00%)	1 / 137 (0.73%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 62 (0.00%)	1 / 137 (0.73%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspepsia			
subjects affected / exposed	1 / 62 (1.61%)	0 / 137 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			
subjects affected / exposed	0 / 62 (0.00%)	1 / 137 (0.73%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal toxicity			
subjects affected / exposed	0 / 62 (0.00%)	1 / 137 (0.73%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterovesical fistula			
subjects affected / exposed	1 / 62 (1.61%)	0 / 137 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Proctitis haemorrhagic			
subjects affected / exposed	1 / 62 (1.61%)	0 / 137 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Proctalgia			
subjects affected / exposed	1 / 62 (1.61%)	0 / 137 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal haemorrhage			

subjects affected / exposed	0 / 62 (0.00%)	1 / 137 (0.73%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subileus			
subjects affected / exposed	0 / 62 (0.00%)	2 / 137 (1.46%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal obstruction			
subjects affected / exposed	1 / 62 (1.61%)	0 / 137 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysphagia			
subjects affected / exposed	1 / 62 (1.61%)	0 / 137 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestine perforation			
subjects affected / exposed	0 / 62 (0.00%)	1 / 137 (0.73%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Bile duct stenosis			
subjects affected / exposed	0 / 62 (0.00%)	1 / 137 (0.73%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	1 / 62 (1.61%)	0 / 137 (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			
Haematuria			
subjects affected / exposed	1 / 62 (1.61%)	3 / 137 (2.19%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	

Dysuria			
subjects affected / exposed	1 / 62 (1.61%)	0 / 137 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hydronephrosis			
subjects affected / exposed	1 / 62 (1.61%)	5 / 137 (3.65%)	
occurrences causally related to treatment / all	0 / 1	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			
subjects affected / exposed	0 / 62 (0.00%)	2 / 137 (1.46%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephrolithiasis			
subjects affected / exposed	0 / 62 (0.00%)	1 / 137 (0.73%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure acute			
subjects affected / exposed	2 / 62 (3.23%)	1 / 137 (0.73%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal impairment			
subjects affected / exposed	0 / 62 (0.00%)	1 / 137 (0.73%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary retention			
subjects affected / exposed	0 / 62 (0.00%)	6 / 137 (4.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract obstruction			
subjects affected / exposed	0 / 62 (0.00%)	1 / 137 (0.73%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			

Adrenocortical insufficiency acute			
subjects affected / exposed	1 / 62 (1.61%)	0 / 137 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	2 / 62 (3.23%)	2 / 137 (1.46%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone pain			
subjects affected / exposed	0 / 62 (0.00%)	2 / 137 (1.46%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoarthritis			
subjects affected / exposed	0 / 62 (0.00%)	1 / 137 (0.73%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lumbar spinal stenosis			
subjects affected / exposed	1 / 62 (1.61%)	0 / 137 (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 / 62 (0.00%)	1 / 137 (0.73%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Bronchitis			
subjects affected / exposed	0 / 62 (0.00%)	1 / 137 (0.73%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulitis			
subjects affected / exposed	0 / 62 (0.00%)	1 / 137 (0.73%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Erysipelas			
subjects affected / exposed	1 / 62 (1.61%)	0 / 137 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	1 / 62 (1.61%)	0 / 137 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gingival abscess			
subjects affected / exposed	0 / 62 (0.00%)	1 / 137 (0.73%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	1 / 62 (1.61%)	1 / 137 (0.73%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Urosepsis			
subjects affected / exposed	1 / 62 (1.61%)	4 / 137 (2.92%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 1	0 / 0	
Urinary tract infection			
subjects affected / exposed	2 / 62 (3.23%)	1 / 137 (0.73%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound infection			
subjects affected / exposed	1 / 62 (1.61%)	0 / 137 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abscess intestinal			
subjects affected / exposed	0 / 62 (0.00%)	1 / 137 (0.73%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			

Dehydration			
subjects affected / exposed	1 / 62 (1.61%)	1 / 137 (0.73%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetes mellitus			
subjects affected / exposed	1 / 62 (1.61%)	1 / 137 (0.73%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			
subjects affected / exposed	1 / 62 (1.61%)	0 / 137 (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	0 / 62 (0.00%)	1 / 137 (0.73%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
subjects affected / exposed	0 / 62 (0.00%)	1 / 137 (0.73%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Placebo	CV9104	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	60 / 62 (96.77%)	137 / 137 (100.00%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	9 / 62 (14.52%)	21 / 137 (15.33%)	
occurrences (all)	9	21	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	4 / 62 (6.45%)	17 / 137 (12.41%)	
occurrences (all)	4	17	

