



Clinical trial results:

An open label Randomised Phase II Trial of RNaActive® Cancer Vaccine (CV9104) in high risk and intermediate risk patients with prostate cancer Summary

EudraCT number	2013-004489-32
Trial protocol	DE
Global end of trial date	12 April 2016

Results information

Result version number	v1 (current)
This version publication date	18 November 2017
First version publication date	18 November 2017

Trial information

Trial identification

Sponsor protocol code	CV-9104-007
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
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, 0049 707198830, info@curevac.com
Scientific contact	Clinical trials Information, CureVac AG, 0049 707198830, info@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	05 September 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	12 April 2016
Global end of trial reached?	Yes
Global end of trial date	12 April 2016
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

Evaluation of induction of immune responses against 6 tumor antigens encoded by CV9104 administered by conventional intradermal injection or with a needle-free intradermal injection device.

Protection of trial subjects:

The investigators and all parties involved in this study conducted the study in adherence to the ethical principles based on the Declaration of Helsinki, the German Act on Medical Devices (Medizinproduktegesetz), International Council for Harmonisation (ICH), Good Clinical Practice guidelines, and the applicable national and local laws and regulatory requirements.

The investigator ensured that no subject underwent any study-related examination or activity before giving written informed consent to participate in the study. The investigator informed the subject of the objectives, methods, anticipated benefits and potential risks, and inconveniences of the study. The subject was given opportunity to ask for clarification of any points he did not understand and if necessary, ask for more information. At the end of the interview, the subject was given ample time to come to a decision.

Insurance coverage for all participating subjects was guaranteed according to applicable legal requirements.

Only subjects that met all study inclusion criteria and none of the exclusion criteria were entered in the study. A subject could withdraw his consent to participate in the study at any time without prejudice.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 February 2014
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 48
Worldwide total number of subjects	48
EEA total number of subjects	48

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)	17
From 65 to 84 years	31
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Subjects were enrolled at 3 centers in Germany. The first subject signed the informed consent form on 23-Jun-2014 and the last subject on 12-Nov-2015.

A total of 48 subjects were randomized out of which 46 were evaluable for their immune responder status.

Pre-assignment

Screening details:

53 subjects were screened, of whom 5 subjects were screening failures because they did not meet the eligibility criteria for the study.

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Arm A

Arm description:

Subjects in Arm A received 4 administrations of CV9104 with the needle-free intradermal injection device (Tropis®) in Weeks 1, 2, 3, and 5 and underwent radical prostatectomy at least 1 week but not later than 2 weeks after the 4th administration (Week 6 or 7).

After surgery, subjects with a confirmed histopathological diagnosis of high risk or very high risk prostate cancer, were offered to receive 2 additional booster administrations of CV9104 starting 8 weeks after surgery (± 1 week) with a 2-week interval.

Arm type	Experimental
Investigational medicinal product name	CV9104
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection in needle-free injector
Routes of administration	Intradermal use

Dosage and administration details:

Subjects received 4 administrations of CV9104 by needle-free intradermal injection. After radical prostatectomy, subjects with high risk or very high risk prostate cancer, were offered to receive 2 additional administrations of CV9104.

One administration with CV9104 included a total of 12 intradermal injections (2 separate injections per individual CV9104 mRNA component) distributed over the 4 limbs (3 injections in each upper arm and thigh). The total dose of CV9104 per administration was 960 μ g mRNA with 80 μ g mRNA per injection (160 μ g per CV9104 mRNA component).

Arm title	Arm B
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Arm description:

Subjects in Arm B received 4 administrations of CV9104 by conventional intradermal injection in Weeks 1, 2, 3, and 5 and underwent radical prostatectomy at least 1 week but not later than 2 weeks after the 4th administration (Week 6 or 7).

After surgery, subjects with a confirmed histopathological diagnosis of high risk or very high risk prostate cancer, were offered to receive 2 additional booster administrations of CV9104 starting 8 weeks after surgery (± 1 week) with a 2-week interval.

Arm type	Experimental
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Investigational medicinal product name	CV9104
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intradermal use

Dosage and administration details:

Subjects received 4 administrations of CV9104 by conventional intradermal injection. After radical prostatectomy, subjects with high risk or very high risk prostate cancer, were offered to receive 2 additional administrations of CV9104.

