1 ABBREVIATED CLINICAL STUDY REPORT

BraVac

A PHASE 2, DOUBLE-BLIND, PLACEBO CONTROLLED STUDY OF RV001V IN MEN WITH BIOCHEMICAL FAILURE FOLLOWING CURATIVELY INTENDED THERAPY FOR LOCALIZED PROSTATE CANCER

Trial ID: RhoVac-002

Investigational Medicinal Product:	RV001
EudraCT no.:	2019-000951-14
Indication:	Therapy of localized prostate cancer
Study Design:	See study title
Sponsor:	RhoVac ApS
Development Phase:	Phase IIb
Study Start Date:	04 November 2019
Study Completion Date:	02 June 2022
Principal Investigator:	Klaus Brasso
Trial sites:	34 sites in 7 countries (BE, DE, DK, FI, SE, UK, US)
Report Version Number:	Version 1.0
Report Date:	07 December 2022

The study was conducted in compliance with the principles of ICH Good Clinical Practice.

2 SYNOPSIS

Name of Sponsor: RhoVac ApS, Denmark		(For National Authority Use Only)
Name of Final Product(s): RV001 0.1 mg/mL	Volume:	
Name of Active Ingredient: RhoC-derived 20mer peptide	Page:	

Title of Study:

A Phase 2, Double-Blind, Placebo Controlled Study of RV001V in Men with Biochemical Failure following Curatively Intended Therapy for Localized Prostate Cancer

Study Principal Investigator:

Professor Klaus Brasso, MD

Study Sites:

Multicenter study with study sites in 7 countries, including the United States (6 sites), Belgium (3 sites), Denmark (6 sites), Finland (5 sites), Germany (6 sites), Sweden (5 sites), and the United Kingdom (4 sites).

Publication:

No publication was published for this study.

Study Period:	**Phase of Development:**
04 November 2019 (first participant screened) to 02 June 2022	Phase IIb

Study objectives:

Primary objective:

- To investigate whether a vaccination regimen with multiple subcutaneous (SC) administrations of RV001 Vaccine 0.1 mg/mL (RV001V) can reduce prostate-specific antigen (PSA) progression compared to the control group.

Secondary objectives:

- To evaluate the safety and tolerability of RV001 Vaccine 0.1 mg/mL (RV001V) following SC administrations to participants who have a biochemical relapse following definitive local therapy prostatectomy or radiation therapy due to prostate cancer.
- To evaluate whether the vaccination regimen can delay the time to subsequent antineoplastic therapy initiation and substantiate other clinical benefits compared to the control group.
- Evaluate the safety and tolerability
- Time to initiation of subsequent antineoplastic therapy and substantiate other clinical benefits to the RV001 vaccine group compared to the placebo group

Study design and methods

This was a phase 2b, randomized, double-blind, placebo-controlled study to investigate whether a vaccination regimen with multiple subcutaneous (SC) administrations of RV001 peptide vaccine can reduce prostate-specific antigen (PSA) progression in men with biochemical failure following curatively intended therapy for localized prostate cancer.

Men aged ≥18 years with an earlier histologic diagnosis of prostatic adenocarcinoma and a biochemical recurrence (BCR) within 3 years of radical prostatectomy (RP) or definitive radical prostatectomy (RT) and no distant metastasis or locoregional recurrence were eligible for inclusion in the study.

The study consisted of a screening period ≤45 days before randomization at the first visit (vaccination 1), a double-blind treatment phase of 13½ months, and a follow-up phase 12 weeks after the End of treatment visit (EoT), and then every 12 weeks until the participant reached the primary endpoint or until the primary analysis was conducted. After randomization, the participants were stratified into groups having received radical prostatectomy (RP) or radiation therapy (RT) and by PSA doubling time (PSADT) <6 months versus ≥6 months.

The primary endpoint was defined as the time from randomization until doubling of PSA from the baseline value, clinical recurrence or death from any cause, whichever occurred first. When the participant reached a primary endpoint, he continued into the extended follow up (E-FU) phase for safety monitoring until the study was terminated 36 months after the first participant's first injection. At the time of the primary analysis all participants who have not yet reached the primary endpoint continued into E-FU for safety until study termination.

Criteria which contributed to the methodology of this trial included ensuring that participants had a biochemical recurrence (BCR) after radical prostatectomy (RP) or definitive radiation therapy (RT) and confirmation by standard imaging that no distant metastasis was present. Furthermore, included participants should comply with an Eastern Cooperative Oncology Group (ECOG) performance status of ≤2 which is defined as "capable of all self-care but not able to carry out any work activity. Up and about more than 50% of waking hours." All participants were treatment naïve to cancer vaccines at baseline, and a thorough assessment and reporting of baseline characteristics was done to ensure comparability between the RV001V group and the placebo group. In both study arms, treatment discontinuation criteria included investigator's decision, unacceptable toxicity, treatment delay of more than 3 weeks, and the participant's need for initiation of a prostatic cancer treatment regimen.

The Data Monitoring Committee (DMC) who reviewed and monitored the safety of the participants in the study consisted of two clinicians with expertise in drug safety and medical knowledge of prostate cancer and one statistician with expertise in statistical methods for clinical research.

Number of Participants (planned and analyzed)

Planned: 180, screened: 257 randomized: 192, analyzed (safety): 192, analyzed (efficacy): 185.

Selection Criteria

Inclusion Criteria

1) Men aged 18 and above with an earlier histologic diagnosis of prostatic adenocarcinoma.
2) Able to understand the study procedures and willing to provide IC.
3) Able and willing to comply with study requirements and complete all visits.
4) Biochemical recurrence (BCR) in compliance with the following 3 conditions: after having finished last definitive treatment (including. those who have received RP/RT followed by any modality of salvage therapy.); no distant metastasis by standard CT imaging with bone scintigraphy or a normal PET-CT; and no locoregional recurrence (including lymph nodes). Locoregional recurrence will be assessed by multi-parametric magnetic resonance imaging (MRI) in all participants treated with curative RT and

should be confirmed with image guided prostatic gland biopsy in case of suspicious lesions. Any prostatic biopsy performed should be negative.

5) Prior definitive treatment. with RP or RT. In case the patient. was subjected. to a RP, all the following will apply:
   a. PSA ≥0.2 ng/mL,
   b. PSA Doubling Time (PSADT)a >3 months and <12 months,
   c. History of Gleason 7 (4 + 3) or higher.

   Conversely, if the participant was treated with definitive RT and not prior RP, all of the following criteria will apply:
   a. PSA >nadir + 2 ng/mL,
   b. PSADTa >3 months and <12 months,
   c. History of Gleason score of 7 (4 + 3) or higher.
6) Eastern Cooperative Oncology (ECOG) performance status ≤2.
7) Laboratory values obtained ≤30 days prior to first vaccination:
   a. Hemoglobin ≥5.6 mmol/L(0.72 g/L)
   b. Absolute granulocyte count ≥1.5 x 109 /L.
   c. Platelets ≥100 x 109 /L.
   d. Total bilirubin ≤1.5 x upper limit of normal (ULN).
   e. Creatinine ≤1.5 x ULN.
   f. Alanine aminotransferase (ALT), aspartate aminotransferase (AST) and alkaline phosphatase (ALP) ≤2.5 x ULN.

Exclusion Criteria

1) Participants who are receiving androgen-deprivation therapy (ADT) or considered a candidate for immediate ADT or are candidate to any local therapy according to applicable clinical guidelines or judged by the investigator
2) Participants who have received prior ADT are not eligible with the exception of those that received ADT ≤36 months in duration and ≥9 months before randomization and administered only in the neoadjuvant/adjuvant setting.
3) Participant is planned for salvage therapy.
4) Castrate level of serum testosterone <50 ng/dL at screening.
5) PSA >10 ng/mL.
6) Small-cell, signet cell and neuroendocrine variants of adenocarcinomas.
7) An active malignancy likely to interfere with protocol treatment or FU.
8) Participants who have undergone major surgery or have had major bleeding within the last month prior to the first vaccination.
9) Prior treatment with any therapeutic cancer vaccine(s).
10) Participants with a condition requiring systemic treatment with either corticosteroids (>10mg daily prednisone equivalent) or other immunosuppressive medications within 14 days of randomization. Inhaled or topical steroids, and adrenal replacement steroid doses >10 mg daily prednisone equivalent, are permitted in the absence of active autoimmune disease.
11) History of alcohol or substance abuse within the last 5 years.
12) Participants receiving any investigational drug(s) or treatment within 30 days prior to inclusion in this trial.
13) History of significant autoimmune disease such as Inflammatory Bowel Disease, Systemic Lupus Erythematosus, Ankylosing Spondylitis, Scleroderma, Multiple Sclerosis.
14) Severe medical conditions, such as but not limited to severe asthma/chronic obstructive pulmonary disease (COPD), New York Heart Association (NYHA) grading 3 or above, poorly regulated insulin dependent diabetes, any significant organ damage as judged by the Investigator.
15) Other medications, conditions or laboratory results that in the Investigator's opinion would contraindicate study participation for safety reasons or interfere with the interpretation of study results.

16) History of known allergy/hypersensitivity to any of the component of the study drug (such as Montanide ISA 51), or intolerance to SC injection.
17) Participants with a prior solid organ/stem cell transplantation
18) Participants with known acquired immunodeficiency disorder (AIDS) or any inherited immunodeficiency disorder

Investigational Medicinal Product, Dose and Mode of Administration, Manufacturer, Batch Number:

RV001V consists of peptide solution RV001 0.1 mg/mL water-in-oil emulsion and the adjuvant Montanide ISA 51 for subcutaneous injection. Two batches of RV001V were used in the study, 18C174-487 and 20C174-541.

Duration of Treatment:

The double-blind treatment phase was 13½ months. During the double-blind treatment phase, neither the participant nor the investigator was informed about which medication the participant received.

Reference Therapy, Dose, and Mode of Administration, Batch Number:

The placebo vaccine contained a 50/50 mixture of the adjuvant Montanide ISA 51 and sterile acetate buffered saline pH 3.5 for subcutaneous injection. Two batches of placebo vaccine were used in the study, 18C174-480 and 20C197-540.

Criteria for Evaluation:

Efficacy: Tumor assessments (CT, Bone Scan, MRI, PET) were performed at baseline and thereafter every 26 weeks (±14 days) or sooner by the Investigator from Visit 2 if clinically indicated and until endpoint analysis.

Safety: Safety was evaluated according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0. Safety assessments were based on medical review of adverse event (AE) reports. For the safety analysis, all AEs which were classified 'Possibly' or 'Probably' or 'Definitely' related to the study drug were considered as treatment related AEs and tabulated and reviewed for potential significance and clinical importance. In addition, any AEs with an established causal relationship to immunization was classified according to the Council for International Organizations of Medical Sciences (CIOMS/World Health Organization (WHO). The reporting period for interim and final evaluation of safety data started when the Informed consent (IC) was signed by the participant and continued until the end of the extension follow up period.

Statistical Methods:

Sample size was based on the time to PSA progression. Time-to-event endpoints are summarized using the Kaplan-Meier method. In the primary analysis, comparison of survival distributions for the RV001V group and the placebo group was done using the stratified log rank test adjusted for baseline values. Cox proportional-hazard models, including the stratification factors at baseline, were used to estimate the hazard ratio (HR) and its 95% confidence interval (CI).

Response endpoints (e.g., PSA response rate) were summarized using descriptive statistics for categorical data by treatment group. The relative risk (treatment: control) was reported along with the associated 95% CIs. The two treatment arms were compared using the stratified Cochran-Mantel-Haenszel test.

The time to doubling was estimated from a log-linear regression of PSA values as dependent variable and considering time as the independent variable in the model. Estimated time to doubling was calculated using log-linear regression.

Analysis sets

Intention to treat (ITT) population:

All randomized participants, whether or not treatment was received.

Modified ITT population

All randomized participants who did receive at least 6 vaccinations.

Safety population:

All randomized participants who received at least one dose of treatment.

Summary of efficacy Results

Primary endpoint: PSA

- The time to PSA doubling in the modified (m-ITT) population showed no statistically significant difference (hazard ratio 1.37 [95% CI: 0.91, 2.07]; p-value 0.1327) between the RV001V arm and the placebo arm. The time to PSA doubling was 7.5 (5.9, 9.2) months in the RV001V arm (n=93) and 9.3 (7.2, 11.3) months in the placebo arm (n=92).
- In the m-ITT population, clinical recurrence occurred in 7 (7.5%) participants in the RV001V arm (n=96), and clinical recurrence occurred in 4 (4.3%) participants in the placebo arm.
- The supportive analysis of time to PSA doubling in the intention-to-treat (ITT) population also showed no statistically significant difference (hazard ratio 1.35 [95% CI: 0.89, 2.03]; p-value 0.1530) between the RV001V arm (n=96) and the placebo arm (n=96).

Secondary endpoints:

- In the m-ITT population, there was no statistically significant difference (hazard ratio 1.27 [95% CI: 0.75, 2.18]; p-value 0.3751) between the RV001V arm and the placebo arm in time to initiation of subsequent antineoplastic therapy (SAT). In the RV001 arm (n=93), 30 (32.3%), of the participants initiated SAT. For the median time of 11.2 months the 95% confidence interval could not be estimated (95% CI: 10.2, not estimable). In the placebo arm (n=92), 28 (30.4%), of the participants initiated SAT, and the median time was 17.6 months (95% CI: 11.1, 20.3).
- In the m-ITT population, there was no statistically significant difference (hazard ratio 1.20 [95% CI: 0.89, 1.62]; p-value 0.2270) between the RV001V arm and the placebo arm in PSA doubling time (PSADT) based on uncensored data. The median time to PSA doubling was 7.9 (5.9, 9.3) months in the RV001V arm (n=93) and 9.2 (7.4, 10.4) months in the placebo arm (n=92), respectively.
- The PSA response was calculated for the m-ITT population at Week 26 and compared to the PSA value at baseline. In the RV001 arm (n=70) no participants had a 50% reduction in PSA, and in the placebo arm (n=74) 2 participants had a 50% reduction in PSA. This outcome was not statistically significant between the two arms (p=0.5798).
- In addition, it was analyzed if any participants in the m-ITT population could achieve a 30% reduction in PSA level at Week 26 compared to the PSA value at baseline. In the RV001 arm (n=70) no participants had a 30% reduction in PSA, and in the placebo arm (n=76) 3 participants had a 30% reduction in PSA. This outcome was not statistically significant between the two arms (p=0.3051).
- Disease-free survival (DFS) was defined as time from randomization to documented clinical recurrence (distant or local), or death from any cause, censoring at the date of last follow-up (FU). In the m-ITT population, clinical recurrence occurred in 12 (12.9%) participants in the RV001V arm (n=93), and

clinical recurrence occurred in 11 (12.0%) participants in the placebo arm (n=92).

Exploratory endpoints:

- The relationship between the immunological response and the biochemical response could not be evaluated as no participant responded to the RV001 vaccine.
- The relationship between immune-response and antitumor-efficacy based on a correlative molecular analysis could not be evaluated as no participant responded to the RV001 vaccine.
- A full HLA tissue type analysis for all participants was performed. However, as no participant responded to the RV001 vaccine this analysis did not result in the identification of candidate predictive biomarkers of response and resistance.
- No participant had distant metastasis or locoregional recurrence (including lymph nodes) at the time of inclusion in this study. After follow-up, 12 (12.9%) of the participants in the RV001 arm (n=93) had developed metastases, and 11 (12.0%) of the participants in the placebo arm (n=93) had developed metastases. This difference was not statistically significant between the two arms (hazard ratio 1.07 [95% CI: 0.47, 2.47]; p-value 0.8752).

Summary of Safety Results

The safety and tolerability of the RV001 vaccine was evaluated by frequency and severity of treatment-emergent adverse events (TEAEs) in the RV001V arm versus TEAEs in the placebo arm. In the safety population, 171 out of 196 participants experienced treatment-emergent adverse events (TEAEs): 87 (90.63%) in the RV001V arm, and 84 (87.50%) in the placebo arm.

- The most frequently reported system organ class (SOC) was General disorders and administration site conditions with the most frequent preferred term (PT) being Injection Site Pain (RV001V arm [33.33%]; placebo arm [37.50%]) followed by PT Injection Site Swelling (RV001V arm [27.08%)]; placebo arm [26.04%]).
- Investigational product (IP)-related TEAEs were reported in 72 (75.00%) of participants in the RV001V arm and in 73 (76.04%) of participants in the placebo arm. All IP-related TEAEs were mild to moderate in severity according to the judgement of the Investigator.
- Treatment-emergent serious adverse events (SAEs) were reported in 7 participants (7.29%) in the RV001V arm and in 5 participants (5.21%) in the placebo arm. According to the Investigator, none of the SAEs were related to the study vaccine.
- One participant (1.04%) in the RV001V group experienced pneumonitis which was a serious TEAE leading to permanent discontinuation of study drug. Three participants in the placebo group (3.13%) experienced a TEAE leading to permanent discontinuation of study drug. One participant experienced headache, and one participant had Chronic Obstructive Pulmonary Disease. These were non-serious TEAEs. One participant died of cardiac arrest. The death was not related to the study vaccine.
- There were 4 deaths during the study. One death occurred before randomization, two deaths occurred in the RV001V arm, and one death occurred in the placebo arm. According to the investigator, all deaths were unrelated to the study vaccine.

Conclusions:

In this randomized Phase 2b study, the aim was to investigate if the synthetic anti-cancer peptide vaccine candidate RV001 targeting the GTPase named RhoC was able to elicit an immune response which could result in a delay of tumor progression or prevent tumor recurrence and metastasis formation with PSA progression being

used as a predictive marker. This study showed no statistically significant difference between the RV001 vaccine group and the control group in reducing PSA progression and failed to demonstrate any treatment benefit.

Peptide vaccines generally seem inherently safe as long as the adjuvants are used in combinations and doses which were previously demonstrated to be safe, and this also applied to this study. The adverse events which were reported during the study and were related to the study vaccine were all mild to moderate in severity.

Date of the Report: 07 December 2022