Fatigue			
subjects affected / exposed	18 / 62 (29.03%)	34 / 137 (24.82%)	
occurrences (all)	18	34	
Chills			
subjects affected / exposed	1 / 62 (1.61%)	25 / 137 (18.25%)	
occurrences (all)	1	25	
Influenza like illness			
subjects affected / exposed	8 / 62 (12.90%)	34 / 137 (24.82%)	
occurrences (all)	8	34	
Injection site erythema			
subjects affected / exposed	25 / 62 (40.32%)	108 / 137 (78.83%)	
occurrences (all)	25	108	
Injection site pruritus			
subjects affected / exposed	1 / 62 (1.61%)	24 / 137 (17.52%)	
occurrences (all)	1	24	
Injection site rash			
subjects affected / exposed	3 / 62 (4.84%)	9 / 137 (6.57%)	
occurrences (all)	3	9	
Pyrexia			
subjects affected / exposed	6 / 62 (9.68%)	52 / 137 (37.96%)	
occurrences (all)	6	52	
Injection site pain			
subjects affected / exposed	3 / 62 (4.84%)	10 / 137 (7.30%)	
occurrences (all)	3	10	
Oedema peripheral			
subjects affected / exposed	11 / 62 (17.74%)	19 / 137 (13.87%)	
occurrences (all)	11	19	
Spinal pain			
subjects affected / exposed	1 / 62 (1.61%)	12 / 137 (8.76%)	
occurrences (all)	1	12	
General physical health deterioration			
subjects affected / exposed	1 / 62 (1.61%)	9 / 137 (6.57%)	
occurrences (all)	1	9	
Reproductive system and breast disorders			

Pelvic pain			
subjects affected / exposed	1 / 62 (1.61%)	10 / 137 (7.30%)	
occurrences (all)	1	10	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	4 / 62 (6.45%)	13 / 137 (9.49%)	
occurrences (all)	4	13	
Dyspnoea			
subjects affected / exposed	4 / 62 (6.45%)	6 / 137 (4.38%)	
occurrences (all)	4	6	
Psychiatric disorders			
Depression			
subjects affected / exposed	4 / 62 (6.45%)	5 / 137 (3.65%)	
occurrences (all)	4	5	
Investigations			
Blood creatinine increased			
subjects affected / exposed	2 / 62 (3.23%)	7 / 137 (5.11%)	
occurrences (all)	2	7	
C-reactive protein increased			
subjects affected / exposed	1 / 62 (1.61%)	7 / 137 (5.11%)	
occurrences (all)	1	7	
Weight decreased			
subjects affected / exposed	5 / 62 (8.06%)	11 / 137 (8.03%)	
occurrences (all)	5	11	
Eastern Cooperative Oncology Group performance status worsened			
subjects affected / exposed	1 / 62 (1.61%)	7 / 137 (5.11%)	
occurrences (all)	1	7	
Nervous system disorders			
Dizziness			
subjects affected / exposed	3 / 62 (4.84%)	11 / 137 (8.03%)	
occurrences (all)	3	11	
Headache			
subjects affected / exposed	3 / 62 (4.84%)	7 / 137 (5.11%)	
occurrences (all)	3	7	
Blood and lymphatic system disorders			

Neutropenia			
subjects affected / exposed	4 / 62 (6.45%)	6 / 137 (4.38%)	
occurrences (all)	4	6	
Anaemia			
subjects affected / exposed	7 / 62 (11.29%)	11 / 137 (8.03%)	
occurrences (all)	7	11	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	8 / 62 (12.90%)	15 / 137 (10.95%)	
occurrences (all)	8	15	
Nausea			
subjects affected / exposed	9 / 62 (14.52%)	21 / 137 (15.33%)	
occurrences (all)	9	21	
Vomiting			
subjects affected / exposed	5 / 62 (8.06%)	8 / 137 (5.84%)	
occurrences (all)	5	8	
Constipation			
subjects affected / exposed	6 / 62 (9.68%)	9 / 137 (6.57%)	
occurrences (all)	6	9	
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	2 / 62 (3.23%)	9 / 137 (6.57%)	
occurrences (all)	2	9	
Nocturia			
subjects affected / exposed	2 / 62 (3.23%)	7 / 137 (5.11%)	
occurrences (all)	2	7	
Musculoskeletal and connective tissue disorders			
Bone pain			
subjects affected / exposed	21 / 62 (33.87%)	27 / 137 (19.71%)	
occurrences (all)	21	27	
Back pain			
subjects affected / exposed	11 / 62 (17.74%)	33 / 137 (24.09%)	
occurrences (all)	11	33	
Arthralgia			
subjects affected / exposed	12 / 62 (19.35%)	28 / 137 (20.44%)	
occurrences (all)	12	28	