One administration with CV9104 included a total of 12 intradermal injections (2 separate injections per individual CV9104 mRNA component) distributed over the 4 limbs (3 injections in each upper arm and thigh). The total dose of CV9104 per administration was 1920 µg mRNA with 160 µg mRNA per injection (320 µg per CV9104 mRNA component).

Arm title	Arm C
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Arm description:

Subjects did not receive any study treatment before the radical prostatectomy.

Subjects with histopathologically confirmed high risk or very high risk disease could receive 6 optional administrations of CV9104 (960 µg mRNA per administration) by needle-free intradermal injection with the Tropis® device 8, 9, 10, 12, 14 and 16 weeks after surgery.

Arm type	No intervention
No investigational medicinal product assigned in this arm	

Number of subjects in period 1	Arm A	Arm B	Arm C
Started	15	17	16
Completed	14	16	16
Not completed	1	1	0
Consent withdrawn by subject	1	-	-
Adverse event, non-fatal	-	1	-

Baseline characteristics

Reporting groups

Reporting group title	Arm A
Reporting group description:	
Subjects in Arm A received 4 administrations of CV9104 with the needle-free intradermal injection device (Tropis®) in Weeks 1, 2, 3, and 5 and underwent radical prostatectomy at least 1 week but not later than 2 weeks after the 4th administration (Week 6 or 7). After surgery, subjects with a confirmed histopathological diagnosis of high risk or very high risk prostate cancer, were offered to receive 2 additional booster administrations of CV9104 starting 8 weeks after surgery (± 1 week) with a 2-week interval.	
Reporting group title	Arm B
Reporting group description:	
Subjects in Arm B received 4 administrations of CV9104 by conventional intradermal injection in Weeks 1, 2, 3, and 5 and underwent radical prostatectomy at least 1 week but not later than 2 weeks after the 4th administration (Week 6 or 7). After surgery, subjects with a confirmed histopathological diagnosis of high risk or very high risk prostate cancer, were offered to receive 2 additional booster administrations of CV9104 starting 8 weeks after surgery (± 1 week) with a 2-week interval.	
Reporting group title	Arm C
Reporting group description:	
Subjects did not receive any study treatment before the radical prostatectomy. Subjects with histopathologically confirmed high risk or very high risk disease could receive 6 optional administrations of CV9104 (960 µg mRNA per administration) by needle-free intradermal injection with the Tropis® device 8, 9, 10, 12, 14 and 16 weeks after surgery.	

Reporting group values	Arm A	Arm B	Arm C
Number of subjects	15	17	16
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)	6	8	3
From 65-84 years	9	9	13
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	65.6	63.8	67.5
standard deviation	± 6.3	± 7	± 3
Gender categorical Units: Subjects			
Female	0	0	0
Male	15	17	16

Reporting group values	Total		
Number of subjects	48		

Age categorical			
Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	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)	17		
From 65-84 years	31		
85 years and over	0		
Age continuous			
Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical			
Units: Subjects			
Female	0		
Male	48		

End points

End points reporting groups

Reporting group title	Arm A
Reporting group description: Subjects in Arm A received 4 administrations of CV9104 with the needle-free intradermal injection device (Tropis®) in Weeks 1, 2, 3, and 5 and underwent radical prostatectomy at least 1 week but not later than 2 weeks after the 4th administration (Week 6 or 7). After surgery, subjects with a confirmed histopathological diagnosis of high risk or very high risk prostate cancer, were offered to receive 2 additional booster administrations of CV9104 starting 8 weeks after surgery (± 1 week) with a 2-week interval.	
Reporting group title	Arm B
Reporting group description: Subjects in Arm B received 4 administrations of CV9104 by conventional intradermal injection in Weeks 1, 2, 3, and 5 and underwent radical prostatectomy at least 1 week but not later than 2 weeks after the 4th administration (Week 6 or 7). After surgery, subjects with a confirmed histopathological diagnosis of high risk or very high risk prostate cancer, were offered to receive 2 additional booster administrations of CV9104 starting 8 weeks after surgery (± 1 week) with a 2-week interval.	
Reporting group title	Arm C
Reporting group description: Subjects did not receive any study treatment before the radical prostatectomy. Subjects with histopathologically confirmed high risk or very high risk disease could receive 6 optional administrations of CV9104 (960 µg mRNA per administration) by needle-free intradermal injection with the Tropis® device 8, 9, 10, 12, 14 and 16 weeks after surgery.	

Primary: Overall immune responders at any post-baseline time point

End point title	Overall immune responders at any post-baseline time point ^[1]
End point description: An overall immune responder (OIR) at any post-baseline time point was a subject being an OIR to at least 1 of the antigens in at least 1 of the analytical methods used (enzyme-linked immunosorbent assay [ELISA], enzyme-linked immunospot assay [ELISpot], intracellular cytokine staining [ICS]) at any of the post-baseline time points (pre-surgical Week [PreS W] or post-surgical Week 8 [PostS W8], but also PreS W and PostS W8).	
End point type	Primary
End point timeframe: Post-baseline time points: 1 week after the 4th CV9104 treatment (before prostatectomy) and 8 weeks after prostatectomy (Arms A and B) or 1 week before and 8 weeks after the prostatectomy (Arm C).	
Notes: [1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point. Justification: No statistical analysis was planned in the protocol.	

End point values	Arm A	Arm B	Arm C	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	14	16	16	
Units: Subjects	12	12	12	

Statistical analyses

No statistical analyses for this end point

Primary: Cellular immune responders at any post-baseline time point

End point title	Cellular immune responders at any post-baseline time point ^[2]
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End point description:

A cellular immune responder (CIR) at any post-baseline time point was a subject being a CIR to at least 1 of the antigens in at least 1 of the analytical methods used for measuring cellular immune responses (ELISpot, ICS) at any of the post-baseline time points (PreS W or PostS W8, but also PreS W and PostS W8).

End point type	Primary
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End point timeframe:

Post-baseline time points: 1 week after the 4th CV9104 treatment (before prostatectomy) and 8 weeks after prostatectomy (Arms A and B) or 1 week before and 8 weeks after the prostatectomy (Arm C).

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No statistical analysis was planned in the protocol.

End point values	Arm A	Arm B	Arm C	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	13	16	16	
Units: subjects	10	8	7	

Statistical analyses

No statistical analyses for this end point

Primary: Humoral immune responders at any post-baseline time point

End point title	Humoral immune responders at any post-baseline time point ^[3]
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End point description:

A humoral immune responder (HIR) at any post-baseline time point was a subject being an HIR with either antigen specific IgG and/or IgM antibodies to at least 1 of the antigens at any of the post-baseline time points (PreS W or PostS W8, but also PreS W and PostS W8).

End point type	Primary
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End point timeframe:

Post-baseline time points: 1 week after the 4th CV9104 treatment (before prostatectomy) and 8 weeks after prostatectomy (Arms A and B) or 1 week before and 8 weeks after the prostatectomy (Arm C).

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No statistical analysis was planned in the protocol.

End point values	Arm A	Arm B	Arm C	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	14	16	16	
Units: subjects	3	7	7	

Statistical analyses

No statistical analyses for this end point

Primary: CD4+ T-cell responders at any post-baseline time point

End point title	CD4+ T-cell responders at any post-baseline time point ^[4]
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End point description:

A CD4+ T-cell responder was a subject considered an immune responder (IR) in the ICS assay measuring CV9104 antigen-specific CD4+ T-cells.

End point type	Primary
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End point timeframe:

Post-baseline time points: 1 week after the 4th CV9104 treatment (before prostatectomy) and 8 weeks after prostatectomy (Arms A and B) or 1 week before and 8 weeks after the prostatectomy (Arm C).

Notes:

[4] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No statistical analysis was planned in the protocol.

End point values	Arm A	Arm B	Arm C	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	12	15	16	
Units: subjects	3	1	2	

Statistical analyses

No statistical analyses for this end point

Primary: CD8+ T-cell responders at any post-baseline time point

End point title	CD8+ T-cell responders at any post-baseline time point ^[5]
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End point description:

A CD8+ T-cell responder was a subject considered an IR in the ICS assay measuring CV9104 antigen-specific CD8+ T-cells.

End point type	Primary
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End point timeframe:

Post-baseline time points: 1 week after the 4th CV9104 treatment (before prostatectomy) and 8 weeks after prostatectomy (Arms A and B) or 1 week before and 8 weeks after the prostatectomy (Arm C).

Notes:

[5] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No statistical analysis was planned in the protocol.

End point values	Arm A	Arm B	Arm C	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	12	15	16	
Units: subjects	8	7	4	

Statistical analyses

No statistical analyses for this end point

Primary: Humoral immune responders with antigen specific IgM antibodies at any post-baseline time point

End point title	Humoral immune responders with antigen specific IgM antibodies at any post-baseline time point ^[6]
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End point description:

A subject being an HIR with antigen specific immunoglobulin M [IgM] antibodies measured via ELISA at any of the post-baseline time points (PreS W or PostS W8, but also PreS W and PostS W8).

End point type	Primary
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End point timeframe:

Post-baseline time points: 1 week after the 4th CV9104 treatment (before prostatectomy) and 8 weeks after prostatectomy (Arms A and B) or 1 week before and 8 weeks after the prostatectomy (Arm C).

Notes:

[6] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No statistical analysis was planned in the protocol.

End point values	Arm A	Arm B	Arm C	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	14	16	16	
Units: subjects	3	4	1	

Statistical analyses

No statistical analyses for this end point

Primary: Humoral immune responders with antigen specific IgG antibodies at any post-baseline time point

End point title	Humoral immune responders with antigen specific IgG antibodies at any post-baseline time point ^[7]
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End point description:

A subject being an HIR with antigen specific immunoglobulin G [IgG] antibodies measured via ELISA at any of the post-baseline time points (PreS W or PostS W8, but also PreS W and PostS W8).

End point type	Primary
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End point timeframe:

Post-baseline time points: 1 week after the 4th CV9104 treatment (before prostatectomy) and 8 weeks after prostatectomy (Arms A and B) or 1 week before and 8 weeks after the prostatectomy (Arm C).

Notes:

[7] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No statistical analysis was planned in the protocol.

End point values	Arm A	Arm B	Arm C	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	14	16	16	
Units: subjects	2	4	7	

Statistical analyses

No statistical analyses for this end point

Secondary: Change in prostate-specific antigen, pre-surgery

End point title	Change in prostate-specific antigen, pre-surgery
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End point description:

End point type	Secondary
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End point timeframe:

Change from Week 1 (Baseline) to Week 6 (Arms A and B) or within 1 week prior to surgery (Arm C).
The radical prostatectomy was performed in Weeks 6-7 in Arms A and B and in Weeks 4-7 in Arm C.

End point values	Arm A	Arm B	Arm C	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	14	16	16	
Units: µg/L				
arithmetic mean (standard deviation)	0.58 (± 2.771)	0.07 (± 1.332)	-0.44 (± 3.326)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change in prostate-specific antigen, post-surgery

End point title	Change in prostate-specific antigen, post-surgery
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End point description:

End point type	Secondary
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End point timeframe:

Change from Week 8 post-surgery to End of Study visit.

End point values	Arm A	Arm B	Arm C	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	14	13	15	
Units: µg/L				
arithmetic mean (standard deviation)	0.02 (± 0.088)	0.16 (± 0.55)	0.02 (± 0.051)	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with treatment-emergent adverse events (TEAEs)

End point title	Number of subjects with treatment-emergent adverse events (TEAEs)
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End point description:

End point type	Secondary
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End point timeframe:

From the date of first CV9104 administration (Arms A and B) or the date of randomization (Arm C) until 28 days after the last CV9104 dose or 12 weeks after surgery (if no CV9104 administered at all or post-surgically)

End point values	Arm A	Arm B	Arm C	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	14	17	16	
Units: subjects				
Any TEAE	14	17	16	
Pre-surgery TEAEs	14	17	6	
Post-surgery TEAEs	10	15	16	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with related TEAEs

End point title	Number of subjects with related TEAEs
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End point description:

End point type	Secondary
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End point timeframe:

From the date of first CV9104 administration (Arms A and B) or the date of randomization (Arm C) until 28 days after the last CV9104 dose or 12 weeks after surgery (if no CV9104 administered at all or post-surgically)

End point values	Arm A	Arm B	Arm C	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	14	17	16	
Units: subjects				
CV9104-related TEAEs	14	17	6	
Procedure-related TEAEs	14	16	7	
Device-related TEAEs	4	5	3	
Prostatectomy-related TEAEs	10	13	13	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with TEAEs of CTCAE Grade 3 or higher

End point title	Number of subjects with TEAEs of CTCAE Grade 3 or higher
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End point description:

End point type	Secondary
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End point timeframe:

From the date of first CV9104 administration (Arms A and B) or the date of randomization (Arm C) until 28 days after the last CV9104 dose or 12 weeks after surgery (if no CV9104 administered at all or post-surgically)

End point values	Arm A	Arm B	Arm C	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	14	17	16	
Units: subjects				
Any TEAE	3	5	3	
CV9104-related TEAEs	0	0	0	
Prostatectomy-related TEAEs	3	4	1	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with treatment-emergent serious adverse events

End point title	Number of subjects with treatment-emergent serious adverse events
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End point description:

End point type	Secondary
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End point timeframe:

From the date of first CV9104 administration (Arms A and B) or the date of randomization (Arm C) until 28 days after the last CV9104 dose or 12 weeks after surgery (if no CV9104 administered at all or post-surgically)

End point values	Arm A	Arm B	Arm C	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	14	17	16	
Units: subjects				
Any SAE	2	3	5	
Post-surgery SAEs	2	3	5	
Prostatectomy-related SAEs	2	3	3	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with TEAEs leading to permanent discontinuation of study treatment

End point title	Number of subjects with TEAEs leading to permanent discontinuation of study treatment
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End point description:

End point type	Secondary
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End point timeframe:

From the date of first CV9104 administration (Arms A and B) or the date of randomization (Arm C) until 28 days after the last CV9104 dose or 12 weeks after surgery (if no CV9104 administered at all or post-surgically)

End point values	Arm A	Arm B	Arm C	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	14	17	16	
Units: subjects	0	1	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with TEAEs leading to death

End point title	Number of subjects with TEAEs leading to death
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End point description:

End point type	Secondary
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End point timeframe:

From the date of first CV9104 administration (Arms A and B) or the date of randomization (Arm C) until 28 days after the last CV9104 dose or 12 weeks after surgery (if no CV9104 administered at all or post-surgically)

End point values	Arm A	Arm B	Arm C	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	14	17	16	
Units: subjects	0	0	0	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the date of first CV9104 administration (Arms A and B) or the date of randomization (Arm C) (= treatment-emergent adverse events) until 28 days after the last CV9104 dose or 12 weeks after surgery (if no CV9104 administered at all or post-surgically)

Assessment type	Non-systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	17
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Reporting groups

Reporting group title	Arm A
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Reporting group description: -	
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Reporting group title	Arm B
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Reporting group description: -	
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Reporting group title	Arm C
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Reporting group description: -	
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Serious adverse events	Arm A	Arm B	Arm C
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 14 (14.29%)	3 / 17 (17.65%)	5 / 16 (31.25%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Acral lentiginous melanoma			
subjects affected / exposed	0 / 14 (0.00%)	0 / 17 (0.00%)	1 / 16 (6.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Post procedural haemorrhage			
subjects affected / exposed	0 / 14 (0.00%)	1 / 17 (5.88%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	0 / 14 (0.00%)	1 / 17 (5.88%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Lymphocele			
subjects affected / exposed	1 / 14 (7.14%)	3 / 17 (17.65%)	2 / 16 (12.50%)
occurrences causally related to treatment / all	0 / 1	0 / 3	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	0 / 14 (0.00%)	1 / 17 (5.88%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Transient ischaemic attack			
subjects affected / exposed	1 / 14 (7.14%)	0 / 17 (0.00%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Systemic inflammatory response syndrome			
subjects affected / exposed	0 / 14 (0.00%)	1 / 17 (5.88%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peritonitis			
subjects affected / exposed	0 / 14 (0.00%)	1 / 17 (5.88%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Ileus			
subjects affected / exposed	0 / 14 (0.00%)	1 / 17 (5.88%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	0 / 14 (0.00%)	0 / 17 (0.00%)	1 / 16 (6.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary retention			

subjects affected / exposed	0 / 14 (0.00%)	0 / 17 (0.00%)	1 / 16 (6.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Appendicitis			
subjects affected / exposed	0 / 14 (0.00%)	0 / 17 (0.00%)	1 / 16 (6.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Arm A	Arm B	Arm C
Total subjects affected by non-serious adverse events			
subjects affected / exposed	14 / 14 (100.00%)	17 / 17 (100.00%)	15 / 16 (93.75%)
Vascular disorders			
Circulatory collapse			
subjects affected / exposed	1 / 14 (7.14%)	0 / 17 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Hypertension			
subjects affected / exposed	1 / 14 (7.14%)	0 / 17 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Lymphocele			
subjects affected / exposed	3 / 14 (21.43%)	4 / 17 (23.53%)	4 / 16 (25.00%)
occurrences (all)	3	6	5
Lymphoedema			
subjects affected / exposed	0 / 14 (0.00%)	0 / 17 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 14 (7.14%)	1 / 17 (5.88%)	0 / 16 (0.00%)
occurrences (all)	1	1	0
Chest pain			
subjects affected / exposed	0 / 14 (0.00%)	0 / 17 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Chills			

subjects affected / exposed	0 / 14 (0.00%)	5 / 17 (29.41%)	1 / 16 (6.25%)
occurrences (all)	0	12	3
Extravasation			
subjects affected / exposed	0 / 14 (0.00%)	0 / 17 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Fatigue			
subjects affected / exposed	1 / 14 (7.14%)	4 / 17 (23.53%)	1 / 16 (6.25%)
occurrences (all)	3	6	3
Influenza like illness			
subjects affected / exposed	2 / 14 (14.29%)	8 / 17 (47.06%)	0 / 16 (0.00%)
occurrences (all)	6	18	0
Injection site erythema			
subjects affected / exposed	13 / 14 (92.86%)	17 / 17 (100.00%)	6 / 16 (37.50%)
occurrences (all)	63	79	34
Injection site haemorrhage			
subjects affected / exposed	1 / 14 (7.14%)	0 / 17 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Injection site pain			
subjects affected / exposed	3 / 14 (21.43%)	1 / 17 (5.88%)	1 / 16 (6.25%)
occurrences (all)	7	4	2
Injection site pruritus			
subjects affected / exposed	1 / 14 (7.14%)	5 / 17 (29.41%)	1 / 16 (6.25%)
occurrences (all)	1	11	2
Local swelling			
subjects affected / exposed	0 / 14 (0.00%)	0 / 17 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Oedema peripheral			
subjects affected / exposed	0 / 14 (0.00%)	0 / 17 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Pain			
subjects affected / exposed	1 / 14 (7.14%)	1 / 17 (5.88%)	0 / 16 (0.00%)
occurrences (all)	1	1	0
Pyrexia			
subjects affected / exposed	0 / 14 (0.00%)	4 / 17 (23.53%)	2 / 16 (12.50%)
occurrences (all)	0	10	5
Immune system disorders			

Drug hypersensitivity subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0	1 / 17 (5.88%) 1	0 / 16 (0.00%) 0
Reproductive system and breast disorders			
Erectile dysfunction subjects affected / exposed occurrences (all)	2 / 14 (14.29%) 2	3 / 17 (17.65%) 3	6 / 16 (37.50%) 6
Pelvic pain subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0	1 / 17 (5.88%) 1	0 / 16 (0.00%) 0
Testicular pain subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0	1 / 17 (5.88%) 1	1 / 16 (6.25%) 1
Testicular swelling subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0	1 / 17 (5.88%) 1	0 / 16 (0.00%) 0
Respiratory, thoracic and mediastinal disorders			
Cough subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0	1 / 17 (5.88%) 1	0 / 16 (0.00%) 0
Dyspnoea exertional subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0	0 / 17 (0.00%) 0	1 / 16 (6.25%) 1
Obstructive airways disorder subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0	0 / 17 (0.00%) 0	1 / 16 (6.25%) 1
Wheezing subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0	0 / 17 (0.00%) 0	1 / 16 (6.25%) 1
Investigations			
Blood bilirubin increased subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1	0 / 17 (0.00%) 0	0 / 16 (0.00%) 0
Blood creatinine increased subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1	1 / 17 (5.88%) 1	0 / 16 (0.00%) 0

Blood thyroid stimulating hormone increased subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0	0 / 17 (0.00%) 0	1 / 16 (6.25%) 1
Blood uric acid increased subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0	0 / 17 (0.00%) 0	1 / 16 (6.25%) 1
Fibrin D dimer increased subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0	0 / 17 (0.00%) 0	1 / 16 (6.25%) 1
Prostatic specific antigen increased subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0	0 / 17 (0.00%) 0	1 / 16 (6.25%) 1
Injury, poisoning and procedural complications Laceration subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0	1 / 17 (5.88%) 1	0 / 16 (0.00%) 0
Congenital, familial and genetic disorders Atrial septal defect subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1	0 / 17 (0.00%) 0	0 / 16 (0.00%) 0
Cardiac disorders Atrioventricular block first degree subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0	0 / 17 (0.00%) 0	1 / 16 (6.25%) 1
Nervous system disorders Dizziness subjects affected / exposed occurrences (all) Dysaesthesia subjects affected / exposed occurrences (all) Headache subjects affected / exposed occurrences (all) Hypoaesthesia	0 / 14 (0.00%) 0 0 / 14 (0.00%) 0 3 / 14 (21.43%) 4	1 / 17 (5.88%) 1 1 / 17 (5.88%) 1 2 / 17 (11.76%) 2	0 / 16 (0.00%) 0 0 / 16 (0.00%) 0 1 / 16 (6.25%) 1

subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0	2 / 17 (11.76%) 2	1 / 16 (6.25%) 1
Motor dysfunction subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0	1 / 17 (5.88%) 1	0 / 16 (0.00%) 0
Paraesthesia subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1	0 / 17 (0.00%) 0	0 / 16 (0.00%) 0
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1	0 / 17 (0.00%) 0	0 / 16 (0.00%) 0
Eye disorders Asthenopia subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0	0 / 17 (0.00%) 0	2 / 16 (12.50%) 2
Gastrointestinal disorders Abdominal pain subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0	2 / 17 (11.76%) 2	0 / 16 (0.00%) 0
Anal fissure subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0	0 / 17 (0.00%) 0	1 / 16 (6.25%) 1
Constipation subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0	1 / 17 (5.88%) 1	0 / 16 (0.00%) 0
Diarrhoea subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 4	0 / 17 (0.00%) 0	1 / 16 (6.25%) 1
Gastritis subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0	1 / 17 (5.88%) 1	0 / 16 (0.00%) 0
Inguinal hernia subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0	0 / 17 (0.00%) 0	1 / 16 (6.25%) 1
Nausea			

subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0	2 / 17 (11.76%) 2	0 / 16 (0.00%) 0
Vomiting subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1	1 / 17 (5.88%) 1	1 / 16 (6.25%) 1
Hepatobiliary disorders Hepatic cyst subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0	0 / 17 (0.00%) 0	1 / 16 (6.25%) 1
Skin and subcutaneous tissue disorders Acne subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1	0 / 17 (0.00%) 0	0 / 16 (0.00%) 0
Dermatitis acneiform subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0	1 / 17 (5.88%) 1	0 / 16 (0.00%) 0
Pruritus subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0	0 / 17 (0.00%) 0	1 / 16 (6.25%) 1
Pruritus generalised subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0	1 / 17 (5.88%) 2	0 / 16 (0.00%) 0
Urticaria subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0	0 / 17 (0.00%) 0	1 / 16 (6.25%) 1
Renal and urinary disorders Bladder dysfunction subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0	0 / 17 (0.00%) 0	1 / 16 (6.25%) 1
Dysuria subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0	1 / 17 (5.88%) 1	0 / 16 (0.00%) 0
Nocturia subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1	1 / 17 (5.88%) 1	1 / 16 (6.25%) 1
Pollakiuria			

subjects affected / exposed	0 / 14 (0.00%)	1 / 17 (5.88%)	1 / 16 (6.25%)
occurrences (all)	0	1	1
Stress urinary incontinence			
subjects affected / exposed	7 / 14 (50.00%)	6 / 17 (35.29%)	11 / 16 (68.75%)
occurrences (all)	7	6	12
Urethral pain			
subjects affected / exposed	0 / 14 (0.00%)	1 / 17 (5.88%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 14 (0.00%)	2 / 17 (11.76%)	0 / 16 (0.00%)
occurrences (all)	0	3	0
Back pain			
subjects affected / exposed	0 / 14 (0.00%)	3 / 17 (17.65%)	0 / 16 (0.00%)
occurrences (all)	0	4	0
Groin pain			
subjects affected / exposed	0 / 14 (0.00%)	0 / 17 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Myalgia			
subjects affected / exposed	0 / 14 (0.00%)	2 / 17 (11.76%)	2 / 16 (12.50%)
occurrences (all)	0	7	3
Neck pain			
subjects affected / exposed	0 / 14 (0.00%)	1 / 17 (5.88%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Pain in extremity			
subjects affected / exposed	0 / 14 (0.00%)	3 / 17 (17.65%)	1 / 16 (6.25%)
occurrences (all)	0	5	1
Spinal column stenosis			
subjects affected / exposed	0 / 14 (0.00%)	0 / 17 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Spinal pain			
subjects affected / exposed	0 / 14 (0.00%)	1 / 17 (5.88%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Infections and infestations			

Bronchitis			
subjects affected / exposed	1 / 14 (7.14%)	1 / 17 (5.88%)	0 / 16 (0.00%)
occurrences (all)	1	1	0
Conjunctivitis			
subjects affected / exposed	1 / 14 (7.14%)	0 / 17 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Epididymitis			
subjects affected / exposed	0 / 14 (0.00%)	0 / 17 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Gastroenteritis			
subjects affected / exposed	0 / 14 (0.00%)	1 / 17 (5.88%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Herpes zoster			
subjects affected / exposed	0 / 14 (0.00%)	1 / 17 (5.88%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Infected lymphocele			
subjects affected / exposed	0 / 14 (0.00%)	0 / 17 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Nasopharyngitis			
subjects affected / exposed	0 / 14 (0.00%)	1 / 17 (5.88%)	1 / 16 (6.25%)
occurrences (all)	0	1	1
Oral herpes			
subjects affected / exposed	1 / 14 (7.14%)	0 / 17 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Respiratory tract infection			
subjects affected / exposed	0 / 14 (0.00%)	1 / 17 (5.88%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Urinary tract infection			
subjects affected / exposed	1 / 14 (7.14%)	1 / 17 (5.88%)	0 / 16 (0.00%)
occurrences (all)	1	1	0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	0 / 14 (0.00%)	1 / 17 (5.88%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Diabetes mellitus			

subjects affected / exposed	0 / 14 (0.00%)	1 / 17 (5.88%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Gout			
subjects affected / exposed	0 / 14 (0.00%)	0 / 17 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Hypercholesterolaemia			
subjects affected / exposed	0 / 14 (0.00%)	1 / 17 (5.88%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Hyperkalaemia			
subjects affected / exposed	0 / 14 (0.00%)	1 / 17 (5.88%)	0 / 16 (0.00%)
occurrences (all)	0	2	0
Hypokalaemia			
subjects affected / exposed	0 / 14 (0.00%)	1 / 17 (5.88%)	1 / 16 (6.25%)
occurrences (all)	0	1	1

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
11 February 2014	It was added that study treatment was to be permanently discontinued in case of disease progression after radical prostatectomy requiring anti-tumor treatment. Considerations for the sample size estimation were added.
28 May 2014	The number of sites was increased from 1 site to approximately 4 sites. Due to the change from a mono-center to a multi-center study, the role of a central pathologist was no longer applicable. Revision of inclusion criterion 2: the requirement for at least 3 biopsies with confirmed adenocarcinoma with at least 50% tumor infiltration in at least 1 biopsy was removed. To allow for a more exact localization of the tumor, optional magnetic-resonance imaging assessment was included. Dipstick as method for the urinalysis was removed to allow the use of different methods. It was clarified that only those serious adverse events (SAEs) were to be reported to the sponsor after end of the observation period that were considered related by the investigator.
18 July 2014	Revision of inclusion criterion 2: the restriction for subjects to have only 1 criterion for high risk disease (Gleason score of 8-10, a serum PSA <20 ng/mL or cT3a without tumor fixation to adjacent organs) was removed. It was clarified that in case no study medication was administered to a subject, the observation period for adverse events (AEs) was to last until 12 weeks after surgery. The handling and follow-up of AEs after the end of study visit was described in more detail.
24 February 2015	Revision of the primary endpoint: The definition of the primary endpoint was extended to include humoral immune response rates against all RNeActive® encoded antigens. Humoral immune response rates were to be measured against all 6 RNeActive®-encoded antigens and not only against 4 of 6 antigens; however ultimately, humoral immune response could only be measured for 4 of the 6 antigens. Blood sampling for HLA-class I and II antigen testing was added for completeness. The reporting requirements of SAEs in regard to the medical device were revised. The definition of the safety analysis set was revised to allow the inclusion of subjects in Arm C.
06 July 2015	Enrolled subjects diagnosed with very high risk prostate cancer after surgery (based on histopathological assessment) were allowed to receive post-surgical administrations of CV9104. It was clarified that the administration of CV9104 was to be completed before the initiation of adjuvant or salvage radiotherapy. It was clarified that if time windows for post-surgical administrations of CV9104 were missed, the respective administration was to be skipped and the next administration was to be performed as scheduled.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