Musculoskeletal chest pain			
subjects affected / exposed	5 / 62 (8.06%)	12 / 137 (8.76%)	
occurrences (all)	5	12	
Pain in extremity			
subjects affected / exposed	9 / 62 (14.52%)	20 / 137 (14.60%)	
occurrences (all)	9	20	
Groin pain			
subjects affected / exposed	5 / 62 (8.06%)	3 / 137 (2.19%)	
occurrences (all)	5	3	
Musculoskeletal pain			
subjects affected / exposed	8 / 62 (12.90%)	10 / 137 (7.30%)	
occurrences (all)	8	10	
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	6 / 62 (9.68%)	15 / 137 (10.95%)	
occurrences (all)	6	15	
Nasopharyngitis			
subjects affected / exposed	4 / 62 (6.45%)	13 / 137 (9.49%)	
occurrences (all)	4	13	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	3 / 62 (4.84%)	10 / 137 (7.30%)	
occurrences (all)	3	10	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
22 May 2012	• Exclusion criterion No. 11 was modified to include the allergies to any study drug component. • Exclusion criterion No. 17 was modified to include severe hypertension according to the WHO criteria. • Exclusion criterion No. 13 was revised to include "clinically relevant urinary retention/hydronephrosis requiring treatment by ultrasound or other appropriate imaging method". • Week 12 blood sample collection timepoint was deleted from the immunological assessments and biomarker and circulating tumour cell assessments and Week 12 assessment was removed from definition and analysis sections of tertiary efficacy endpoints. • New text was added in study design to explain the similarity that the vaccination schedule in both Phase I and II for patients treated in the safety lead-in (Phase I) portion is identical to the schedule to be applied in the randomised portion (Phase II). • The Schedule of Assessments was revised. • A figure for vaccination schedules for Phase II was added. • Added to Safety Lead-in-portion (Phase I): o Treatment with study drug will initially be administered in Weeks 1, 2 and 3. In case no DLTs will be observed, the patients can continue vaccinations in Weeks 5, 7, 9, 12, 15, 18 and 24, then every 6 weeks for up to 12 months after the first vaccination and then every 3 months thereafter until one of the criteria for study treatment discontinuation is met. o During the Safety Lead-in portion, patients will initially receive 3 vaccinations in Weeks 1, 2 and 3. Patients will be monitored for adverse events and DLT evaluation will take place in Week 4. o Following the DLT observation period (Week 4), safety lead-in patients may continue to receive CV9104 in Weeks 5, 7, 9, 12, 15, 18 and 24, then every 6 weeks for up to 12 months after the first vaccination and then every 3 months thereafter until one of the criteria for study treatment discontinuation is met.
09 April 2013	• Inclusion criterion No. 2 modified: rephrased to clarify that patients who have received combined androgen blockade followed by anti-androgen withdrawal as second-line anti hormonal manipulation may be included in the trial / confirmation of progression by elevations of PSA was further specified to clarify that an anti-androgen withdrawal response must have been excluded after discontinuation of anti-androgen therapy only in patients having received initial combined androgen blockade or have shown a decline in PSA for ≥3 months after administration of an anti-androgen. • Per request from the Swedish competent authority (MPA): Inclusion criterion No. 7 was amended to follow the ICH (M3) guidelines concerning contraception aimed at prevention with high efficiency (risk according to Pearl Index <1) / Exclusion criterion No. 3 was modified / Exclusion criterion No. 12 (allergies to penicillins or other β-lactam antibiotics) was added due to the fact that ampicillin is used during the production process of RNActive / Exclusion criterion No. 15 was modified to include hydronephrosis / EOT criterion was added to exclude patients with active HIV or hepatitis B or C infection / observation period after administration in the randomised portion was extended to 2 hours following the first 3 vaccinations / statement clarifying the adequate treatment of urinary retention was added. • Per request from a Swiss EC, the process of publication of individual study data was amended. • Exclusion criterion No. 13 was modified to specify the applicable timepoint. • Exclusion criterion No. 5 was expanded to the exclusion of any immunomodulating agents including herbal remedies. • The blinding and unblinding process was modified to clarify the process of unblinding and avoid misunderstanding. • Definitions of secondary endpoints were further clarified.

09 June 2015	• Secondary objectives were updated to include comparison of combined progression free survival (S-PFS) between CV9104 and placebo groups and to exclude comparison of circulating tumour cells frequencies. • Secondary endpoints were updated: / included AEs of special interest / "NCI-CTCAE toxicity Grades ≥3" added for laboratory summaries / efficacy endpoint "Overall progression-free survival, radiographic progression-free survival and PSA progression-free survival from randomisation to second progression (S-PFS)" was added / endpoints to assess the effect of CV9104 treatment on circulating tumour cells frequencies were removed / humoral immune response rates was adapted to include response rates against all RNActive encoded antigens / Overall immune response rates against the 6 RNActive-encoded antigens added / time to symptom progression added / EQ-5D questionnaire: calculation of area under the curve (AUC) was added / Removal of absolute change from baseline of FACT-P total score and subscores. • EOT section was amended in order to specify how patients were to be treated in the case of unblinding the study. • Definition of the end of the study was updated. • Clarification for analysis of the primary and key secondary clinical endpoints based on PP and mITT sets in efficacy analysis section. • Covariates and the model building of the multivariate Cox regression approach were changed for analysis of primary endpoint. • Subgroup analyses: clarified that subgroup analysis was to be performed on the ITT set only for OS, PFS1, PFS2 and S-PFS. • Safety assessments section was updated to include analyses of TEAEs and additional safety variables (e.g., AESIs).
11 April 2016	• Changed the text regarding the storage of non-reconstituted CV9104 to reflect the storage conditions for all the study drug kits used in the study. • Editorial changes

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported