Clinical Development

DCVAC/PCa

Clinical Trial Protocol SP005

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

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Signatures/Protocol Approval and Release

We, the undersigned, have read this protocol and the appendices and agree that they contain all the necessary information required for the conduct of the study.

For SOTIO a.s.

Özlem Ataman, MD, PhD
Chief Medical Officer
SOTIO a.s.

Signature _____

Date 9. 3. 2018

Ladislav Pecen, PhD
Statistician
SOTIO a.s.

Signature _____

Date 08-MAR-2018

Declaration by the Investigator

I have read this protocol and agree that it contains all the necessary details for carrying out this study. I will conduct the study as described and will complete the study within the time designated. I verify that I am suitably qualified by education, scientific medical training and experience to conduct the study. Documentation of my qualifications and professional affiliations are contained in my up-to-date curriculum vitae.

I will provide the supplied copies of the protocol and all information relating to pre-clinical and prior clinical experience (e.g. Investigator's Brochure) to all staff in my unit who participate in this study. I will discuss this material with them to ensure that they are fully conversant with medical treatment and the conduct of the study, and that they will handle the data and information generated in the study confidentially.

I will conduct the study in accordance with Good Clinical Practice, the Declaration of Helsinki, the study protocol and the moral, ethical and scientific principles that justify medical research. The study will be conducted in accordance with the relevant laws and regulations relating to clinical studies and the protection of subjects of the country in which the study will be performed. All subjects will be informed comprehensively about the nature of the study and will give their written consent to participate before entry into the study. They will be informed that they may withdraw from the study at any time. I will use only an information sheet and consent form approved by SOTIO and the Independent Ethics Committee (IEC)/ Institutional Review Board (IRB) which has reviewed this study. I will supply SOTIO with any material written by myself (e.g. summary of study) which is given to the EC in support of the application.

Where applicable and required the information contained in the case report forms will be transcribed from my records, reports and manuscripts. The case report form may be the original source document for certain items. Either I or an appointed person will attest to the authenticity of the data and accuracy and completeness of the transcription by signing the case report form. I agree to the audit and monitoring procedures that involve verification of study records against the original records by direct access. Should it be requested by government regulatory agencies, I will make available additional background data from my records, and where allowed from the hospital or institution where the study was conducted. I certify that any laboratory, excluding the central laboratory(s) appointed for the study in which laboratory parameters will be determined is subject to regular external quality control.

I understand that the case report forms and other data pertinent to this study are the property of SOTIO and are confidential. I will supply SOTIO with the study data in such a way that the subject normally cannot be personally identified.

I consent to SOTIO's and CRO's collection, processing, transfer, use and storing of my personal data and details relating to my professional activities for the purposes of the study.

I understand that the study may be terminated or enrolment suspended at any time by the Sponsor, with or without cause, or by me if it becomes necessary to protect the best interests of the study subjects.

Investigator Signature: _____

Date: _____

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OTHER CONTACT INFORMATION:

Full contact details for each Investigational site, the Sponsor, and key coordinating and operational personnel involved in this clinical trial will be maintained in the Trial Master File and in each Site Study File.

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ABBREVIATIONS

Abbreviation or Term*	Definition/Explanation
ACE	angiotensin converting enzyme
ACI	active cellular immunotherapy
ADR	adverse drug reaction
ADT	androgen deprivation therapy
AE	adverse event
AESI	Adverse Events of Special Interest
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANA	antinuclear antibodies
ANCA	anti-neutrophil-cytoplasmic antibodies
aPTT	activated partial thromboplastin time
ARS	all randomized subjects
AST	aspartate aminotransferase
ATC	Anatomic Therapeutic Class
ATMP	advanced-therapies medicinal products
Ca^{2+}	Calcium ion
CBC	complete blood count
CHMP	Committee for Medicinal Products for Human Use
CMV	cytomegalovirus
Cl^-	chloride ion
CRF	case report form
CRO	Contract Research Organization
CRP	C-reactive protein
CRPC	castration-resistant prostate cancer
CT	computed tomography
DC	dendritic cell
DCVAC/PCa	Autologous active cellular immunotherapy consisting of dendritic cells for prostate cancer treatment
DMSO	Dimethyl sulfoxide
DNA	Deoxyribonucleic acid
DQF	Data Query Form
DSUR	Development Safety Update Report

EBV	Epstein-Barr Virus
EC/IEC	Ethics Committee / Independent Ethics Committee
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EC	European Commission / European Community
EDC	Electronic Data Capture
EMA/EMEA	European Medicines Agency
EOT	End of Treatment
EOS	End of Study
EORTC	European Organization for the Research and Treatment of Cancer
EQ-5D	Euro Quality of Life 5 Dimensions
EU	European Union
FACT-P	Functional Assessment of Cancer Therapy - Prostate
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GLP	Good Laboratory Practices
GM-CSF	granulocyte macrophage colony stimulating factor
GMP	Good Manufacturing Practice
GMT	gamma-glutamyltransferase
GnRH/LHRH	gonadotropin releasing hormone/ luteinizing hormone-releasing hormone
HBc Ab	Hepatitis B Core Antibody
HBs Ag	Hepatitis B Surface Antigen
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HHP	high hydrostatic pressure
HIV	human immunodeficiency virus
HLA	human leukocyte antigen
HPF	high-power field
HR	heart rate
HTLV	human T-lymphotropic virus
IB	Investigator Brochure
ICF	Informed Consent Form
iDCs	immature dendritic cells
IDMC	Independent Data Monitoring Committee

IEC	Independent Ethics Committee
IMP	Investigational medicinal product
IRB	Institutional Review Board
IgA	Immunoglobulin A
IgE	Immunoglobulin E
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IND	Investigational New Drug
IRB	Investigational Review Board
IRF	Independent Review Facility
ITT	Intent to treat
IVRS/IWRS	Interactive Voice Response System / Interactive Web Response System
K	Potassium
Kg	Kilogram
LDH	lactate dehydrogenase
LNCaP	androgen-sensitive prostate cancer cell line derived from lymph node metastasis
LOCF	last observation carried forward
LVEF	Left Ventricular Ejection Fraction
NK cells	Natural killer cells
mCRPC	Metastatic Castration Resistant Prostate Cancer
mDCs	mature dendritic cells
MDSC	myeloid derived suppressor cells
MedDRA	Medical Dictionary for Drug Regulatory Activities
Mg	Magnesium
MHC	major histocompatibility complex
M_R	median reference
MRI	magnetic resonance imaging
MS	Median survival
M_T	median test
MUGA	multiple gated acquisition
Na	Sodium
NaCl	sodium chloride
NCCN/EAU	National Comprehensive Cancer Network /European Association of Urology

NCI CTCAE	National Cancer Institute - Common Terminology Criteria for Adverse Events
NP	nurse practitioner
OS	overall survival
PA	physician Assistant
PBMC	peripheral blood mononuclear cells
PCa	prostate cancer
PCR	polymerase chain reaction
PCWG	Prostate Cancer Working Group
PE	physical examination
PD	progressive disease
rPFS	radiographic progression free survival
pH	negative logarithm of hydrogen ion concentration ("power of hydrogen")
PP	per protocol set of subjects
PR	partial response
PSA	prostate-specific antigen
PSADT	prostate-specific antigen doubling time
PT	prothrombin time
QoL	quality of life
RBC	red blood cell
RECIST	response evaluation criteria in solid tumors
RF	rheumatoid factors
RNA	ribonucleic acid
RPE	radical prostatectomy
SAE	serious adverse event
SAP	Statistical Analysis Plan
SAR	serious adverse reaction
SD	stable disease
SIV	site initiation visit
SmPC	Summary of Product Characteristics
SOC	Standard of Care
SPECT	single-photon emission computed tomography
SRE	skeletal related events
SUKL	State Institute for Drug Control (e.g. Czech Competent Authority in the Czech Republic)
SUSAR	Suspected Unexpected Serious Adverse Reaction

TSH	thyroid - stimulating hormone
TTP	time to progression
ULN	upper limit of normal
USP	United States Pharmacopeia
VHP	Voluntary Harmonisation Procedure
WBC	white blood cell
WHO	World Health Organization

ONCOLOGY CLINICAL STUDY PROTOCOL SYNOPSIS

Name of Sponsor / Company	SOTIO a.s.
Investigational drug	DCVAC/PCa, active cellular immunotherapy containing autologous dendritic cells (DC) activated by transient exposure to killed prostate cancer cells *ex-vivo*
Protocol no.	SP005
Study phase	Phase III
Study title	A Randomized, Double Blind, Multicenter, Parallel-Group, Phase III Study to Evaluate Efficacy and Safety of DCVAC/PCa Versus Placebo in Men with Metastatic Castration Resistant Prostate Cancer Eligible for 1st Line Chemotherapy
Background	DCVAC/PCa is an active autologous cellular immunotherapy consisting of dendritic cells (DCs) produced *ex-vivo* from a patient's monocytes which are pulsed with tumor cells killed by high hydrostatic pressure (HHP) and subsequently activated by a maturation agent. When the activated autologous DCs are injected back into the patient with mCRPC an immune response is established against the cancer which may inhibit progression and improve overall survival (OS).
Purpose/rationale	Addition of DCVAC/PCa to Standard of Care (SOC) Chemotherapy (docetaxel plus prednisone) will result in a prolongation in OS in mCRPC subjects.
Objectives	**Primary:** The primary objective is to show superiority of treatment with DCVAC/PCa in addition to SOC (docetaxel plus prednisone) over placebo in addition to SOC (docetaxel plus prednisone) in men with mCRPC as measured by OS. **Key Secondary:** The key secondary objectives include assessments of safety, treatment group comparison with regards to radiographic progression free survival, time to prostate-specific antigen progression, time to first occurrence of skeletal related events (SRE). **Other Secondary:** Show clinical benefit of treatment with DCVAC/PCa in addition to SOC over placebo in addition to SOC with regard to time to radiographic progression or to skeletal related events and proportion of patients with SRE. **Exploratory Objective:** Treatment group comparison for the following measures: Proportion of subjects requiring second line treatment introduction and time to second line therapy, changes in quality of life (QoL) and exploratory studies for search of potential biomarkers

Endpoints	**Primary efficacy endpoint:**
	• Overall Survival (OS)
	
	Key Secondary efficacy endpoints:
	• Radiological progression free survival (rPFS), composite of
	  ○ radiographic progression of bone lesions
	  ○ radiographic progression of soft tissue lesions
	  ○ death due to any cause
	• Time to prostate-specific antigen (PSA) progression
	• Time to first skeletal related events (SRE)

	Other Secondary efficacy endpoints: • Time to radiographic progression or SRE • Proportion of patients with SRE **Safety endpoints:** Adverse events, including laboratory abnormalities, change in vital signs and change in ECOG performance status. **Exploratory endpoints:** • Evaluation of QoL using the standardized questionnaires FACT-P and EQ-5D (EQ-5D only in Europe) • Proportion of subjects requiring second line treatment introduction and time to second line therapy • Exploratory studies for search of potential biomarkers
Study design	This is a randomized, double blind, placebo controlled, multicenter, international, parallel-group Phase III study to evaluate the efficacy and safety of DCVAC/PCa versus placebo in men with metastatic castration resistant prostate cancer (mCRPC) eligible for 1st line chemotherapy with docetaxel plus prednisone. The sample size was established as 1170 subjects, and final analysis is planned after 657 deaths have occurred. The study will consist of: • Screening Period (up to 28 days). • Randomization – Interactive Voice/Web Response System (IVRS/IWRS) central randomization – 2:1 randomization Standard of Care Chemotherapy (docetaxel plus prednisone) + DCVAC/PCa or Standard of Care chemotherapy (docetaxel plus prednisone) + placebo. • Leukapheresis Period – all subjects will undergo a leukapheresis evaluation prior the leukapheresis procedure. The leukapheresis procedure itself will be performed within 14 days of randomization. • Concurrent Treatment Period – First line Standard of Care chemotherapy with docetaxel plus prednisone will begin 3 to 7 days after the leukapheresis procedure. All subjects will receive treatment per the prescribing information for the Standard of Care chemotherapy (docetaxel plus prednisone). DCVAC/PCa or placebo will be administered concurrently every 3 weeks. DCVAC/PCa or placebo will be administered at least 7 days before or at least 7 days after the nearest chemotherapy (Day 8-15 of chemotherapy cycle) starting after second cycle of Standard of Care chemotherapy (docetaxel+prednisone). • Maintenance Boosting Period – should first line Standard of Care chemotherapy (docetaxel plus prednisone) be completed or withdrawn for any reason, the patient will continue on DCVAC/PCa or placebo every 4 weeks until the completion of a total of 15 doses, refusal, intolerance or introduction of the 2nd line of antitumor therapy. After completion or withdrawal of DCVAC/PCa or placebo an End of Treatment Visit (EOT) will be performed. • Follow-up Period – All subjects will be followed until refusal, death or study closure. Final Analysis will be performed upon reaching the targeted number of events for analysis (657 deaths). Upon completion of the follow-up period patients will have the End of Study visit performed.
Population	Men with mCRPC who are eligible to receive first line Standard of Care chemotherapy with docetaxel plus prednisone
Inclusion/exclusion criteria	**Inclusion** • Male 18 years and older. • Histologically or cytologically confirmed prostate adenocarcinoma.

	• Presence of skeletal and/or soft-tissue/visceral/nodal metastases according to one of the following criteria: ~ Confirmed pathological fracture related to the disease. OR ~ Confirmation of distant bone and/or soft-tissue and/or visceral metastases through at least one imaging modality including CT or MRI or scintigraphy scan (confirmation by independent review facility (IRF) required) OR ~ Positive pathology report of metastatic lesion. • Disease progression despite androgen deprivation therapy (ADT) as indicated by: ~ PSA increase that is ≥ 25% and ≥ 2 ng/mL above the minimum PSA as reached during ADT or above the pre-treatment level, if no response was observed and which is confirmed by a second value 1 or more weeks later. OR ~ Progression of measurable lymph nodes (short axis ≥ 15 mm) or visceral lesion measurable per RECIST v1.1 criteria (confirmation by IRF required); OR ~ Two or more new lesions appearing on bone scan/imaging compared with a previous scan (confirmation by IRF required) • Maintenance of castrate condition: Subjects, who have not had a surgical orchiectomy, must continue with hormone therapy (GnRH/LHRH agonists or antagonists) to reach levels of serum testosterone of ≤ 1.7 nmol/L (50 ng/dL). The duration of the castration period must be at least 4 months before screening. • Laboratory criteria: ~ White blood cells greater than 4,000/mm^3 (4.0 x10^9/L). ~ Neutrophil count greater than 1,500/mm^3 (1.5 x10^9/L). ~ Hemoglobin of at least 10 g/dL (100g/L). ~ Platelet count of at least 100,000/mm^3 (100 x10^9/L). ~ Total bilirubin within normal limits (benign hereditary hyperbilirubinaemias, e.g. Gilbert´s syndrome are permitted). ~ Serum alanine aminotransferase, aspartate aminotransferase, and creatinine <1.5 times the ULN. • Life expectancy of at least 6 months based on Investigator´s judgment. • Eastern Cooperative Oncology Group (ECOG) performance status 0-2. • At least 4 weeks after surgery or radiotherapy before randomization. • A minimum of 28 days beyond initiation of bisphosphonate or denosumab therapy before randomization. • Recovery from primary local surgical treatment, radiotherapy or orchiectomy before randomization. • Signed informed consent including patient's ability to comprehend its contents. **Exclusion** • Confirmed brain and/or leptomeningeal metastases (other visceral metastases are acceptable). • Current symptomatic spinal cord compression requiring surgery or radiation therapy. • Prior chemotherapy for prostate cancer • Patient co-morbidities: ~ Subjects who are not indicated for chemotherapy treatment with first line Standard of Care chemotherapy (docetaxel and prednisone). ~ HIV positive, HTLV positive. ~ Active hepatitis B (HBV), active hepatitis C (HCV), active syphilis.

	~ Evidence of active bacterial, viral or fungal infection requiring systemic treatment. ~ Clinically significant cardiovascular disease including: ▪ symptomatic congestive heart failure. ▪ unstable angina pectoris. ▪ serious cardiac arrhythmia requiring medication. ▪ uncontrolled hypertension. ▪ myocardial infarction or ventricular arrhythmia or stroke within a 6 months before screening, known left ventricular ejection fraction (LVEF) < 40% or serious cardiac conduction system disorders, if a pacemaker is not present. ~ Pleural and pericardial effusion of any CTCAE grade. ~ Peripheral neuropathy having a CTCAE ≥ grade 2. ~ History of active malignant disease (with the exception of non-melanoma skin tumors) in the preceding five years. ~ Active autoimmune disease requiring treatment. ~ History of severe forms of primary immune deficiencies. ~ History or anaphylaxis or other serious reaction following vaccination. ~ Known hypersensitivity to any constituent in of the DCVAC/PCa or placebo product ~ Uncontrolled co-morbidities including, psychiatric or social conditions which, in the Investigator's opinion, would prevent participation in the trial. • Systemic corticosteroids at doses greater than 40 mg hydrocortisone daily or equivalent for any reason other than treatment of prostate cancer (PCa) within 6 months before randomization. • Ongoing systemic immunosuppressive therapy for any reason. • Treatment with anti-androgens, inhibitors of adrenal-produced androgens or other hormonal tumor-focused treatment performed on the day of randomization (except for GnRH/LHRH agonists or antagonists), to exclude possible anti-androgen withdrawal response. This criterion is not applicable to subjects who have never responded to anti-androgen treatment, as there is no risk of anti-androgen withdrawal response. • Treatment with immunotherapy against PCa within 6 months before randomization. • Treatment with radiopharmaceutical within 8 weeks before randomization. • Participation in a clinical trial using experimental therapy within 4 weeks before randomization. • Participation in a clinical trial using immunological experimental therapy (e.g., monoclonal antibodies, cytokines or active cellular immunotherapies) within 6 months before randomization. • Refusal to sign the informed consent.
Patient numbering	Subjects will be centrally randomized and assigned a unique study number using an IVRS/IWRS system.
Investigational and Standard of Care drugs	**Investigational therapy:** DCVAC/PCa is an active autologous cellular immunotherapy produced under GMP-conditions. DCVAC/PCa is prepared on an individual basis from the peripheral blood mononuclear cells (PBMC) of the patient obtained by leukapheresis. DCs are generated from the harvested PBMCs using IL-4 and GM-CSF. Subsequently, the immature DCs (iDCs) are exposed to killed tumor cells (LNCaP) at a DC: tumor cell ratio of 5:1. Tumor cell-pulsed DCs are then matured by TLR-3 ligand. Cells are then cryopreserved and stored in liquid nitrogen. On the day of drug injection, a suspension of 1×10^7 LNCaP-pulsed mature DCs is unfrozen, re-suspended in 0.9% saline to a total volume of 5 ml and then injected subcutaneously in the inguinal and axillary lymph node area in two 2.5 mL volumes. The placebo used for the study will be identical to the study drug without the active drug substance (DCVAC/PCa).

	Medication labels will comply with the legal requirements of each country and will be printed. Labels will contain the unique identification number of the patient and the LOT number. The storage conditions for study drug will be described on the secondary package label. **Standard of Care therapies:** Investigators should use Standard of Care therapy (docetaxel plus prednisone) with authorization for their country and should reference the prescribing information provided with the product when treating the subjects.
Dose, regimen, treatment cycle	Subjects receiving DCVAC/PCa or placebo will all receive prepared study medication according to the treatment plan. Concurrently with Standard of Care (docetaxel plus prednisone) DCVAC/PCa or placebo will be given in 3 weeks intervals (with an acceptable window of ± 7 days). DCVAC/PCa or placebo will be administered at least 7 days before or and at least 7 days after the nearest chemotherapy (Day 8-15 of chemotherapy cycle). After discontinuation of Standard of Care chemotherapy for any reason, each following dose of DCVAC/PCa or placebo will be given in 4 weeks intervals (with an acceptable window of -7/+14 days) for up to a total of 15 doses. All subjects will receive first line Standard of Care chemotherapy (docetaxel plus prednisone) until completion, refusal, intolerance, disease progression or death and may be treated with subsequent therapies at the Investigator's discretion (see section 6.1.2) until completion, refusal, death or study closure. When 2nd line therapy is introduced to patient, DCVAC/PCa will be discontinued.
Supply, preparation, and administration	DCVAC/PCa is an autologous cellular suspension, 15 doses are manufactured from an autologous sample, 1 mL i.e. 1×10^7 pulsed mature DCs per dose, every dose diluted with 0.9% saline to a final volume of 5 mL. Each dose is given in 2 separate 2.5 mL subcutaneous injections, one injection to an inguinal lymph node area and one to an axillary lymph node area. Treatments are rotated to alternate areas.
Visit schedule and assessments	• Laboratory evaluations during the Concurrent Treatment Period, while patient is on first line chemotherapy: ~ Hematology every 3 weeks. ~ Blood biochemistry every 3 weeks (includes ALP and LDH). ~ TSH every 12 weeks ~ PSA every 12 weeks (coordinated with imaging assessments). ~ Urinalysis every 6 weeks. • Laboratory evaluations during the Maintenance Boosting Period, after termination of first line chemotherapy: ~ Hematology every 4 weeks until End of Treatment Visit. ~ Blood biochemistry every 4 weeks (includes ALP and LDH) until End of Treatment Visit. ~ TSH every 12 weeks until End of Treatment Visit. ~ PSA every 12 weeks (coordinated with imaging assessments) until confirmed progression or introduction of 2nd line therapy. ~ Urinalysis every 12 weeks until visit End of Treatment visit • Blood sampling for research purposes – at Randomization, prior to the 5th dose of DCVAC/PCa or placebo, at the End of Treatment visit. • Serum testosterone level at screening if historically measured value (older than 4 months before screening) doesn´t exist. • Complete Physical exam at screening. • Symptom Directed Physical exam, vital signs every visit post screening. • Imaging will be conducted every 12 weeks (± 7 days) (skeletal scintigraphy/CT (MRI)) until confirmed progression or until introduction of 2nd line therapy.

Special safety assessment(s)	Safety assessments consist of monitoring and recording of all AEs, including serious adverse events (SAEs), the regular monitoring of hematology, blood biochemistry and urine values, clinical evaluation of vital signs, physical examinations, performance status using ECOG scale, and radiological examinations. An independent Data Monitoring Committee (IDMC) will be constituted to regularly evaluate blinded safety data.
Patient reported outcomes	QoL based on the questionnaires FACT-P and EQ-5D (EQ-5D only in Europe).
Biomarkers	PSA measured as part of secondary endpoint of disease progression.
Exploratory Biomarker Immunogenicity studies	Blood samples for research purposes will be obtained from all subjects at Randomization, at cycle 5 week 2, and at the End of Treatment visit. Serum and cells will be frozen for biomarker research evaluation.
Independent DMC	The IDMC will meet regularly per the charter to review accruing safety data. It is expected that the IDMC will consist of five members, including one statistician. The frequency of IDMC meetings will be spelled out in the IDMC charter.
Statistical methods and data analysis	It is planned that the data from all centers that participate in this protocol will be used, so that an adequate number of subjects will be available for analysis (ITT population). Data will be summarized with respect to demographic and baseline characteristics, efficacy observations and measurements, and safety observations and measurements. The assessment of efficacy will be based on a sample size of approximately 1170 subjects (i.e., events of 657 deaths). The study will have 80% power to detect a hazard ratio of 0.792 for death in the group receiving DCVA/PCa plus Standard of Care chemotherapy (docetaxel plus prednisone) as compared with the group receiving placebo plus Standard of Care Chemotherapy (docetaxel plus prednisone). This sample size was calculated by assuming a median survival of 24 months for the DCVAC/PCa group and 19 months for the control group, with a two-sided significance level (alpha) of 0.05, allocation ratio 2:1 of DCVA/PCa versus placebo arm, an enrollment period of approximately 18 months, and total study duration of approximately 40 months to observe the required event-driven timeframe of 657 total events for the final analysis. If the anticipated 657 events are not attained during the trial timeline, the study could be extended by SOTIO. The primary efficacy analysis is a stratified log-rank test of the overall survival (OS) endpoint to compare subjects receiving DCVAC/PCa in addition to Standard of Care (docetaxel plus prednisone) (Arm A) versus those receiving placebo in addition to Standard of Care (docetaxel plus prednisone) (Arm B) for the Intent-to-Treat (ITT) population. Patients will be randomized in a 2:1 ratio, stratified by region (US vs Other), prior therapy (abiraterone or enzalutamide or neither of the two) and, ECOG Score (0, 1 vs 2). The overall type I error rate will be controlled at 0.05. At the final analysis, a final p-value of ≤ 0.0455 is required to be considered statistically significant. (East 5.4 software with 'Null' variance was used for total events and statistical significance boundary determination). The Cox proportional hazards regression model will be used to analyze OS data. Estimated hazard ratio and corresponding two-sided 95% confidence interval will be calculated. Estimated median survival time and survival rate will be calculated and presented by treatment group. The assessment of safety will be based mainly on the comparison of frequency of AEs and related AEs (ADRs) between groups. Adverse events will include clinically significant laboratory abnormalities. Patient reported outcomes will be assessed using the questionnaires FACT-P and EQ-5D (EQ-5D only in Europe).

Number of subjects, centers and location, predicted duration	Total number of subjects: Number of sites: Number of subjects per site: Location of sites: Predicted duration:	1170 subjects 280 – 320 centers 4 – 12 per site Europe, the USA and Canada 40 months

1 BACKGROUND

1.1 Overview of Prostate Cancer

Prostate cancer (PCa) is the second most common form of cancer and the sixth leading cause of cancer death among men worldwide with an estimated 899,000 new cases and 258,000 new deaths in 2008.[1] The worldwide PCa burden is expected to grow to 1.7 million new cases and 499,000 new deaths by 2030 simply due to the growth and aging of the global population.[1] The incidence of prostate cancer varies greatly in individual geographic regions and countries of the world. The highest incidence in 2008 was estimated to be in France (Martinique 173.3/100,000) and in Northern Europe (Ireland 126.3/100,000, Norway 115.6/100,000, and Sweden 114.2/100,000). In Australia and New Zealand the estimated incidence in 2008 was 104.2/100,000. In Central and Eastern Europe the average incidence of prostate cancer in 2008 was estimated to be 28.5/100,000 (57,554 cases), in Northern Europe 75.2/100,000 (67,638 cases), in Southern Europe 50.2/100,000 (79,923 cases) and in Western Europe 94.1/100,000 (170,007 cases). In the USA, prostate cancer accounted for an estimated 186,220 new cases in 2008 (incidence 83.8/100,000 men).[2] It is estimated that 240,890 men were diagnosed with the disease and 33,730 died of it in the USA in 2011.[3] An estimated 238,590 new cases of prostate cancer will occur in the US during 2013 with an estimated 29,720 deaths in 2013, prostate cancer is the second-leading cause of cancer death in men in the US.[4]

Well-established risk factors for PCa are older age, black race/ethnicity, and a family history of the disease.[5] Race is a prostate cancer risk factor and a cancer prognostic factor. Currently, African-American or black men have a risk of diagnosis that is 1.6 times above the risk in white men and risk of death that is 2.5 times greater.[6]

Prostate cancer treatment options include surgery (prostatectomy), radiotherapy, hormonal manipulation and chemotherapy.[7,8] Prostate cancer can be cured at the stage of localized organ-confined disease, in which 10-year survival is between 75 and 93%.[9] In spite of good results of radical prostatectomy (RPE) or primary curative radiotherapy, relapses occur in approximately 30% of subjects within 5 years after primary curative treatment. Relapse risk factors include Gleason score and PSA value at diagnosis.

Subjects with locally advanced or metastatic carcinoma have significantly poorer prognosis. Treatment of locally advanced disease consists of a combination of surgery or radiotherapy and androgen deprivation therapy (ADT). Subjects with metastatic disease are candidates for ADT by orchiectomy or pharmacological agents. ADT leads to apoptosis of primary tumor cells as well as metastases. ADT reduces symptoms and delays the time to progression (TTP), however, it does not prolong the OS.

Average responsiveness to castration for men with metastases varies between 18 and 48 months. Frequently, despite ADT, disease progression occurs, due to the emergence of resistant tumor cells and castration-resistant disease develops. Median survival of metastatic castration-resistant subjects varies between 12–36 months depending on the risk factors. Palliative targeting of bone metastases with bisphosphonates, RANK ligand inhibitors, or beta-emitting radiopharmaceuticals improves quality of life but has no effect on the overall survival. Several

therapies have now been approved by the Food and Drug Administration (FDA) agency, for the treatment of castration resistant prostate cancer (CRPC) including chemotherapy (docetaxel and cabazitaxel), secondary hormonal manipulation (abiraterone, enzalutamide), radiopharmaceutical Radium-223 dichloride to treat bone metastases and cell-based immunotherapy (sipuleucel-T). Each of these prolongs median survival by a few months. As a result, there is a clear unmet medical need for an agent that can provide clinically relevant improvement in the OS or/and progression free survival (PFS) without adding to the existing burden of intolerability. DCVAC/PCa is being considered as an additional option for the mCRPC subjects requiring Standard of Care 1st line chemotherapy, to prolong OS.

1.2 Immunotherapy in Prostate Cancer

In light of the recent advances in understanding the biology of the immune response and the importance of an anti-tumor immune response for long-term prognosis of cancer, immunotherapy has emerged as another treatment modality with the potential to contribute to further improvements in survival.[10] Recently, the FDA approved the first cell-based immunotherapy (*sipuleucel-T; April 29, 2010; BL 125197/0; License No. 1749*) as the first application of this new approach in clinical practice.

Immunotherapy is based on the induction of tumor cell specific immune response that subsequently recognizes and destroys tumor cells. Cell-based immunotherapy must stimulate specific immune responses against cancer cells, and the immune responses must be sufficient to overcome the immuno-suppressive mechanisms of tumor tissue micro-environment.[11] These mechanisms represent the main obstacle limiting the efficacy of immunotherapy in advanced stages of cancer if applied as monotherapy. Thus, the combination of chemotherapy drugs with immunotherapy seems to be a rational approach in CRPC subjects. Chemotherapy, which is broadly viewed as immuno-suppressive, might to some extent boost an anti-tumor response.[12,13] Indeed, studies have shown that chemotherapy can be combined with a cell-based immunotherapy for prostate-cancer without blunting the immune response to the immunotherapy.[13] A summary of immunotherapy of prostate cancer is provided in the Investigator's Brochure (IB).

The approach tested in this study represents a patient specific active cellular immunotherapy (ACI) using autologous dendritic cells differentiated from peripheral blood monocytes and presenting tumor antigens derived from prostate cancer cell line killed by an immunogenic cell death. In the present study, ACI will be combined with the first line chemotherapy (docetaxel plus prednisone) in accordance with the concept of "chemo-immunotherapy".

1.3 Overview of DCVAC/PCa

DCVAC/PCa is an autologous active cellular immunotherapy which was previously considered to be a medical treatment, not requiring drug-status authorization. In 2007 the European Union (EU) legislation classified this cellular therapy as a drug belonging to the category of advanced-therapies medicinal products (ATMP) according to EC 1394/2007. In the USA, Human Cells, Tissues, and Cellular and Tissue Based Products are under regulation 21 CFR part 1271 issued in 2001. From October 2011 active cellular immunotherapy for cancer treatment is guided by Guidance for Industry: Clinical Considerations for Therapeutic Cancer Vaccines**.**

In compliance with these regulations and guidelines, DCVAC/PCa is produced under Good Manufacturing Procedure (GMP) conditions. DCVAC/PCa is prepared individually from the patient's autologous peripheral blood mononuclear cells (PBMCs) obtained by leukapheresis. Immature DCs (iDCs) are differentiated from peripheral blood monocytes in the presence of IL-4 and GM-CSF. Subsequently the iDCs are exposed to a human prostate adenocarcinoma cell line (LNCaP) killed by an immunogenic cell death at a DC: tumor cell ratio of 5:1. LNCaP-pulsed DCs are then matured by TLR-3 ligand (Poly I:C), incubated for 12 to 20 hours at 37°C/5% CO_2. Cells are then cryopreserved in CryoStor CS10 freeze medium at a concentration of $1x10^7$/mL and stored in liquid nitrogen. These cells are stable for at least 18 months and aliquots can be stored at a drug depot and distributed to the clinical sites. On the day of drug administration, an aliquot of 1×10^7 LNCaP-pulsed mature DCs is thawed, re-suspended in 0.9% saline to a volume of 5 mL, and divided into two 2.5 mL injections for the patient's comfort. The dose is then injected subcutaneously in the inguinal or and axillary regions within 30 minutes after re-suspension.

1.3.1 Pre-clinical development

Extensive *in-vitro* studies have been conducted to characterize the potency of DCVAC/PCa and to determine the biological activity of this cell-based immunotherapy. The guidelines on human cell-based medicinal products (EMEA/CHMP/410869/2006) state that *in-vitro* studies may replace animal studies if relevant animal models have not been developed. As animal models are not relevant for this kind of product due to its autologous nature, the pharmacokinetic properties and safety of the product were evaluated in human pilot studies.

The capacity to activate antigen specific cytotoxic lymphocytes is a hallmark of mature DCs. The capacity of mature DCs to induce antigen specific T cells is tested in the potency assay. In this test, mature DCs are pulsed with the mixture of HLA class I binding peptides from influenza virus, CMV and EBV and tested for their capacity to expand virus specific T cells. As documented in internal validation study "Potential of mature dendritic cells as with regards to activation of specific cytotoxic T-lymphocytes" (VAL-54), mature DCs present in the DCVAC/PCa efficiently expand virus specific T cells after one week of co-culture with autologous T lymphocytes.

The ability to induce tumor-specific cytotoxic CD8+ T lymphocytes can also be tested using mature DCs pulsed with killed tumor cells. DCs possess the capacity to present exogenous antigens (such as apoptotic tumor cells) at MHC class I molecules and thus can activate both CD4 and CD8 tumor cells specific T lymphocytes. DCVAC/PCa activates both CD4 and CD8 LNCaP specific T lymphocytes after two weeks of culture.[14]

1.3.2 Clinical development

Phase I/II

The first-in-human study with DCVAC/PCa was initiated in 2008 (after GMP approval of manufacturing process by Czech national regulatory authority: SUKL - certificate for manufacturer No 21442/2/INS/07) in University Hospital Motol, Prague, Czech Republic. After local ethical committee approval, DCVAC/PCa was administered to the initial first patient, a

69 year old man with CRPC who failed docetaxel treatment.[15] An additional nine CRPC subjects (60-83 years, median 69 years) have been treated with DCVAC/PCa after the first line chemotherapy failure, concomitantly with the first line chemotherapy or cell-based immunotherapy alone if chemotherapy was contraindicated. The median survival of these subjects with very advanced CRPC was longer than the survival estimated by the Halabi nomogram[16] (for details, see IB). Up to 25 doses of DCVAC/PCa were administered in 5-7 weeks intervals and no serious adverse reactions (SARs) have been reported.

The investigator-driven academic study registered as **EudraCT 2009-017295-24** was initiated in July 2010. In this on-going study, 17 subjects - median age 68 years (58-78 years), have been treated by with chemo-immunotherapy. DCVAC/PCa is administered in combination with docetaxel at the standard dose of 75 mg/m^2 every 3 weeks and prednisone 5 mg twice daily. The primary endpoint of this study was safety, secondary endpoint was OS and the presence of tumor specific immune response.

As part of this study, a **bio-distribution** study was performed using DCVAC/PCa labeled with indium (^{111}In)-oxine. Labeled DCVAC/PCa in the final volume of 1 mL (6 MBq/mL) was administered subcutaneously into the bilateral axillary and inguinal areas. Nuclear scintigraphy and SPECT fused with low-dose CT images were used to visualize the migration of DCVAC/PCa to the lymph nodes. The effectiveness of labeling was 81%. Scintigraphic images of these areas were carried out for at 1, 4, 24, and 48 hours. Over the period of 48 hours, fused SPECT/low-dose CT scans were performed targeting the application site. Imaging methods showed that after DCVAC administration, labeled DCs migrated into the regional lymph nodes (see IB).

In 2010, another investigator-driven academic phase I/II single-center open-label study was initiated in prostate cancer subjects with rising PSA within 2 years after primary prostatectomy or at any time after salvage radiotherapy (**EudraCT: 2009-017259-91)**. The primary end-point is safety and toxicity, secondary end-points are PSA response and immunological response.

The number of subjects enrolled in this study was extended from 15 to 25 by a protocol amendment in 2011. In this study, DCVAC/PCa is administered every 4 weeks as a monotherapy for the period of one year. Metronomic cyclophosphamide 50 mg daily for one week is administered prior to the initiation of the active cancer immunotherapy. In a protocol amendment, extension of the administration period has been approved in those subjects who experienced prolongation of the PSADT on immunotherapy in comparison with the pre-treatment period. This study is still ongoing, 24 subjects were enrolled in the study. Median age of this group of enrolled subjects is 63 years (51-74 years). Preliminary data show the prolongation of PSADT in the majority of subjects during immunotherapy in comparison with the pre-treatment period (see IB).

Safety

All subjects are followed for possible induction of auto-immunity at one month intervals. Evaluated parameters include: serum antibody concentrations (IgG, IgA, IgM, IgE),

complement C3 and C4 concentrations, detection of monoclonal M component, antinuclear antibodies (ANA), anti-neutrophil – cytoplasmic antibodies (ANCA), anti-Fc Ig antibodies (rheumatoid factors in IgG, A and M isotypes – RF IgG, RF IgA and RF IgM), anti-transglutaminase antibodies, CRP. So far, there have been no significant laboratory changes in screened parameters before, during or after the study treatment. One patient had detectable RF IgM without clinical signs of rheumatic disease before immunotherapy and the level did not fluctuate during the treatment period.

As of March 2013, 738 doses of DCVAC ACI have been administered to the 50 subjects in the phase I/II studies; 40 subjects in the framework of the two clinical trials (EudraCT 2009-017259-91 and 2009-017295-24) and 10 subjects on an individual basis outside the scope of the clinical trials starting in 2008.

Out of 45 reported SAEs within the phase I/II clinical studies with DCVAC/PCa including subjects treated on individual basis (cumulative number from DSUR #1 and DSUR #2), none were assessed as a DCVAC/PCa-related SAE and the majority of them were associated with the progression of underlying disease. During the current reporting period, the ongoing clinical program with DCVAC/PCa has not raise any new safety concerns associated with the investigated immunotherapy. The most commonly reported AEs encompassed fatigue, gastrointestinal conditions, infections including renal and urinary disorders, and musculoskeletal pain. Autoimmunity examinations performed has not indicated any higher risk of autoimmunity in the subjects receiving DCVAC/PCa. No suspected unexpected serious adverse reaction (SUSAR) was reported by the investigator or Sponsor. No adverse events were recorded linked to the leukapheretic procedure. The first dose was administered to hospitalized subjects and vital signs were monitored. All other applications were administered in out-patient departments with 1 hour of observation. As no acute SAR related to study drug application administration has occurred so far, for future studies, out-patient department DCVAC/PCa administration is recommendable.

Phase II

A low production capacity in the University Hospital Motol GMP laboratory (2-3 individual DCVAC/PCa per month) and limited financial academic resources did not allow for further extension of clinical trials to fulfill all requirements necessary for the registration of this individual product. The biopharmaceutical company SOTIO a.s. assumed the responsibility for the further clinical development of DCVAC/PCa. The SOTIO a.s. production facility (with capacity for up to 60 individual DCVAC/PCa productions monthly) was opened in spring 2011 and received GMP status in autumn 2011.

SOTIO has conducted regulatory meetings with the European Medicinal Agency (EMA) and Food and Drug Administration (FDA) to discuss the manufacturing and clinical development plan of DCVAC/PCa.

- October 2010, EMA scientific advice for manufacturing processes EMEA/CHMP/SAWP/261301/2011.

- December 2011 SOTIO a.s. received a certificate of GMP compliance as a manufacturer from Czech Regulatory Authority (State institute for drug control – SUKL) Ref. No. sukls127848/2011 which fulfills EMA requirements.
- January 2012, EMA scientific advice on preclinical and clinical development plan EMEA/CHMP/SAWP/99235/2012 and EMEA/CHMP/SAWP/99234/2012.
- March 2012, SOTIO a.s. had a pre-IND face-to-face meeting with FDA.

Based on the outcomes from the meeting with the EMA in 2010, four phase II trials were designed in 2011. These were approved by the Czech State Institute for Drug Control (SUKL) in December 2011 and initiated in March 2012:

Clinical Trial SP001 (Eudra CT: 2011-004735-32): randomized, open-label, parallel-group, multi-center phase II clinical trial of active cellular immunotherapy with product DCVAC/PCa in patients with castrate-resistant prostate cancer. (In combination with docetaxel)

Clinical Trial SP002 (Eudra CT: 2011-004986-34): randomized, open-label, parallel-group, multi-center phase II clinical trial of active cellular immunotherapy with product DCVAC/PCa in combination with hormone therapy in patients with metastatic prostate cancer.

Clinical Trial SP003 (Eudra CT: 2011-004985-14): randomized, open-label, parallel-group, multi-center phase II clinical trial of active cellular immunotherapy with product DCVAC/PCa in patients with localized prostate cancer after primary radical prostatectomy.

Clinical Trial SP004 (Eudra CT: 2011-004967-65): randomized, open-label, parallel-group, multi-center phase II clinical trial of active cellular immunotherapy with product DCVAC/PCa in patients with localized high-risk prostate cancer after primary radiotherapy.

As of February 2013, there were 233 subjects enrolled/screened in total in the four phase II trials, 183 of them being randomized by May 6, 2013. 79 of these had the immune therapy treatment started.

A DSUR covering the period 28-December 2011 through 27-December-2012, was submitted in February 2013. There were 16 SAEs reported in 8 subjects from clinical trials during the reporting period covered by this DSUR. Only two SAE subjects out of those 8 were exposed to DCVAC/PCa at the time of the event. None of the reported SAEs were related to the study drug DCVAC/PCa. No SUSAR has been reported in that period.

Phase III

SOTIO is trying to find the most effective way to a complete global clinical development process. Based on discussions with the FDA and the EMA, the proposed phase III clinical trial targets USA and European subjects with mCRPC, who are eligible for the initiation of docetaxel treatment. Enrolled subjects will receive DCVAC/PCa or placebo in combination with docetaxel plus prednisone. We believe that the mCRPC population selection will serve to demonstrate clinical efficacy while maintaining clinical trial feasibility. Targeting earlier stages of the disease might translate into better efficacy, however, the cost and duration of the clinical

trial would be prohibitive. The lack of reliable endpoint acceptance by the regulatory authorities also complicates clinical testing in subjects at earlier stages of the disease. The mCRPC patient population is selected based on the fact that the OS is the most acceptable endpoint from a regulatory point of view. The current protocol for phase III reflects these assumptions.

1.4 Overview of Standard of Care Therapies in mCRPC

Based on improved survival benefits from two studies, docetaxel 75mg/m^2 and prednisone 5 mg bid every 3 weeks was approved by the FDA in 2004 and has become the "standard of care" first-line chemotherapy for CRPC.[17,18] The first study of one thousand and six subjects, TAX 327, showed an OS rate significantly higher (P=0.009) in the group treated every 3 weeks with docetaxel compared to treatment with mitoxantrone. The median duration of survival was 18.9 months in the group given docetaxel compared to 16.5 months in the mitoxantrone group (P=0.002). The second study compared the combination of docetaxel/estramustine to mitoxantrone/prednisone in 684 subjects. The median duration of survival was significantly improved with docetaxel/estramustine over mitoxantrone/prednisone (17.5 vs. 15.6 months, respectively, (p=0.01) and superior median TTP was also detected (6.3 vs 3.2 months, respectively, p=0.001) in subjects treated with docetaxel/estramustine.

Four drugs were approved for the treatment of mCRPC subjects after docetaxel failure (post-docetaxel

- Cabazitaxel in combination with prednisone is indicated for the treatment of subjects with mCRPC previously treated with a docetaxel based regimen.
- Abiraterone is indicated with prednisone or prednisolone for the treatment of mCRPC in adult men whose disease has progressed on or after a docetaxel-based chemotherapy regimen.
- Enzalutamide was approved for adult mCRPC subjects with metastatic castration-resistant prostate cancer who have progressed on or after docetaxel therapy. Enzalutamide doesn't require concomitant steroids.
- Radium-223, an alpha particle-emitting radioactive therapeutic agent was approved for the treatment of subjects with castration-resistant prostate cancer, symptomatic bone metastases and no known visceral metastatic disease.

Abiraterone has also been recently approved in a pre-docetaxel setting. This protocol allows for use of abiraterone in the pre-docetaxel setting in line with the approved indication. Prior treatment with abiraterone (or enzalutamide) represents one of the stratification criteria at randomization to ensure similar proportion of abiraterone pre-treated subjects within DCVAC/PCa and placebo treatment arms.

1.5 History of Amendments

SP005 Protocol version (date)	**Prepared for submission**	**Key points for creation of an updated protocol version** *(not all changes are listed in this overview)*
v.1.1 (07Mar2013)	VHP No. 201302 (positive decision 19Mar2013)	For version 1.1 positive decision was received in VHP submission.

SP005 Protocol version (date)	**Prepared for submission**	**Key points for creation of an updated protocol version** *(not all changes are listed in this overview)*
v.02 (10May2013)	IND No. 015255 (initial submission 28May2013)	Version 02 was based on v.1.1 and was modified for IND submission to FDA in USA. (Key changes included – specification of 1st line chemotherapy as docetaxel and prednisone and update of DCVAC/PCa safety information based on DSUR issued in February 2013; specification of exploratory studies on biomarkers; updated list of approved 2nd line chemotherapies).
v.03 (01Aug2013)	IND No. 015255 (Follow up submission 09Aug2013)	Version 03 was based on v.02 and was modified per feedback received from FDA. (Key changes included – Discontinuation of DCVAC/PCa or placebo with 2nd line chemotherapy; Treatment period divided into 2 periods - concurrent treatment of 1st line chemotherapy with DCVAC/PCa or placebo and Maintenance Boosting period post docetaxel-prednisone & prior 2nd line-chemotherapy; changes connected with this design change; updated list of approved 2nd line chemotherapies; Amendment of stratification criteria, updated statistical section]
v.04 (05Dec2013)	VHP No.201302 Substantial Amendment / IND No. 015255 Follow up submission	Version 04 is based on v.03 and mostly operational details have been adjusted to match properly the new design in v.03 (Study drug discontinuation, End of Treatment, Follow-up for survival); secondary endpoints were modified to better fulfill PCWG2 recommendations; inclusion and exclusion criteria were modified per PCWG2 guidelines; corrected statistical section and decreased number of stratification criteria)
v.05 (16Oct2014)	VHP Substantial Amendment No.2 / IND No. 015255 Follow up submission	Version 05 includes updates based on current experience from the clinical trial - clarified inclusion/exclusion criteria; updated sections on patient follow-up for long term survival; sections related to safety were updated to improve understanding. Sections on interim analysis and statistical analyses were updated based on feedback received from FDA. Section on exploratory studies was updated to include possibility of pharmacogenomics research.
v.05.1 (13Jan2015)	IND No. 015255 (Follow up submission) US specific protocol	Change in the exclusion criterion. It is possible to shorten the washout period for ADT.
v. 05.2 (03Aug2015)	IND No. 015255 (Follow up submission) US specific protocol	Version 05.2 introduces: clarification of follow-up procedures applicable to patients for whom leukapheresis or production failed, or who have not received DCVAC/PCa or placebo for other reasons; clarification that no further radiological examinations of a patient will be required for this trial after confirmation of radiological progression or introduction of 2nd line chemotherapy; changes related to transfer of pharmacovigilance responsibilities for safety monitoring and reporting from Chiltern to SOTIO; administrative changes in the Declaration of the Investigator

SP005 Protocol version (date)	**Prepared for submission**	**Key points for creation of an updated protocol version** *(not all changes are listed in this overview)*
v. 06.0 (28Aug2015)	VHP Substantial Amendment No.04	Version 06.0 includes the same changes as US-specific versions 05.1 and 05.2 : change in wording of the exclusion criterion that shortens the ADT washout period; clarification of follow-up procedures applicable to patients for whom leukapheresis or production failed, or who have not received DCVAC/PCa or placebo for other reasons; clarification that no further radiological examinations of a patient will be required for this trial after confirmation of radiological progression or introduction of 2nd line chemotherapy; changes related to transfer of pharmacovigilance responsibilities for safety monitoring and reporting from Chiltern to SOTIO; administrative changes in the Declaration of the Investigator; Version 06.0 additionally includes the introduction of the EQ-5D questionnaire (only in Europe) and clarification that ECOG performance status is measured also at Randomization.
v. 07.0 (08Mar2018)	VHP Substantial Amendment No.08/IND No. 015255 (Follow up submission)	• Deletion of information on third-party vendors • Deletion of information on interim analysis which will not be performed • Clarification that the date of randomization is Day 1 and not Day 0 • Update of the sections on statistics according to the updated SAP • Clarification that ECOG performance status is measured also at Randomization (already in European v. 06.0) • Introduction of the EQ-5D questionnaire (only in Europe) (already in European v. 06.0) • Safety reporting clarifications

2 STUDY RATIONALE/PURPOSE

For prostate cancer subjects with metastatic disease, androgen ablation with surgery or drugs remains the standard of care. The majority of subjects initially respond, but despite androgen ablation, all eventually progress and become castration resistant after a median duration of approximately 18-48 months. Docetaxel is currently the only primary first-line chemotherapy option in subjects who have developed symptomatic or rapidly progressive hormone refractory/castration resistant metastatic PCa with a survival advantage of about 3 months.[7,8]

Single agent autologous immunotherapy has demonstrated survival benefit in CRPC in subjects who are asymptomatic or minimally symptomatic or non-symptomatic.[19] Combination therapy with autologous immunotherapy and standard of care chemotherapy may prove to have even greater survival benefit to subjects.

2.1 Rationale for Chemo-immunotherapy

The goal of immunotherapy in advanced cancer subjects is not the complete eradication of tumor cells but rather a reversal from the escape phase back to the equilibrium stage.[12] Therefore appropriate combination of tumor mass reduction and neutralization of tumor-induced immuno-suppression might set the right conditions for the induction of anti-tumor immune response by the active immunotherapy of choice.

In contrast to the prevailing view of chemotherapy as an immuno-suppressive regimen, there is now ample evidence of chemotherapy promoting the immune response. It has been shown that certain forms of chemotherapy can cause immunogenic cancer cell death and thus promote induction of anticancer immunity.[13]

In the proposed study population DCVAC/PCa immunotherapy will be added to the chemotherapy with docetaxel and prednisone. Docetaxel is a taxane which binds to the β-subunit of tubulin and affects microtubule polymerization, leading to cell-cycle arrest at the G2/M stage and subsequent cell death. In humans, there is circumstantial evidence that taxanes can stimulate the anti-cancer immune response. A cohort of subjects with breast cancer treated with taxanes showed enhanced T cell and NK-cell functions compared to subjects untreated with taxanes.[20]

Furthermore, docetaxel administration considerably decreased myeloid derived suppressor cells (MDSC) proportion in mice models. A recent study showed that docetaxel could reverse MDSC-mediated immune suppression and modulate the tumor micro-environment, thereby improving the efficacy of immune-based therapies.[21]

A clinical trial showing that docetaxel can be administered safely with immunotherapy without inhibiting immunotherapy specific T-cell responses has been performed in subjects with castration resistant prostate cancer. In this trial, subjects previously treated with an anti-cancer immunotherapy may respond longer to docetaxel compared with a control group of subjects receiving docetaxel alone.[22,23]

Chemotherapy, which is broadly viewed as immunosuppressive, might to some extent boost an anti-tumor response.[12,13] For example docetaxel may have a relatively potent

immunomodulatory effect, enhance lymphocyte proliferation as well as the cytotoxic activity of natural killer and lymphokine-activated killer cells, while reducing Treg cell populations.[24] In addition, clinical studies have shown that chemotherapy can be combined with a cell-based immunotherapy for prostate cancer without blunting the immune response to the immunotherapy.[25] Other studies have shown that chemotherapy administered following immunotherapy may enhance the immunologic response by introducing immunologically relevant antigens to a heightened immune system upon destruction of the tumor, thereby acting as a immunotherapy boost in addition to reducing tumor burden.[24-26] Initiation of chemotherapy prior to vaccination would be an option, if we want to reduce the level of suppressive cells. Thus, the combination of chemotherapy with immunotherapy is an attractive strategy that merits clinical investigation in mCRPC.

The strategy of Sotio's clinical program in cancer immunotherapy is based on the assumption that cancer immunotherapy as a standalone treatment may be efficacious at the stage of the low tumor cell burden, ideally at the stage of the minimal residual disease. At advanced stages of the disease, cancer immunotherapy alone has little chance to affect the established population of tumor cells and overcome the immunosuppressive microenvironment of the tumor tissue. In advanced stages of the disease, immunotherapy should be combined with other treatment modalities that have the capacity to reduce the number of tumor cells, increase the sensitivity of tumor cells to the lysis by the effector cells of the immune system and to reduce the immunosuppression mediated by the tumor microenvironment.[10,27] Studies in the past 5-7 years have challenged the classical view of chemotherapy as exclusively immunosuppressive regimen and have revealed multiple immune stimulating effects of conventional anticancer drugs.[23] Chemotherapeutics, which are broadly viewed as immunosuppressive, might to some extent boost an anti-tumor response. For example taxane-based chemotherapy may have a relatively potent immunomodulatory effect, enhances lymphocyte proliferation as well as the cytotoxic activity of natural killer and lymphokine-activated killer cells, while reducing Treg cell populations.[24] Other studies have shown that chemotherapy administered following immunotherapy may enhance the immunologic response by introducing immunologically relevant antigens to a heightened immune system upon destruction of the tumor, thereby acting as an immunotherapy boost in addition to reducing tumor burden.[13,24-26] This led to the postulation of the concept of combined chemo-immunotherapy that explores the capacity of the chemotherapy to reduce the number of tumor cells and to deplete inhibitory cells, such as regulatory T-cells.[28] Chemotherapy is then followed, after a period of immune system recovery, by the stimulation of tumor cell specific effector T-cells by active cancer immunotherapy. We have determined a time window after the chemotherapy when the T cells regain the capacity to be stimulated in the antigen specific manner and the protocol design reflects those findings.

Induction of tumor specific T-cell-mediated immune response takes time and frequency of tumor-specific T-cells needs to be maintained by repeated boosting. This mechanism of action of cancer immunotherapy has to be reflected in the clinical trial designs to ensure sufficient exposure of patients to the tested treatment. DCVAC/PCa should thus be administered over prolonged period of time, until the initiation of the next line treatment initiated for the confirmed radiological progression to maximize its immunostimulating potential.

DCVAC/PCa has been shown to induce detectable tumor-specific immune responses *in-vivo* when administered concomitantly with docetaxel.[15] From ongoing phase I/II trials there is evidence that long-term application of DCVAC/PCa has an acceptable safety profile. Thus, there is a rational background that the chemo-immunotherapy approach of enhancing the immune response by repeated administration of DCVAC/PCa with standard of care chemotherapy may have an impact on the survival benefit to subjects. DCVAC/PCa is being considered as an add-on option for subjects requiring docetaxel and as a maintenance boosting of immune system after docetaxel treatment completion or discontinuation to prolong OS.

3 OBJECTIVES

This is a Phase III confirmatory study to evaluate the overall survival superiority of treatment with DCVAC/PCa plus Standard of Care (docetaxel plus prednisone) over placebo plus Standard of Care (docetaxel plus prednisone) in men with mCRPC.

3.1 Study Objectives

Primary:

The primary objective is to show superiority of treatment with DCVAC/PCa in addition to Standard of Care chemotherapy (docetaxel plus prednisone) over placebo in addition to Standard of Care chemotherapy (docetaxel plus prednisone) in men with mCRPC as measured by OS.

Key Secondary:

The key secondary objectives include assessments of safety, treatment group comparison with regards to Radiographic progression free survival (rPFS), time to prostate-specific antigen progression, time to first occurrence of skeletal related events (SRE).

Other Secondary:

To show clinical benefit of treatment with DCVAC/PCa plus Standard of Care over placebo in addition to Standard of Care with regard to time to radiographic progression or SRE, proportion of patients with skeletal related events (SRE).

Exploratory Objective:

Treatment group comparison for the following measures:

Proportion of subjects requiring second line treatment introduction and time to second line therapy, changes in quality of life (QoL) and exploratory studies for search of potential biomarkers.

3.2 Study Endpoints

3.2.1 Primary Efficacy Endpoint

Overall survival is defined as the time from randomization until death due to any cause.

3.2.2 Secondary Efficacy Endpoints

The definitions of secondary endpoints are based on the PCWG2 guidelines:[29]

1. Radiological progression free survival (rPFS)
   is defined as the time from randomization to the date of earliest objective evidence of either:
   - radiographic progression of bone lesions
     or

- radiographic progression of soft tissue lesions
  or
- death due to any cause.

2. Time to PSA progression
   is defined as the time from randomization to the date of earliest objective evidence of PSA progression
3. Time to first Skeletal Related Event
   is defined as the time from randomization to the date of first skeletal related events

Other Secondary efficacy endpoints:

- Time to radiographic progression or SRE
- Proportion of patients with Skeletal Related Events (SRE)

3.2.3 Safety Endpoints

Safety endpoints will include incidence of adverse events, clinically significant laboratory abnormalities, change in vital signs and change in ECOG performance status.

3.2.4 Exploratory Endpoints

Patient reported outcomes will include evaluation of QoL using the questionnaires FACT-P and EQ-5D (EQ-5D only in Europe).

Proportion of subjects requiring second line treatment introduction and time to second line treatment introduction will be evaluated.

Exploratory studies for potential biomarkers will be performed to search for parameters that would indicate the biological effect of trial treatment or identify subjects profiting from it.

Additional exploratory studies may be conducted based on the future advances in the field of biomarker research.

4 STUDY DESIGN

This is a randomized, double blind, placebo controlled, multi-center, international, parallel-group phase III study. Subjects with mCRPC who are candidates to receive standard of care first line chemotherapy with docetaxel plus prednisone, will be randomized 2:1 into one of two arms: an investigational arm (DCVAC/PCa) and a control arm (placebo) in addition to Standard of Care chemotherapy (docetaxel plus prednisone).

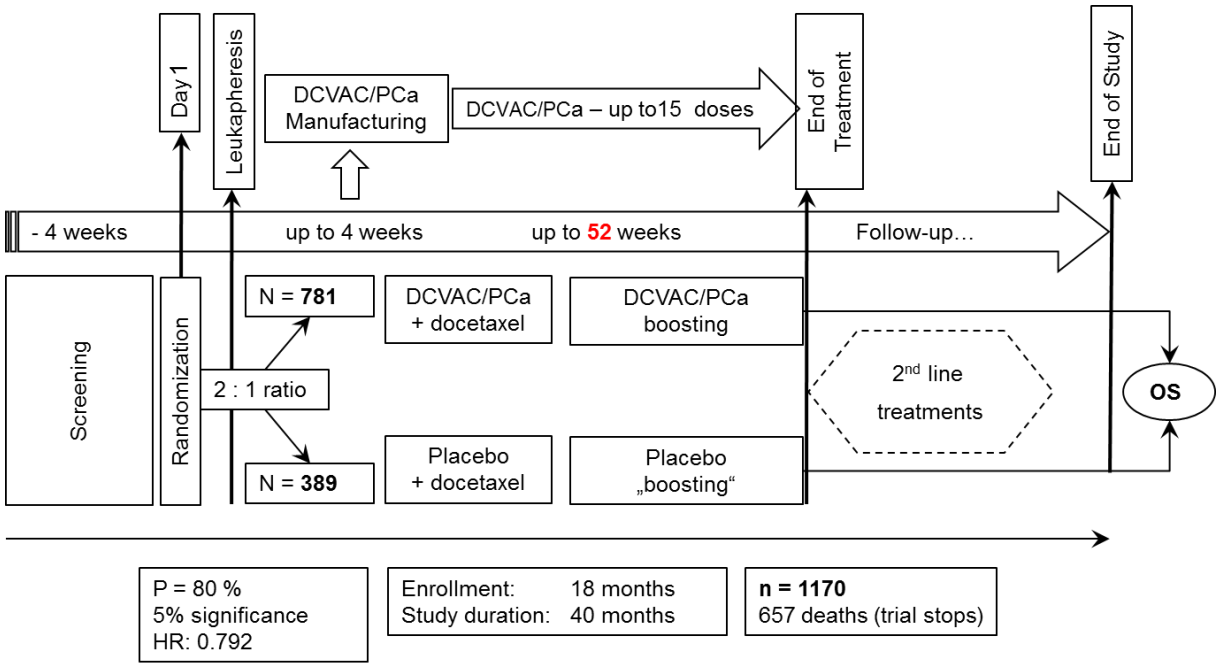
If disease progression occurs on either arm of the study, the patient may be treated with subsequent therapy at the Investigator's discretion (see section 6.1.2). Administration of DCVAC/PCa or placebo will continue until start of second line treatment. DCVAC/PCa or placebo administrations can continue after documented Disease Progression until the 2nd line treatment is started.

All subjects will receive up to 15 injections of DCVAC/PCa or placebo or until refusal, intolerance, introduction of 2nd line treatment or death occurs. All subjects will also receive Standard of Care chemotherapy until refusal, intolerance, completion, disease progression, or death. DCVAC/PCa treatment will continue as a Maintenance Boosting Phase after Standard of Care chemotherapy completion, refusal, intolerance or discontinuation for other reasons. Subjects may be treated with subsequent non-immunological therapies at the Investigator's discretion until refusal, death or study closure.

After screening (up to 28 days) and within 14 days of randomization, all subjects will have leukapheresis procedure. For those randomized to receive DCVAC/PCa, PBMCs obtained by leukapheresis will be processed by *ex-vivo* manipulation (up to 4 weeks). All subjects randomized to receive placebo injections will have a placebo prepared. Manufacturing personnel, involved in DCVAC/PCa or placebo production process, and defined investigational site unblinded team members (preparing the subcutaneous injections for both treatment arms) are the only persons that will not be blinded. All others associated with the study, including the apheresis center staff, will remain blinded to the randomization.

Standard of Care chemotherapy (docetaxel plus prednisone) will begin 3 to 7 days after completion of leukapheresis. DCVAC/PCa or placebo administration will begin approximately 5 weeks after leukapheresis and more than 7 days after the application of second cycle of Standard of Care chemotherapy. DCVAC/PCa or placebo is given as subcutaneous injections for up to 15 doses following the study schedule (see Table 1) or until refusal, intolerance, introduction of 2nd line therapy, or death. Final analysis is planned when the target number of events is reached (657 deaths) which is anticipated to occur approximately 40 months from initiation of the study.

Figure 1: DCVAC/PCa Phase III study design



5 POPULATION

Adult (age ≥18 years) men with histologically or cytologically confirmed adenocarcinoma of the prostate with clinical or radiologic evidence of metastatic disease that has progressed despite androgen deprivation therapy (ADT) and who already prior to study entry are candidates to receive first line Standard of Care chemotherapy (docetaxel plus prednisone), will be enrolled in this study. A total of approximately 1,170 subjects will be randomized at a 2:1 ratio to receive either DCVAC/PCa or placebo after introduction of the first line Standard of Care chemotherapy with docetaxel plus prednisone.

5.1 Inclusion/Exclusion Criteria

The Investigator or his/her designee shall ensure that all subjects who meet the following inclusion and exclusion criteria are offered enrollment in the study.

5.1.1 Inclusion criteria

- Male 18 years and older.
- Histologically or cytologically confirmed prostate adenocarcinoma.
- Presence of skeletal, or soft-tissue/visceral/nodal metastases according to one of the following criteria:
  - ~ Confirmed pathological fracture related to the disease

    OR
  - ~ Confirmation of distant bone and/or soft-tissue and/or visceral metastases on CT or MRI scan or bone scintigraphy.
    - According to RECIST 1.1 a lymph node may be considered malignant if its short axis is ≥ 10 mm.
    - Note that presence of disease at the primary site alone is not considered metastatic disease in accordance with PCWG2 and therefore not sufficient for entry.
    - Scans of the screening time point must be submitted to the image review facility (IRF) for confirmation of presence of metastases. The IRF will return a read result report which will prevail over the site's interpretation.

    OR
  - ~ Positive pathology report of metastatic lesion.
- Disease progression despite ADT as indicated by:
  - ~ PSA increase that is ≥ 2 ng/mL and ≥ 25% above the minimum PSA as reached during ADT or above the pre-treatment level, if no response was observed and which is confirmed by a second value 1 or more weeks later.

    OR
  - ~ Progression of measurable lymph nodes (short axis ≥ 15 mm) or visceral lesion measurable per RECIST v1.1 criteria[30] (confirmation by IRF required);

    OR
  - ~ Two or more new lesions appearing on bone scan/imaging compared with a previous scan (confirmation by IRF required)
- Maintenance of castrate conditions: patients, who have not had a surgical orchiectomy, must continue with hormone therapy (GnRH/LHRH agonists or antagonists) to reach levels

of serum testosterone of ≤ 1.7 nmol/L (50 ng/dL). The duration of the castration period must be at least 4 months before screening as evidenced by combination of clinical/laboratory data (see section 6.8.1).

- Laboratory criteria:
  - White blood cells (WBC) greater than 4,000/mm^3 (4.0 x10^9/L)
  - Neutrophil count greater than 1,500/mm^3 (1.5 x10^9/L).
  - Hemoglobin of at least 10 g/dL (100 g/L).
  - Platelet count of at least 100,000/mm^3 (100 x 10^9/L).
  - Total bilirubin within normal limits (benign hereditary hyperbilirubinemias, e.g. Gilbert's syndrome, are permitted).
  - Serum alanine aminotransferase, aspartate aminotransferase, and creatinine < 1.5x times the upper limit of normal (ULN).
- Life expectancy of at least 6 months based on Investigator's judgment.
- Eastern Cooperative Oncology Group (ECOG) Performance status 0-2.
- At least 4 weeks after surgery or radiotherapy before randomization.
- A minimum of 28 days beyond initiation of bisphosphonate or denosumab therapy before randomization.
- Recovery from primary local surgical treatment, radiotherapy or orchiectomy before randomization.
- Signed informed consent including patient's ability to comprehend its contents.

5.1.2 Exclusion criteria

- Confirmed brain and/or leptomeningeal metastases (other visceral metastases are acceptable).
- Current symptomatic spinal cord compression requiring surgery or radiation therapy.
- Prior chemotherapy for prostate cancer.
- Patient co-morbidities:
  - Subjects who are not indicated for chemotherapy treatment with first line Standard of Care chemotherapy (docetaxel and prednisone).
  - HIV positive, HTLV positive.
  - Active hepatitis B (active HBV defined in Section 7.6.8), active hepatitis C (HCV), active syphilis.
  - Evidence of active bacterial, viral or fungal infection requiring systemic treatment.
  - Clinically significant cardiovascular disease including:
    - symptomatic congestive heart failure.
    - unstable angina pectoris.
    - serious cardiac arrhythmia requiring medication.
    - uncontrolled hypertension.
    - myocardial infarction or ventricular arrhythmia or stroke within a 6 months before screening, known left ventricular ejection fraction (LVEF) < 40% or serious cardiac conduction system disorders, if a pacemaker is not present.
  - Pleural and pericardial effusion of any NCI CTCAE grade.
  - Peripheral neuropathy having a NCI CTCAE ≥ grade 2.

  - ~ History of malignant disease (with the exception of non-melanoma skin tumors) in the preceding five years.
  - ~ Active autoimmune disease requiring treatment.
  - ~ History of severe forms of primary immune deficiencies.
  - ~ History of anaphylaxis or other serious reaction following vaccination.
  - ~ Known hypersensitivity to any constituent of the DCVAC/PCa or placebo product.
  - ~ Uncontrolled co-morbidities including, psychiatric or social conditions which, in the Investigator's opinion, would prevent participation in the trial.
- Systemic corticosteroids at doses greater than 40 mg hydrocortisone daily or equivalent for any reason other than treatment of PCa within 6 months before randomization.
- Ongoing systemic immunosuppressive therapy for any reason.
- Treatment with anti-androgens, inhibitors of adrenal-produced androgens or other hormonal tumor-focused treatment performed on the day of randomization (except for GnRH/LHRH agonists or antagonists) to exclude possible anti-androgen withdrawal response. This criterion is not applicable to subjects who have never responded to anti-androgen treatment, as there is no risk of anti-androgen withdrawal response.
- Treatment with immunotherapy against PCa within 6 months before randomization.
- Treatment with radiopharmaceutical within 8 weeks before randomization.
- Participation in a clinical trial using non-immunological experimental therapy within 4 weeks before randomization.
- Participation in a clinical trial using immunological experimental therapy (e.g., monoclonal antibodies, cytokines or active cellular immunotherapies) within 6 months before randomization.
- Refusal to sign the informed consent.

6 TREATMENTS

6.1 Description of Treatments

6.1.1 Study drug/placebo

During the concurrent treatment period, DCVAC/PCa or placebo is administered to the patient subcutaneously, every 3 weeks (+/- 7 days) concurrently with Standard of Care chemotherapy. DCVAC/PCa or placebo will be administered at least 7 days before or at least 7 days after the nearest dose of chemotherapy (Day 8-15 of chemotherapy cycle).

During the Maintenance Boosting period, DCVAC/PCa or placebo is administered to the patient every 4 weeks (-7/+14 days) starting with the dose administered after the last Standard of Care chemotherapy until a maximum of 15 doses are administered (the total number incl. concurrent treatment period).

DCVAC/PCa is a cell-based immunotherapy consisting of DCs obtained from autologous monocytes cultured in the presence of GM-CSF and IL-4 and pulsed with the PCa cell line LNCaP killed by high hydrostatic pressure (HHP). The tumor cell–pulsed DCs are then activated by poly I:C, a Toll-like receptor 3 (TLR-3) ligand. DCVAC/PCa induces an immune response against tumor cells *in-vivo*.

The safety profile of DCVAC/PCa is described in Section 1.3.2. For additional details refer to the IB.

The placebo will be similar enough in appearance and the syringe will be blinded adequately to prevent the patient and blinded staff from knowing the identity of the treatment. The placebo contains only freezing medium, the same used when producing DCVAC/PCa: CryoStor CS10. It is an aqueous, serum-free, animal protein-free balanced electrolyte solution, that includes various sugars, salts, and other components that provide pH buffering, oncotic/osmotic support, free radical scavenging, and energy substrates. It also contains 10% dimethylsulphoxide (DMSO). It is manufactured according to GMP with USP grade components.

It is unknown if the placebo will have AEs. Subjects in both treatment arms could have potential sensitivity reactions to the freezing medium.

6.1.2 Standard of Care therapies

Investigators should use authorized Standard of Care chemotherapy (docetaxel plus prednisone) and should reference the prescribing information provided with the product when treating the subjects.

- Docetaxel in combination with prednisone or equivalent is indicated for the treatment of subjects with mCRPC. The recommended dose of docetaxel is 75mg/m^2 intravenously after reconstitution and dilution. Prednisone 5mg orally twice daily or equivalent is administered continuously.
- All subjects will receive Standard of Care chemotherapy (docetaxel plus prednisone) until completion, refusal, intolerance, disease progression, or death.

Following discontinuation of docetaxel and study drug/placebo, all subjects may be treated with subsequent non-immunological therapy at the Investigator's discretion using the protocol defined list of treatment options:

Defined list of second line treatment options

The defined list of second line treatment options allowed for use in mCRPC patients after docetaxel failure (in alphabetic order, based on NCCN guidelines, Version 2.2013)[30]: abiraterone, cabazitaxel, docetaxel, enzalutamide, mitoxantrone, radium-223.

- Abiraterone and enzalutamide represents secondary hormonal manipulation and have shown survival benefit in clinical trials.
- Cabazitaxel is cytotoxic chemotherapy that has shown survival benefit when used after docetaxel.
- Radium-223 has shown survival benefit in patients with bone metastases and without visceral metastases.
- Docetaxel rechallenge can be used in patients who have not demonstrated definitive evidence of progression on prior docetaxel therapy.
- Mitoxantrone has not demonstrated survival improvement in post-docetaxel use but remains a palliative option, particularly in men who are not candidates for cabazitaxel therapy.

After failure of second line therapy, the selection of treatment options is at investigator's discretion. There are some other cytotoxic agents that are used as a salvage therapy[7](e.g. reintroduction of docetaxel, vinorelbine, vinblastine, doxorubicin, etc.).

6.2 How The Study Drug is supplied

6.2.1 Study drug/placebo

Each individual dose of DCVAC/PCa or placebo is delivered to the study site in a temperature controlled shipping container that must be handled per the instructions in the Supply Chain Manual. Over the course of the study the site will receive up to 15 individual doses made specifically for a patient.

Each individual dose contains 1mL of DCVAC/PCa or placebo in a cryovial sealed in a secondary package (plastic bag). Each dose is produced for a specific patient and will be labeled accordingly.

Three separate self-adhesive labels which are identical to the primary label are included and will be used for labeling the syringe for administration and documentation purposes.

The completed IMP Administration Checklist is then provided to the blinded study team member and this check list must be inserted into the source documentation later (see section 6.3.1 and IMP Administration manual).

6.2.2 Standard of Care therapies

Standard of Care therapies with marketing authorization will be used for this protocol and will be obtained by the site as per regulatory or institutional standards.

6.3 Storage, Preparation and Administration

6.3.1 DCVAC/PCa / placebo

Storage

DCVAC/PCa or placebo will be transported to the clinical site frozen in liquid nitrogen vapors (referred to as dry shipper) at a temperature below -150 °C or on dry ice at a temperature below -50 °C (referred to as thermo box) according to the clinical site location.

After dilution, the DCVAC/PCa or placebo needs to be stored at room temperature until administration.

Preparation

Prior to obtaining monocytes, patients were tested and found negative for HIV, HBV, HCV and Syphilis. DCVAC/PCa and placebo treatment are sterile. Refer to the IMP Administration manual for detailed instructions regarding the product handling and preparation. Standard caution should be taken to protect the Investigational medicinal product (IMP) aliquot (DCVAC/PCa or placebo) from contamination when preparing for administration. DCVAC/PCa or placebo need to be handled and administered as standard sterile subcutaneous medicinal preparation.

Administration

- The subcutaneous injections must be administered within 30 minutes after the product dilution. Diluted product must be stored at room temperature until administration. Caution should be taken so as not to leave the prepared dose in direct sunlight.
- The subcutaneous injection is then divided into two 2.5 mL doses for better tolerability. Both injections are given in the lymph node area using 23 gauge (0.6 mm) subcutaneous injection needle.
- Insert completed IMP Administration Checklist into the source documentation.

6.3.2 Study Drug Injection Sites

The doses are repeated every 3- 4 weeks (see Table 1) and should be rotated to an alternate anatomical area different to the previous injection, i.e. either right axillary area and left groin area or vice versa (for details see IMP Administration manual).

6.3.3 Standard of Care therapies

Standard of Care therapies with marketing authorizations used for this protocol will be prepared and stored according to the prescribing information provided with the product.

6.4 Patient Numbering

Each patient is uniquely identified in the study by a "Subject ID" consisting of a protocol number (SP005), the site number (Cxxx) and a subject sequential number (Bxxx). The site number is assigned by SOTIO to the Investigative site. Upon signing the informed consent form (ICF), the patient is assigned a sequential subject number by the Investigator. At each site, the first patient is assigned patient number 1 (B001), and subsequent subjects are assigned consecutive numbers (e.g. the second patient is assigned patient number 2; the third patient is assigned patient number 3). The Investigator or his/her staff will contact the IVRS/IWRS and provide the requested identifying information for the patient to register him into the IVRS/IWRS. Once assigned to a patient, the subject number will not be re-used.
If the patient fails to be found eligible after all screening procedures are complete, the IVRS/IWRS must be notified within 3 days that the patient will not be randomized and screen failure will be recorded in the source documentation. Subjects may undergo up to one additional screening for eligibility (re-screening, see Section 6.7.1). In such occasion the subject will get a new „Subject ID".

6.5 Treatment Assignment

At Randomization visit, all eligible subjects will be centrally randomized in a 2:1 DCVAC/PCa to placebo allocation ratio via IVRS/IWRS. The randomization schedule is computer generated and will be stratified by:

- Region (US or other)
- Prior therapy (abiraterone or enzalutamide or neither of the two)
- ECOG status (0 - 1 or 2)

Although, race is not used as a stratifying factor, special considerations will be given to include sites with a majority of African-American subjects in order to ensure a representation of racial and ethnic groups.

The treatment assignment will be generated using the following procedure to ensure that treatment assignment is unbiased. A patient randomization list will be produced by the IVRS/IWRS provider using a validated system that automates the random assignment of treatment. The Investigator or his/her delegate will call or log on to the IVRS/IWRS and confirm that the patient fulfills all the inclusion/exclusion criteria.

Randomization assignment will be available to the SOTIO unblinded team members who are responsible for the drug manufacturing and packaging. Each package of study drug will contain the unique identification code containing "Subject ID" and LOT number.

6.6 Treatment Blinding

Subjects, investigational site staff, personnel performing the assessments and monitoring, personnel performing leukapheresis, and data analysts will remain blinded to the identity of the study treatment from the time of randomization until database lock, using the following methods:

(1) Randomization data are kept strictly confidential until the time of unblinding, and will not be accessible by anyone else involved in the treatment study with the following exceptions:

- SOTIO personnel that coordinate and manufacture DCVAC/PCa and placebo products.
- Independent statistician who will prepare information for IDMC.
- IDMC members will routinely review blinded data, unless a safety signal has been identified and IDMC has decided to unblind the relevant cases to assess the signal.
- Unblinded SOTIO pharmacovigilance personnel performing assessment of SAEs and their potential qualification as SUSARs and further distribution to regulatory bodies based on the treatment allocation.
- Site staff receiving IMP dose from shipper and preparing the DCVAC/PCa or placebo for diluted and ready-to-inject form.

(2) The identity of the treatments will be concealed by leukapheresis procedure in both treatment arms, the use of study drug/placebo that are identical in packaging, labeling, and schedule of administration. The placebo will be similar enough in appearance and the syringe will be blinded adequately to prevent the patient and blinded staff from knowing the identity of the treatment.

Unblinding will only occur in the case of patient emergencies (see Section 6.14), for regulatory reporting purposes and at the conclusion of the study.

6.7 Patient Treatment Sequence

6.7.1 Screen/Randomize

All subjects will be screened for eligibility to the study for up to 4 weeks before randomization. Central randomization will occur on Day 1 when subjects are determined to have met all of the inclusion and none of the exclusion criteria. Subjects may undergo up to one additional screening for eligibility (re-screening).

6.7.2 Schedule leukapheresis procedure

All subjects will undergo an evaluation for leukapheresis by technically qualified personnel either at the leukapheresis center or at investigational site to fulfill local requirements. This visit (or visits – if necessary) must be performed prior to the leukapheresis procedure itself. The purpose of this visit is to assess technical aspects such as the patient's venous access (eventually a possibility to insert central venous catheter), to collect blood samples if required by legislations/regulations and to provide further information to the patient regarding the procedure. Venous access check will be done by technically qualified personnel. Serological tests will be performed according to local regulations in recommended timelines. Additional blood tests might be required per leukapheresis facility requirements.
Subjects are not allowed to use ACE inhibitors 24 hours prior to leukapheresis. Calcium might be administered to the patient as a precaution measure to supplement Ca^{2+} blood levels during the leukapheresis procedure. All leukapheresis centers will have been approved as part of the study. The patient will be scheduled for the leukapheresis procedure to occur within 14 days after randomization and before the first dose of the Standard of Care chemotherapy. Detailed information is available in the relevant study manual.

6.7.3 The Leukapheresis Procedure

All subjects will undergo just one leukapheresis in a facility approved for the study. A volume of more than 40 mL with a minimum of $4x10^9$ PBMCs will be obtained. Maximum volume of leukapheresis product is 500 mL containing suspension of PBMCs with possible addition of autologous plasma. Following the leukapheresis procedure the cells will be transported under specified and controlled conditions to the processing facility. Complete specifications on the leukapheresis process, relevant safety information and list of potential complications can be found in the relevant study manuals. The processing of the cells for the manufacturing of the DCVAC/PCa or placebo requires up to 4 weeks.

6.7.4 Treatment with Standard of Care chemotherapy plus DCVAC/PCa or placebo and consequently with DCVAC/PCa or placebo alone

Treatment period will consist of two parts. Concurrent treatment period - first line Standard of Care chemotherapy with docetaxel plus prednisone administered every 21 days will begin 3 to 7 days after the leukapheresis procedure. The initial dose of DCVAC/PCa or placebo will be administered subcutaneously at least 7 days after the second cycle of docetaxel, which is approximately 5 weeks after the leukapheresis procedure. All doses administered concurrently with Standard of Care (docetaxel plus prednisone) will be given in 3 week intervals (+/- 7 days). DCVAC/PCa or placebo will be administered at least 7 days before or at least 7 days after the nearest chemotherapy dose, e.g. at Day 8-15 of the chemotherapy cycle.
After Standard of Care chemotherapy is completed or discontinued, DCVAC/PCa or placebo will be given in Maintenance Boosting period. Frequency of DCVAC/PCa or placebo application will continue in 4 week intervals with an acceptable window of - 7/+14 days for up to total 15 doses.

After the first dose of DCVAC/PCa or placebo, the patient will be observed for 2 hours in a supervised out-patient setting for AEs. For the second dose and all subsequent doses of DCVAC/PCa or placebo administration the patient will be observed for at least 30 minutes post-injection in a supervised out-patient setting.

A significant and potentially beneficial immune response may cause transient increases in the size of lymph nodes or tumor masses, which could be identified as progressive disease based on modified RECIST 1.1 criteria.[31] Additionally, currently used immunological treatments (e.g., ipilimumab) tend to show that despite initial signs of cancer progression there is a higher chance for the subjects to gain prolongation of survival. For these reasons, the application of DCVAC/PCa or placebo will continue irrespective of progression, however, it must be discontinued at the moment of introduction of 2nd line antitumor treatment. Following a confirmed documented radiological progression, Standard of Care chemotherapy will be discontinued and the second line treatment may be introduced at the Investigator's discretion using the protocol defined list of second line treatments (see section 6.1.2).

6.8 Ancillary Treatments

6.8.1 Androgen deprivation therapy

All subjects who have not had a surgical orchiectomy must continue with hormone therapy (GnRH/LHRH agonists or antagonists) to reach levels of serum testosterone ≤ 1.7 nmol/L (≤ 50 ng/dL). The duration of the castration period (orchiectomy or GnRH/LHRH agonists or antagonists) must be at least 4 months before screening of the patient into the study and continue throughout the entire trial. Confirmation of the castrate condition must be corroborated by the evidence of the first GnRH/LHRH analog administration more than 6 months before screening, and serum testosterone level ≤ 1.7 nmol/L measured either more than 4 months before screening or at screening. Secondary hormonal manipulation, if used (e.g. abiraterone, enzalutamide), must be discontinued on the day of randomization at the latest and may be introduced only after DCVAC/PCa or placebo is discontinued.

6.8.2 Rescue medication

Basic life support equipment as defined by respective national standards of care must be available at sites, where application of DCVAC/PCa or placebo is performed.

Investigators should comply with institutional standards of care in managing subjects who exhibit life-threatening symptoms while receiving treatment under this protocol. Specific country references to Resuscitation Guidelines such as those for the UK found on the web site http://www.resus.org.uk/pages/guide.htm#updates are recommended.

Subjects having a serious allergic reaction to DCVAC/PCa or placebo must be withdrawn from the treatment phase of the study.

6.8.3 Other concomitant medications

The Investigator should instruct the patient to notify the study site about any new medications taken from screening. All medications and significant non-drug therapies (including physical therapy and blood transfusions) administered after screening must be listed on the Concomitant Medications/Significant Non-drug Therapies eCRF. Active immunization with anti-infectious vaccines when appropriately indicated is allowed according to prescribing information as well as administration of intravenous immunoglobulins for the correction of secondary hypogammaglobulinemia.

6.8.4 Prohibited Medications

Prohibited medications include:

- Systemic immuno-suppressive therapy, including systemic corticosteroids at doses greater than 40 mg of hydrocortisone daily or equivalent, for any reason other than the treatment of prostate cancer.
- Immunotherapy with other approved medications including monoclonal antibodies, active cellular therapies and cytokines.
- Other investigational medicinal products.

- Concomitant anti-androgens other than GnRH/LHRH agonists or antagonists for maintaining castrate condition.
- ACE inhibitors 24 hours prior to leukapheresis.
- Concomitant use of alpha particle-emitting radioactive therapeutic agent (e.g. radium-223), or other radioactive isotopes indicated for systemic treatment of bone metastases.

6.9 Permitted Dosing Modifications

Administration of Standard of Care first line chemotherapy (docetaxel plus prednisone) will be performed according to the approved prescribing information provided with the product. The recommended dose of docetaxel is 75 mg/m^2. Prednisone or prednisolone 5 mg orally twice daily (or equivalent) is administered continuously. Docetaxel should be administered when the neutrophil count is ≥ 1,500 cells/mm^3. In patients who experienced either febrile neutropenia, or neutrophil count < 500 cells/mm^3 for more than one week, or severe or cumulative cutaneous reactions, or severe peripheral neuropathy during docetaxel therapy, the next dose of docetaxel should be reduced from 75 mg/m^2 to 60 mg/m^2. If the patient continues to experience these reactions at 60 mg/m^2, the treatment should be discontinued. All changes in dosage must be recorded in the eCRF.

For the study drug DCVAC/PCa or placebo, the full dose will be administered across all applications and dosing modification is not applicable. Each dose during the Concurrent Treatment period will be administered between two chemotherapy cycles and the gap between DCVAC/PCa or placebo and previous and subsequent chemotherapy must be at least 7 days. If the chemotherapy application is delayed for any reason, DCVAC/PCa or placebo will be administered at least 7 days after the last chemotherapy administration. In case of acute infection or fever, DCVAC/PCa or placebo application has to be postponed until patient has recovered from the condition. When interruption of treatment is needed, DCVAC/PCa or placebo is allowed to be re-introduced within 12 weeks.

6.10 Study drug discontinuation/End of Treatment

Subjects are expected to remain on study treatment until completion or until introduction of 2nd line antineoplastic therapy. After discontinuation for any reason or completion of all doses of DCVAC/PCa or placebo per protocol, subjects should be considered off-DCVAC/PCa or placebo treatment and to be evaluated at the next regularly scheduled visit within 30 days from the last dose of DCVAC/PCa or placebo (End of Treatment Visit). It is highly recommended to evaluate disease progression prior to introduction of 2nd line antineoplastic therapy if the decision is made before completion of study treatment.

Maximum gap between two consequent DCVAC/PCa or placebo administrations should not exceed 12 weeks. If interruption of DCVAC/PCa or placebo lasts for more than 12 weeks, the study medication should be stopped.

All randomized patients who subsequently permanently discontinue the treatment, will still be followed up according to section 6.12 (even if the subject discontinued for the following reasons):

- Emergency unblinding of treatment assignment when investigator or patient are unblinded (see section 6.14).
- Protocol violation requiring patient withdrawal as assessed by the Investigator or the Sponsor.
- Patient unable to tolerate the leukapheresis procedure.
- Failure to produce DCVAC/PCa or placebo in the Sponsors manufacturing facilities.
- Patients having a serious allergic reaction to DCVAC/PCa or placebo must be withdrawn from the treatment phase of the study.

6.11 Follow-up for toxicities

All subjects will be followed-up for AEs at the next regularly scheduled visit following the last dose of treatment (End of Treatment Visit) up to 30 days from last administration of study medication or up to introduction of 2nd line antineoplastic therapy, whichever occurs first. An unscheduled visit may be added if clinically indicated.

6.12 Follow-up for survival

Subjects for whom leukapheresis or production failed, or who have not received DCVAC/PCa or placebo for other reasons, will be followed up for survival only. The survival data will be collected every 12 weeks by directly contacting the subject (or a relative/caretaker). Subjects who discontinue either DCVAC/PCa or placebo treatment should enter the follow-up phase of the study. See Table 1 for the required assessments for these subjects during follow-up. If applicable, subjects should continue on 2nd line antineoplastic therapies (see section 6.1.2) for prostate cancer and then other therapies. All randomized patients will remain in the study and will be followed until ICF withdrawal, death or study closure regardless their future treatment and /or participation in different clinical trials. Final analysis will be performed upon reaching the targeted number of events. If subject refuses to return to the site for follow/up assessment, the investigator will make every effort to contact the subject (or a relative/caretaker) to collect survival information. The investigator should show “due diligence” by documenting in the source documents steps taken to contact the patient, i.e., dates of telephone calls, registered letters, etc.

6.13 Premature patient withdrawal / End of Study

Subjects may voluntarily withdraw from the study or be discontinued at the discretion of the Investigator at any time. If such withdrawal occurs, or if the patient fails to return for visits, the Investigator shall determine the primary reason for a patient’s premature withdrawal from the study and record this information on the End of Study eCRF and notify the IVRS/IWRS.

Subjects **must** be withdrawn from the study prematurely for one of the following reasons:

- Informed consent withdrawn for continued study participation.
- Death.

If premature study withdrawal occurs for any reason, the Investigator must make every effort to contact the patient and determine the primary reason for a patient's premature withdrawal from the study and record this information on the End of Study eCRF. The End of Study visit assessments should be performed wherever possible; however, at a minimum, subjects will be contacted for a safety evaluation assessment up to 30 days from last administration of study medication.

6.14 Emergency unblinding of treatment assignment

Emergency unblinding should only be undertaken when it is essential to treat the patient safely and efficaciously. Most often, study drug discontinuation and knowledge of the possible treatment assignments are sufficient to treat a study patient who presents with an emergency condition. Emergency code breaks are performed using the IVRS/IWRS. The study medical monitor will be contacted before unblinding, wherever possible, and when the patient's safety is not compromised. When the Investigator contacts the system to unblind a patient, he/she must provide the requested patient identifying information and confirm the necessity to unblind the patient. The Investigator will then receive details of the drug treatment for the specified patient and a fax or email confirming this information. The system will automatically inform the SOTIO representatives that the code has been broken.

There may be instances where unblinding may be required for a safety review at the request of the IDMC or for a Regulatory Authority. If this is not considered to be emergency unblinding, the assigned treatment is not revealed to the site Investigator, the study Principal Investigator, or the clinical or data management staff of the Sponsor or the CRO, the patient will continue with study treatment until protocol criteria for withdrawal are met.

7 VISIT SCHEDULE AND ASSESSMENTS

Screening Period
All subjects will be evaluated for inclusion in the study during the Screening Period. Procedures to be performed are described in Table 1.

Randomization Visit
At the day of Randomization Visit subjects will be re-evaluated for inclusion in the study, relevant tests and safety information will be collected (see Table 1) and subjects who are eligible for the study based on screening assessments will be randomized on Day 1 as described in Section 6.5.

Leukapheresis Evaluation and Leukapheresis Timeline
Per section 6.7.2 and prior to the leukapheresis (not more than 7 days where required by the local law and regulation) procedure all subjects will undergo leukapheresis evaluation (laboratory tests and vein access check). Laboratory tests must be performed according to local law and regulations. All subjects will undergo leukapheresis procedure within 14 days after randomization.

Concurrent Treatment Period
During the Concurrent Treatment Period patients will receive Standard of Care chemotherapy with docetaxel plus prednisone plus DCVAC/PCa or placebo every 21 days. Patients will begin the study receiving first line chemotherapy (docetaxel and prednisone) and DCVAC/PCa treatment will be added after the second cycle of docetaxel.

The end of the Concurrent Treatment Period starts when the first line Standard of Care chemotherapy has been discontinued for any reason.

Maintenance Boosting Period
During the Maintenance Boosting Period subjects will continue to receive DCVAC/PCa or placebo every 28 days until completion of all manufactured 15 doses or refusal, intolerance, introduction of 2nd line treatment or death. Based on the Investigator's decision, the second line Standard of Care therapy may be introduced if considered to be beneficial. DCVAC/PCa administration must be discontinued in this case. The end of the Maintenance Boosting Period starts when the DCVAC/PCa or placebo treatment has been discontinued for any reason.

End of Treatment
The End of study treatment visit to be done within 30 days from the last application of DCVAC/PCa or placebo.

Follow-up Period
During the Follow-up period subjects will be off the DCVAC/PCa or placebo treatment but may continue Standard of Care therapy. Subjects are followed until refusal, death or study

closure. See Section 6.13 for the reasons subjects are considered to be prematurely withdrawn from the study.

End of Study visit

The End of Study visit occurs when the patient is withdrawn from the study for any reason. It is primarily captured when a subject has a documented date of death.

The Visit Evaluation Schedule (Table 1) lists all of the assessments and indicates with an "X" the visits when they are performed. All data obtained from these assessments must be supported in the patient's source documentation. Assessments that are transferred to the database electronically (e.g. laboratory data) are listed by test name. Please note that the Visit Evaluation Schedule indicates visits and evaluations to be performed under ideal circumstances. For some assessments (e.g. PSA and CT/MRI/bone scan), the interval between evaluations (e.g. 12 weeks) should be observed if the visit schedule is modified for any reason. Therefore, such assessments might be performed at other visits than shown here.

Table 1: Visit Evaluation Schedule

Study period	Screening	Randomization	Leukapheresis	Concurrent Treatment Period*																		Maintenance Boosting Period†						EOT[1]	Follow Up	EOS[2]
				3 week cycles																		4 week cycles						4Weeks	12 week cycles	4 weeks
Cycle				1	2		3		4		5		6		7		8		9		10		1	2	3	4	5	6			
Week of Cycle				1	1	2	1	2	1	2	1	2	1	2	1	2	1	2	1	2	1	2	1	1	1	1	1	1			
Informed consent	X																														
Treatment Assignment		X																													
Demographic data	X																														
Medical history	X																														
Hematology	X	X		X	X		X		X		X		X		X		X		X		X		X	X	X	X	X	X	X		
Biochemistry (incl. ALP, LDH)	X	X		X	X		X		X		X		X		X		X		X		X		X	X	X	X	X	X	X		
PSA[3]	X	X							X								X						X			X			X	X[3]	
TSH	X								X								X						X			X			X		
Urinalysis	X	X		X			X				X				X				X				X			X			X		
HIV, syphilis, HTLV, Hepatitis B and C	X		X[5]																												
Testosterone	X[16]																														
aPTT / Quick (PT)	X																														
Full PE and height	X																														
Symptom directed PE		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Vital signs & weight	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
ECOG score	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	

Study period	Screening	Randomization	Leukapheresis	Concurrent Treatment Period*																				Maintenance Boosting Period†						EOT[1]	Follow Up	EOS[2]
				3 week cycles																				4 week cycles						4Weeks	12 week cycles	4 weeks
Cycle				1	2		3		4		5		6		7		8		9		10		1	2	3	4	5	6			
Week of Cycle				1	1	2	1	2	1	2	1	2	1	2	1	2	1	2	1	2	1	2	1	1	1	1	1	1			
FACT-P questionnaire	X			X			X				X				X				X				X	X	X	X	X	X	X		
EQ-5D questionnaire (only in Europe)	X						X								X[18]								X[18]			X[18]			X[18]	X[18]	
Samples for research[6]		X											X																X		
Leukapheresis evaluation[7]			X[4]																												
Leukapheresis procedure[8]			X																												
DCVAC/PCa or placebo in process			X	X	X																										
First line chemotherapy[9,*]				X	X		X		X		X		X		X		X		X		X										
DCVAC/PCa or placebo s.c.injection[10,†]						X		X		X		X		X		X		X		X		X	X	X	X	X	X	X[11]			
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[12]	X[12]
Documentation of any SRE		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Disease assessment[14] CT(MRI[13])/bone scan	X[15]								X								X						X			X				X[14]	
Concomitant Medications		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Survival Follow-up[17]																															X	X

*The first line chemotherapy may be discontinued early if subject refuses or has intolerance. Subjects are then eligible to continue in the Maintenance Boosting period, receiving DCVAC/PCa or placebo as monotherapy in 4 weeks intervals.

†When subjects finish or stop receiving DCVAC/PCa or placebo, they complete the End of Treatment procedures within 30 days after the last dose of the study drug (End of Treatment Visit) and enter the Follow-up period.

[1] End of Treatment (EOT) visit procedures are performed within 30 days after discontinuation of DCVAC/PCa or placebo.

[2] End of Study (EOS) visit procedures are performed within 30 days after premature withdrawal for ICF withdrawal, death, or study closure.

[3] Until progression, introduction of 2nd line therapy or end of clinical trial, every 12 weeks.

[4] Vein access check at investigational site or by technically qualified personnel.

[5] Per local regulations for infectious diseases (HBV, HCV, HIV, HTLV, syphilis) as applicable. Additional blood tests might be required per apheresis center requirements.

[6] Blood sample for research purposes to be taken at randomization, before administration of the 5th dose of DCVAC/PCa or placebo, at EOT visit.

[7] Leukapheresis evaluation to be scheduled before leukapheresis procedure according to local law and regulations.

[8] Leukapheresis procedure to be performed within 14 days of randomization.

[9] First line chemotherapy with docetaxel plus prednisone must begin 3 to 7 days after leukapheresis.

[10] The subcutaneous injection of DCVAC/PCa or placebo must be given at least 7 days before or at least 7 days after the nearest dose of standard of care chemotherapy.

[11] Until total number of 15 doses of DCVAC/PCa / placebo, depending on number of first line chemotherapy cycles; until introduction of 2nd line chemotherapy

[12] Serious Adverse Reactions (SARs) and Adverse Events of Special Interest (AESIs) with a plausible causal relationship to investigational product.

[13] In case of sensitivity to i.v. contrast medium, the CT chest scan should be performed without i.v. contrast medium and the abdomen and pelvis should be imaged using MRI.

[14] Imaging will be performed every 12 weeks as close as possible to the PSA sampling until radiological progression, introduction of 2nd line therapy or end of clinical trial.

[15] Not earlier than 28 days before screening, and preferably not later than 14 days before randomization to allow for timely confirmation of radiographic eligibility by central reading.

[16] To be measured in case that historical (older than 4 months before screening) serum testosterone value doesn´t exist.

[17] Subjects for whom leukapheresis or production failed, or who have not received DCVAC/PCa or placebo for other reasons, will be followed up for survival only

[18] Every 12 weeks until progression and at 6 months and 12 months after progression.

7.1 Patient Demographics/Other Baseline Characteristics

Screening evaluations will occur in a period of up to 28 days from the first screening evaluation to randomization unless otherwise specified. The purpose of the screening period is to assure that subjects meet all entry criteria and that they adequately comprehend the protocol and its requirements. More than one clinic visit may be required in order to complete all screening evaluations.

The screening/baseline procedures will collect the following information:

- Disease History:
  - Histological or cytological diagnosis of prostate adenocarcinoma.
  - Date of initial diagnosis.
  - Staging, Gleason score and PSA level at initial diagnosis.
  - Two last historical PSA values before screening including dates
  - Details of primary treatment for prostate cancer including dates of therapy (radiation, surgery, steroids and/ or hormones), prior use of sipuleucel-T, abiraterone and enzalutamide.
  - Physician's assessment of progression of disease to qualify for study.
  - Castration history and duration of treatment before screening. Serum testosterone level must be measured at screening in case that historical (older than 4 months before screening) serum testosterone value doesn´t exist. In such case investigator must document that patient started GnRH/LHRH analogs more than 6 months before screening.
  - Bisphosphonate or denosumab or opioid analgesic or corticosteroids use and duration of treatment prior to study entry.
  - History/baseline of SRE.
- Patient Demographics – age, ethnicity, race.
- Life expectancy based on investigator's judgment.
- Medical history – significant historical events or findings and any pre-existing conditions – history of anaphylaxis or other serious reactions following vaccination, history of severe forms of primary immune deficiencies.
- Physical exam – concurrent illness, height, weight, vital signs (blood pressure, heart rate and temperature), peripheral neuropathy, pleural and pericardial effusions.
- Eastern Cooperative Oncology Group (ECOG) Performance Status, Quality of life (QoL) questionnaires FACT-P and EQ-5D (EQ-5D only in Europe).
- Disease assessment by CT, bone scan (historical scans can be up to 2 years old, screening scans can be performed within additional 4 weeks before screening period starts, only if results can be forwarded for central review).
- Hematology and Biochemistry including LDH, ALP, TSH and PSA. Urine analysis will be performed.
- HIV, HTLV, syphilis, HBV and HCV status.
- Vein access check at investigational site or by technically qualified personnel.

7.2 Treatments

Standard of Care therapy treatments will be recorded in the eCRFs documenting date of therapy, dosage, route of administration, and reasons for dose modifications and discontinuation.
DCVAC/PCa or placebo treatment will be recorded in the eCRFs documenting date and time of therapy and site of injection. Hypersensitivity reactions or other untoward events will be recorded in the AE eCRF page.

7.3 Efficacy

Trial objectives and outcomes include OS, Radiographic progression free survival (rPFS), Time to PSA progression, Time to first skeletal related events and proportion of patients with skeletal related events.

1. Overall survival (OS) is defined as the time from randomization until death due to any cause. Overall survival can be determined by collection of the date of death using autopsy reports, death certificates, and/or hospital/clinic records indicating date of death and source of information.

2. Radiological progression free survival (rPFS)
   is defined as the time from randomization to the date of earliest objective evidence of either:
   a. radiographic progression of bone lesions
      or
   b. radiographic progression of soft tissue lesions
      or
   c. death due to any cause

3. Time to PSA progression is defined as the time from randomization to the date of earliest objective evidence of PSA progression.

4. Time to first skeletal related events is defined as the time from randomization to the date of first skeletal related events. Proportion of patients with skeletal related events is defined as the proportion of patient after randomization

7.3.1 Prostate-specific antigen

PSA levels will be assessed every 12 weeks (+/-7 days) as close as possible to imaging assessments (see Visit Evaluation Schedule, Table 1).

The evidence of PSA progression is defined as: time from randomization to the date of PSA absolute increase ≥ 2 ng/mL and ≥ 25% above nadir or baseline values confirmed by a second consecutive value obtained at least 3 weeks later.

7.3.2 Soft Tissue and Bone Lesions

7.3.2.1 Schedule of Imaging Time points

Imaging will be performed at screening (not earlier than 28 days before screening, and preferably not later than 14 days before randomization to allow for timely confirmation of radiographic eligibility by central reading) and after randomization at 12 week (±7 days) intervals. Confirmation of imaging progression is required on a follow-up imaging time point at earliest 6 weeks later, preferably at the following regular imaging time point date, if the progression occurs at week 12 and 24. After confirmation of radiological progression or after introduction of 2nd line therapy, no more imaging examinations of the patient will be required for this trial.

If the patient did not progress but was removed from study treatment (EOT), the every 12 week schedule (+/-7 days) for imaging assessment will be followed until progression, introduction of 2nd line therapy or end of clinical trial to assess radiological progression. It is highly recommended to evaluate disease progression prior to introduction of 2nd line antineoplastic therapy if the decision is made before completion of study treatment.

7.3.2.2 Mandatory Imaging Modalities at Each Imaging Time point

- Contrast (intravenous and oral) enhanced spiral CT of the chest, abdomen and pelvis
    - In case of sensitivity to i.v. contrast medium, the CT chest scan should be performed without i.v. contrast medium and the abdomen and pelvis should be imaged using MRI.
    - Positive oral contrast media (iodine or barium) is preferred over negative oral contrast media (pure water or solutions of mannitol or methylcellulose).
- Technetium bone scan of the whole body

Ultrasound is not accepted for tumor evaluation. **Note that the same imaging techniques must be used at all time points.**

An imaging guidance document will be provided to the sites for a detailed description of the imaging procedures.

7.3.2.3 Site Radiologist

All scans obtained from all subjects enrolled at each site should be reviewed by the local radiologist who together with the Investigator will determine the local assessment of response and progression.
If possible, the same radiologist/physician should perform the evaluation for the entire duration of the study.

7.3.2.4 Image Review Facility (IRF)

All study defined imaging data must be sent to the IRF immediately after acquisition.

The IRF will quality control the imaging data quality and review them for response and progression.
The specifics of the review procedure will be described in a separate Imaging Charter.

7.3.2.5 Review of Bone and Soft Tissue Disease

Bone and Soft Tissue Disease will be evaluated for Progression according to the Prostate Cancer Working Group 2 (PCWG2) recommendations for clinical trial conduct in castration-resistant disease.[29] The following minor modifications will be applied to the PCWG2 criteria:

- Progressive disease (PD) of bone or soft tissue lesions must be confirmed on a second scan at earliest 6 weeks later, preferably at the following regular imaging time point date if the progression occurs at weeks 12 and 24
- Progressive disease (PD) of soft tissue lesions will be assessed using modified RECIST 1.1 criteria.[31] The RECIST 1.1 modifications relate to the minimal dimensions of malignant lymph nodes and to the evaluation of disease in the prostate bed.

Assessment of Bone Lesions
Progressive disease on bone scan is considered when a minimum of two new lesions is observed. Defining disease progression requires a confirmatory scan performed at earliest 6 weeks later, preferably at the following regular imaging time point date.

- If at the first 12-week time point two or more new lesions are observed, PD must be confirmed by at least two additional new lesions on the confirmatory scan.
- If at the 24-week time point two or more new lesions are observed, at least two of them must be confirmed on the confirmatory scan for calling PD.

When progression is documented on the confirmatory scan, the date of progression recorded for the study is the date of the first scan that shows the change.

Assessment of Soft Tissue Lesions
Visceral and nodal disease will be evaluated according to RECIST 1.1[31] with the following modifications:

- Nodal disease: To be considered a new malignant node or a measurable node, the short axis must be ≥ 15 mm and the longest diameter ≥ 20 mm.
- Disease in the prostate bed is defined as non-measurable disease.
- PD of Soft Tissue Lesions has to be confirmed by a confirmatory scan performed at earliest 6 weeks later, preferably at the following regular imaging time point date, if the progression occurs at weeks 12 and 24. When progression is documented on the confirmatory scan, the date of progression recorded for the trial is the date of the first scan that shows the change.

The RECIST 1.1 rules and definitions to be used in this study are listed below:

- Measurable disease at baseline
  - Threshold for lesion measurability:
    The minimum diameter which can be reproducibly measured is twice the reconstruction interval. For spiral CT scans of ≤ 5 mm slice reconstruction

the value is 10 mm. If larger reconstruction intervals are used (not recommended), the threshold value increases accordingly.

- Visceral disease
  - Longest diameter ≥ 10 mm.
  - Disease in the prostate bed is defined as non-measurable disease irrespective of its size. (modification to RECIST 1.1)
- Nodal disease
  - short axis ≥ 15 mm and
  - longest diameter ≥ 20 mm (modification to RECIST 1.1)

- Non-measurable disease at baseline
  - Visceral disease
    - Any lesion too small to be measurable disease.
    - Truly non-measurable lesions: leptomeningeal disease, ascites, pleural or pericardial effusion, lymphangitic involvement of skin or lung.
    - Disease in the prostate bed is defined as non-measurable disease. (modification to RECIST 1.1)
  - Nodal disease
    - Any pathological lymph node with a short axis ≥ 10 mm but too small to be measurable disease.
- New Lesions
  The finding of new lesions on follow-up time points should be unequivocal.
  For lymph nodes to be considered new disease the following size criteria will apply:
    - short axis ≥ 15 mm (modification to RECIST 1.1) and
    - longest diameter ≥ 20 mm (modification to RECIST 1.1)

A short summary of the RECIST 1.1 evaluation procedure to be applied for the response evaluation of Soft Tissue Lesions is provided below. For more details please refer to the RECIST 1.1 publication.[31]

- At baseline all lesions are classified either as target or as non-target lesions to estimate the baseline tumor burden.
  - Target lesions are a subset of measurable lesions.
    Up to a maximum of 5 lesions in total and a maximum of 2 per organ are selected and measured.
    The baseline sum of diameters (longest for non-nodal lesions, short axis for nodal lesions) will be calculated.
  - Non-target lesions are all other lesions.
    Non-target lesions will have their location reported. Their size does not contribute to the sum of diameters.
- At each follow-up time point each lesion category will be evaluated for progression or non-progression
  - Target lesion Progressive Disease (PD):

- At least a 20% increase in the sum of diameters, taking as reference the smallest sum on study (this is not necessarily the baseline sum diameters). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm.

- Non-target lesion Progressive Disease (PD)
  - Unequivocal progression of existing non-target lesions.
- New Lesion:
  - The appearance of one or more new lesions is considered progressive disease (PD).

- For each follow-up time point the response outcome for each lesion category will be combined to an overall time point response as illustrated in the table below.

Target Lesions	Non-target Lesions	New Lesions	Overall Response
Non-PD	Non-PD	No	Non-PD
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

7.3.3 Skeletal related events

Skeletal related events include:

- radiation therapy to bone,
- pathologic bone fracture,
- spinal cord compression,
- surgery to bone or
- change in antineoplastic therapy to treat bone pain.

7.4 Discontinuation of first line chemotherapy

The variability of the decision by the Investigators to discontinue first line chemotherapy with docetaxel plus prednisone may have an impact upon the primary endpoint of OS. Discontinuation of first line chemotherapy can occur for intolerance to therapy, clinical or radiological disease progression, and patient refusal. The Investigator will make the decision for discontinuation of first line chemotherapy based on all available patient information. The blinding of the study treatment should minimize potential bias in the selection of second line therapy.

7.5 Disease progression

If the decision to change antineoplastic therapy is based on clinical symptoms that indicate disease progression e.g. obstructive uropathy attributable to cancer, skeletal related event, significant performance decline, increased pain requiring opioid treatment, pleural or peritoneal

effusion related to metastatic disease, fatigue, unintentional weight loss, progressive anemia that cannot be explained due to any other reason, these should be carefully documented. It is highly recommended to evaluate objective disease progression (bone and soft tissue lesions as per Section 7.3.2) prior to introduction of 2nd line antineoplastic therapy if the decision is made before completion of study treatment.

In the absence of other indicators of disease progression, antineoplastic therapy should NOT be switched solely on the basis of a rise in PSA.

7.6 Safety

Safety evaluations will include safety laboratory and immunological assessments, clinical evaluation of vital signs, physical examinations, performance status using ECOG scale, radiological examinations, and recording of all AEs.

7.6.1 Adverse events

An AE is the appearance of (or worsening of any pre-existing) undesirable and unintended sign (e.g. tachycardia, enlarged liver), symptom (e.g. nausea, chest pain), or the abnormal results of an investigation (e.g. laboratory findings) occurring after signing the informed consent till 30 days after the last dose of DCVAC/PCa or placebo (EOT) even if the event is **not** considered to be related to the study drug(s) or procedure(s).

The definition used by this protocol is consistent with the international definition provided in ICH E2A standard:

"Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment."

All Investigators should follow the protocol and the local regulations. The attending physician is responsible for describing, diagnosing and treating all AEs in accordance with the best standards of medical care.

Please refer to Section 6.1 and 7.2 for the protocol-specific definitions of study drug and study procedures.

AEs will be assessed according to the NCI Common Toxicity Criteria for Adverse Events (CTCAE) version 4.03. If NCI CTCAE grading does not exist for an AE, the severity of mild, moderate, severe, life-threatening and death, **or** grades 1 – 5, will be used.

AEs occurring before starting study treatment but after signing the ICF are also collected and recorded on the Adverse Event eCRF. This includes AEs observed before, during and after study procedures (e.g. screening, leukapheresis). All SAEs must be additionally documented on a "Serious Adverse Event Report Form".

Abnormal laboratory values, vital signs or test results constitute AEs only if they are considered clinically significant, in particular if accompanied by clinical signs or symptoms, require therapy or another medical intervention (e.g. hypokalemia that requires saline substitution), lead to change in medication dosing or administration, or require that the patient changes the study schedule. Abnormal hematological laboratory values should be recorded on the Adverse Events eCRF under the signs, symptoms or diagnosis associated with them (e.g. neutropenia, Grade 2). In case that laboratory value or vital sign is a sign of a medical condition, the condition should be reported as an AE and not the sign.

Surgical procedures are not AEs but therapeutic measures for conditions that require surgery. Therefore, the condition for which the surgery is required has to be reported as an AE. Pre-planned surgery (before signing off ICF) or other interventions permitted by the study protocol and the conditions leading to these measures are not AEs.

The occurrence of AEs will be recorded on an ongoing basis and patients will be asked specifically whether they have noticed any unexpected or unusual symptoms at each scheduled or unscheduled visits. AEs also may be detected when they are volunteered by the patient during or between visits or through physical examination, laboratory test, or other assessments. Reports from patient relatives or caregivers should be recorded, once verified.

If possible, each AE should be evaluated to determine:

- AE term or description of the AE in medical terms (not as reported by the patient)
- The severity grade (grade 1-5 as listed in NCI CTCAE v4.03)
- Its causal relationship to the IMP, first line chemotherapy (suspected/not suspected) and study procedure of leukapheresis
- Event duration including start date and end date, or if continuing at End of Treatment (EOT) or End of Study (EOS) visits
- Action taken with the IMP due to reported event (no action taken; delay of further application; permanently discontinued; other)
- Action taken with first line chemotherapy due to reported event (no action taken; dose adjusted; dose interrupted; delay of further application; permanently discontinued)
- Other action taken (hospitalization required; change in concomitant medication; medical procedure or intervention required; other or unknown).
- Event seriousness (serious or non-serious): a serious adverse event (SAE) is any untoward medical occurrence that at any dose fulfills one or more of the following criteria:
  - ~ Results in death.
  - ~ Is immediately life-threatening.
    The term "life-threatening" in the definition of serious refers to an event in which the patient was at immediate risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
  - ~ Results in persistent or significant disability/incapacity.
  - ~ Is a congenital anomaly/birth defect.

- ~ Requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
  - Routine treatment or monitoring of the studied indication including hospitalization due to trial related procedures (e.g. leukapheresis) not associated with any deterioration of patient´s status.
  - Elective or pre-planned treatment (prior to signing the informed consent form) for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent.
  - Treatment on an emergency outpatient basis for an event not fulfilling any of the definitions for an SAE and not resulting in hospital admission.
  - Social reasons and respite care in the absence of any deterioration in the patient's general condition.
  - Underlying disease progression and events which are unequivocally related to the disease progression.
- ~ Is other medically significant event, i.e., defined as an event that may not be immediately life- threatening or result in death or hospitalization but may jeopardize the patient or may require medical or surgical intervention to prevent one of the outcomes listed above.

Hospitalization is defined as an in-patient overnight stay that can be shorter than 24 hours.

Unlike routine safety assessments, SAEs are monitored continuously and have special reporting requirements; see Section 8.1.

If an AE (SAE) increases in severity, the event will be reported at the higher severity grade or frequency as a new AE (SAE). The onset date of the new AE will be the date that the severity increased. A decrease in severity should not be reported as a new AE.

All AEs should be acted upon. Such acts may include changes in study drug treatment including possible interruption or discontinuation, starting or stopping concomitant treatments, changes in the frequency or nature of assessments, hospitalization, or any other medically required intervention.

AEs causally not related to the IMP / procedure will be monitored (followed-up) until resolution, stabilization (becoming permanent condition) or the end of the clinical trial. Clinically relevant laboratory abnormalities will be followed-up until they return to normal or become stabilized (permanent condition).

Any AE which is or might be related to the IMP / procedure as well as all SAEs will be followed-up until the event is resolved or stabilized (permanent condition).

AE assessment should be made at each visit (or more frequently, if necessary) of any changes in diagnosis, severity, suspected relationship to the IMP, procedure or first line chemotherapy, interventions required to treat the event, and its outcome.

Information about adverse reactions (causally related events) already known for the investigational product can be found in the Investigator´s Brochure (IB) or will be communicated between IB updates in the form of Dear Investigator Letter. Basic information will be included in the patient informed consent and should be discussed with the patient during the study as needed.

7.6.2 Physical examination, weight, height

Physical examinations will be performed by a licensed physician (or physician's assistant or nurse practitioner) at screening. Symptom-directed exams will be performed on Day 1 of each cycle of Standard of Care chemotherapy and each application of DCVAC/PCa or placebo until End of Treatment visit and may be performed by a licensed physician, NP, PA, or nurse. All examinations should assess the patient for clinical signs of autoimmune disease.

Height in centimeters (cm) and body weight (to the nearest 0.1 kilogram [kg] in indoor clothing, but without shoes) should be measured at Screening, and weight will be measured at each dosing visit of Standard of Care chemotherapy during Concurrent treatment period and at each DCVAC/PCa or placebo administration visit in the Maintenance Boosting period and at the End of Treatment Visit.

7.6.3 Vital signs

Vital signs (body temperature, sitting blood pressure and sitting pulse) will be measured at Screening and at each dose of Standard of Care chemotherapy and DCVAC/PCa or placebo as well as at End of Treatment Visit.
Measurements of heart rate, body temperature, blood pressure and respiratory rate will be made after the patient has been resting supine for a minimum of 5 minutes. Subjects will be closely monitored during and for up to 2 hours following their first DCVAV/PCa or placebo administration and for 30 minutes following each subsequent administration.

7.6.4 Performance status

Eastern Cooperative Oncology Group (ECOG)[32] performance status will be measured at Screening, at Randomization, and on Day 1 of each cycle of Standard of Care chemotherapy and each injection of DCVAC/PCa or placebo and at the End of Treatment Visit.

ECOG Performance status should be documented according to Table 2.

Table 2: ECOG performance status scale

Grade	ECOG
0	Fully active, able to carry on all pre-disease performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g. light house work, office work.
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

7.6.5 Laboratory evaluations

The standard clinical laboratory analysis described below is to be performed by a central laboratory according to the Visit Evaluation Schedule, outlined in Table 1 and will be documented in the eCRF. Details on the collections, shipment of samples and reporting of results by the central laboratories are provided to Investigators in the Laboratory Manual.

More frequent evaluations may be performed at the Investigator's discretion if medically indicated; results should be recorded on the Unscheduled Visit eCRFs. Due to unanticipated circumstances, if at any time a patient has laboratory parameters obtained from a local laboratory, SOTIO must be provided with a copy of the certification and a tabulation of the normal ranges for that laboratory.

Laboratory values that are out of reference ranges should be evaluated for their clinical significance. Abnormal laboratory values or test results that constitute AEs or underlying conditions should be recorded together with the respective AEs or underlying diagnosis. Only laboratory abnormalities that are considered clinically significant e.g. due to induction of clinical signs or symptoms, lead to a change in medication dosage or administration, requiring concomitant therapy, or other medical intervention (e.g. hypokalemia that need saline substitution or hematologic abnormality that requires cytokine treatment) or require that the patient changes the study schedule should be recorded on the AE eCRF page. Whenever possible, a diagnosis, rather than a symptom should be provided on the AE eCRF page (e.g. anemia instead of low hemoglobin).

It should be noted that severity and seriousness are different criteria for AE evaluation. Therefore, grade 3 and grade 4 laboratory events (evaluated as per NCI CTCAE v4.03) do not automatically classify as SAEs unless they meet seriousness criteria as defined in section 7.6.1 or as per Investigator's discretion.

7.6.5.1 Hematology

Hematologic tests include: a complete blood count (CBC) consisting of red blood cells (RBCs), a total WBC with differential (total neutrophil, lymphocyte, monocyte, eosinophil, and basophil counts), hemoglobin, hematocrit, and platelet counts.

Hematology will be collected every 3 weeks (or Day 1 (-3 days) of each chemotherapy cycle) during the Concurrent Treatment Period with DCVAC/PCa or placebo and first line chemotherapy with docetaxel plus prednisone. Should first line chemotherapy be discontinued hematology should continue to be collected every 4 weeks (-7days/+14 days) until the discontinuation of DCVAC/PCa or placebo.

In the Follow-up period when the patient is no longer receiving DCVAC/PCa or placebo, hematology will be collected once at End of Treatment Visit. More frequent evaluations may be performed at the Investigator's discretion if medically indicated; results should be recorded on the Unscheduled Visit eCRFs.

7.6.5.2 Coagulation

Coagulation tests (aPTT and Quick) should be drawn at screening for evaluation purposes to leukapheresis.

7.6.5.3 Biochemistry

Biochemistry includes Na^+, K^+, Cl^-, Ca^{2+}, glucose, AST, ALT, ALP, LDH, bilirubin, creatinine, uric acid, CRP, total protein, and albumin.

Biochemistry will be collected every 3 weeks (or Day 1 (-3 days) of each chemotherapy cycle) during the Concurrent Treatment Period with DCVAC/PCa or placebo and first line chemotherapy with docetaxel plus prednisone.
Should first line chemotherapy be discontinued, biochemistry should continue to be collected every 4 weeks (-7days/+14 days) until the discontinuation of DCVAC/PCa or placebo.
TSH will be obtained every 12 weeks.
In the Follow-up Period when the patient is no longer receiving DCVAC/PCa or placebo, biochemistry will be collected once at End of Treatment Visit. More frequent evaluations may be performed at the Investigator's discretion if medically indicated; results should be recorded on the Unscheduled Visit eCRFs.

7.6.5.4 Urinalysis

Urinalysis including dipstick analysis (pH, protein, glucose, ketones, bilirubin, blood, leucocyte esterase) will be collected every 6 weeks (+/-7 days) during the Concurrent Treatment period and every 12 weeks (-14/+7 days) in Maintenance Boosting period.
In the Follow-up Period when the patient is no longer receiving DCVAC/PCa or placebo, urinalysis will be collected once at End of Treatment Visit. A microscopic (WBC/high power field (HPF), RBC/HPF, and any additional findings) exam need only be performed if the urinalysis result is abnormal.

7.6.6 Pregnancy

Pregnancy outcomes must be collected for a female partner of the patient administered the investigational product until 30 days after the last administration of DCVAC/PCa or placebo.

7.6.7 Radiological examinations

Please refer to sections 7.3.2 and 7.3.3.

7.6.8 HIV, HTLV, syphilis, Hepatitis B and C

Before randomization, subjects will be tested for HIV. Subjects with positive HIV results at screening are excluded from the study. Should the patient refuse testing, his participation will be terminated in the screening phase.

National and local guidance and regulations should be followed for HIV testing, additional testing before leukapheresis may be required. Investigators should follow national guidelines on reporting and patient referral for follow-up.

Before randomization subjects will be tested for HTLV. Subjects with positive HTLV results at screening are excluded from the study. Should the patient refuse testing, his participation will be terminated in the screening phase. National and local guidance and regulations should be followed for HTLV testing. An additional test before leukapheresis may be required based on local regulation.

At screening, subjects will be tested for HBV markers - HBs Ab, HBs Ag, and anti-HBc Ab. Patients with positive HBs Ag at screening have evidence of active disease and are directly excluded from the study participation. Eligibility of patients with positive HBs Ab and/or anti-HBc Ab, must be confirmed with the medical monitor and leukapheresis center first. National and local guidance and regulations should be followed for HBV testing (or clinically equivalent test). An additional test before leukapheresis may be required.

Before randomization subjects will be tested for HCV Ab and HCV RNA-PCR test at Screening (depending on local regulations). Subjects with detectable HCV RNA at screening and evidence of active disease are not eligible. National and local guidance and regulations should be followed for HCV testing. An additional test before leukapheresis may be required.

Before randomization subjects will be tested for syphilis. Subjects with positive syphilis results at screening and evidence of active disease are excluded from the study. Should the patient refuse testing, his participation will be terminated in the screening phase. National and local guidance and regulations should be followed for syphilis testing. An additional test before leukapheresis may be required.

7.6.9 Cardiac examinations

7.6.9.1 Electrocardiogram (ECG)

There are no required ECGs for this study. The Investigator should follow institutional guidelines and best clinical practice when assessing the suitability of the patient for leukapheresis procedure, and administration of trial treatment, including the assessment of cardiac function with ECGs.

7.6.9.2 Cardiac imaging - MUGA (multiple gated acquisition) scan or echocardiogram

The patient's medical records should be reviewed for evidence of cardiac disease of myocardial infarction or ventricular arrhythmias or stroke within a 6 month period prior to inclusion. This also includes known LVEF < 40% or serious cardiac conduction system disorders if a pacemaker is not present. MUGA scans or echocardiograms are not required at baseline screening to rule out evidence of cardiac co-morbidity.

7.7 Patient-Reported Outcomes

For the purpose of determining the effect of treatment on QoL the patient-reported questionnaires FACT-P and EQ-5D (EQ-5D only in Europe) will be utilized for this study (see Section 14.1). The questionnaire FACT-P will be completed by the patient at screening, on Day 1 before the first chemotherapy and every 6 weeks during the Concurrent Treatment period and every 4 weeks during Maintenance Boosting period, and at the End of Treatment visit. The questionnaire EQ-5D will be completed by patients in Europe at screening, on Day 1 of Cycle 3 of the Concurrent Treatment period and then every 12 weeks until disease progression (e.g. under ideal circumstances during the Concurrent Treatment period on Day 1 of Cycle 7, during the Maintenance Boosting period on Day 1 of Cycle 1 and on Day 1 of Cycle 4, at the End of Treatment visit, and at visits during the Follow-up period). The questionnaire EQ-5D will also be completed at 6 months and 12 months after disease progression either by the patient or by the Investigator based on information provided by the patient during follow-up telephone contacts.

7.8 Pharmacokinetics

Pharmacokinetic samples will not be drawn for this study.

7.9 Biomarkers

See section 7.3.1 for section on PSA.

7.10 Exploratory studies for search of potential biomarkers

The purpose of those exploratory studies is to search for parameters that would indicate the biological effect of trial treatment or identify subjects profiting from it. Blood samples for exploratory studies will be collected at Randomization, prior to the 5th dose of DCVAC/PCa or placebo, and at the End of Treatment Visit. Samples will be processed at the central lab and cryopreserved. Upon request, samples will be shipped to SOTIO facilities and analyzed.
The list of planned exploratory immune response studies includes:

- Monitoring of circulating tumor cells in the peripheral blood
- Analysis of the immune cells subsets in the peripheral blood (myeloid dendritic cells, plasmacytoid dendritic cells, CD4 T cells, CD8 T cells, CD19 B cells, NK cells, activated HLA-DR+ T cells)
- Monitoring peripheral blood FoxP3+ regulatory T
- Monitoring of myeloid derived suppressor cells
- Quantification of tumor antigen specific T cells in the peripheral blood by intracellular staining for IFN-γ, IL-2 and TNF
- Quantification of PSA, PSMA and NY-ESO1 specific CD8 T cells in the peripheral blood by tetramer staining in HLA-A2 positive subjects

Genomic studies may be performed, if the patient consented to participate in pharmacogenomic research. A separate patient information sheet and/or consent form is to be presented to the patient. Consent to participate in pharmacogenomic research is optional and not a prerequisite for entry into the study.

Peripheral blood samples will be used for the isolation of nucleic acids (DNA or RNA). Purified genomic DNA (gDNA) will then be fragmented, and a gDNA library will be prepared. Regions of gDNA will be sequenced using appropriate next generation sequencing techniques. For the purpose of gene expression profiling the total RNA will be purified and reversely transcribed into the complementary DNA (cDNA). cDNA will be used for gene expression profiling and for the detection of expression levels of potential cancer related genes. RNA samples can also be used as a template for RNA sequencing techniques.

The aim of the genomic studies is to identify any genetic alterations as well as new potential biomarkers that could be used for evaluation of risk of disease progression in patients with prostate cancer and for the identification of those patients, who could benefit from cancer immunotherapy.

Additional exploratory studies may be conducted based on the future advances in the field of biomarker research. Performing of the above mentioned experimental studies is subject to the availability of sufficient number of peripheral blood mononuclear cells from subjects. Complete instructions for collection and processing will be provided in a study Laboratory Manual.

Clinical signs of possible autoimmune disease will be assessed during each physical exam. If there is any suspicion of autoimmune disease at any time during the study, appropriate laboratory evaluation should be performed at the Investigator’s discretion.

8 SAFETY MONITORING

8.1 Serious adverse event reporting

Investigator or any investigational site staff must immediately (at the latest within 24 hours of awareness) notify / report to pharmacovigilance department all SAEs, **regardless of suspected causality**. All SAEs must be reported from the date of the patient signing the informed consent form until 30 days after the last administration of DCVAC/PCa or placebo (EOT).

Recurrent episodes and complications of reported SAE must be also reported within 24 hours of the Investigator receiving this information, if seriousness criteria have been met. An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one should be reported separately as a new event. The SAE must be documented and medically assessed by the Investigator.

If the investigator detects an SAE in a patient after the EOT, i.e. after 30 days from the last administration of the investigational product, and considers the event causally related to the IMP, this event has to be reported within 24 hours of learning of its occurrence.

Serious AE information is collected and recorded on the Serious Adverse Event (SAE) Report Form. The Investigator must complete the electronic SAE Report Form in English, and submit the completed and signed form via eCRF (EDC system) within 24 hours. The SAE notification will be delivered to Pharmacovigilance Department.

In case of any issues related to electronic SAE reporting where an electronic SAE Report Form cannot be completed in eCRF and forwarded by the Investigator within 24 hours of awareness, a paper SAE Report Form has to be completed instead and this report has to be forwarded to SOTIO Pharmacovigilance using the contact details below:

Fax: +420 224 175 498 *or local toll free fax lines*
Email: safety.viable@sotio.com
Phone: +420 725 385 443
Address: SOTIO a.s., Jankovcova 1518/2, 170 00 Prague 7, Czech Republic

New or additional information concerning SAE has to be reported as a follow-up report within same timelines and using the same route as noted above to SOTIO Pharmacovigilance by completing SAE Report Form stating that this is a follow-up to the previously reported SAE. The follow-up information should describe additional or new medically relevant information, whether the event has resolved or continues, if and how it was treated and whether the patient continued or withdrew from study participation.

If serious adverse reaction is not listed in the IB, i.e. unexpected and causally related to the investigational product, the sponsor may urgently require further information from the Investigator due to regulatory reporting obligations.

8.1.1 Serious Adverse Events related to disease progression

Progression of underlying disease or AEs unequivocally related to disease progression in line with the study protocol (see section 7.5), regardless of their outcome and regardless whether they otherwise would fulfill seriousness criteria, do not need to be reported as SAEs. However, these events have to be captured on AE eCRF page as non-serious events. If the patient was hospitalized due to PD related event this must be marked on AE eCRF page.

An SAE must be reported only if there are clinical signs / symptoms that cannot be without doubt associated to the underlying disease progression.

Events with fatal outcome that are unequivocally related to progression of underlying disease are excluded from SAE reporting and expedited reporting as SUSARs. Overall survival is the primary endpoint of the trial. Therefore, it is essential to complete the End of Study Information eCRF page to capture the death information. If a patient dies due to the progression of underlying disease the EOS eCRF page should include the EOS reason as 'Death' and the cause of death must be reported as 'Disease Progression'.

8.1.2 Adverse Events of Special Interest

Adverse Events of particular importance to product's ongoing safety and scientific monitoring are referred as AEs of Special Interest (AESIs). These events require ongoing monitoring and rapid communication by the investigator to the sponsor.

SAE report form is used for reporting of AESIs. AESIs have to be reported within the same timelines as SAEs. Further details are specified in relevant study manual.

The following AESIs must be reported:

1. Patient's premature discontinuation from the DCVAC/PCa or placebo treatment due to an AE (drop-out).
2. Systemic allergic reactions related to IMP administration (other than local inflammatory reaction or irritation at injection site).
3. Severe systemic infections related to IMP administration (e.g. sepsis due to transmission of infectious agents).
4. Secondary malignancy.
5. Autoimmune disorder (only symptomatic / clinically relevant).

Only AESIs with plausible causal relationship to investigational product must be reported after 30 days from the last IMP administration (EOT).

8.1.3 Pregnancies

Men who are fertile must use a medically accepted birth control during the study and for 30 days after the last administration of investigational product. If their partner becomes pregnant within 30 days after the last administration of DCVAC/PCa or placebo, the patient must inform their

study doctor without delay. Pregnancy outcomes must be collected for the female partners of any males administered DCVAC/PCa or placebo. Consent to report information regarding these pregnancy outcomes should be obtained from the mother.

Every new pregnancy of female partner of a study patient and the outcome of the pregnancy has to be reported via a 'Pregnancy Data Collection Form' (hard copy) which must be submitted within 24 hours of learning of its occurrence using the same route and timelines as described for SAEs.

8.2 Independent Data Monitoring Committee

An independent Data Monitoring Committee (IDMC) will be constituted prior to the randomization of the first patient. It is expected that the IDMC will consist of five members including one statistician. The IDMC will operate according to IDMC Charter which will be developed prior to the start of the study. The IDMC Charter will outline the data format and the process for all data tabulations that will be submitted to the IDMC for their review. The Charter will also describe the roles and responsibilities of the IDMC members and the timing and scope of all IDMC meetings.

The purpose of the IDMC will be to provide an independent mechanism for ongoing review of key adverse events and SAEs. As will be noted in the IDMC Charter, all meetings of the IDMC will be confidential and there will be no data dissemination to sponsor representatives.

In addition, the IDMC will monitor the DCVAC/PCa or placebo manufacturing failure rate in the context of the rate of lost to follow-up (LTF) subjects. The LTF rate is assumed to be 3% for the study. Should the rate of LTF be higher than expected, the IDMC may suggest trial modifications.
The IDMC may make these recommendations to SOTIO:

- To continue the trial as planned without modification (e.g. no safety issues, ethical to continue the trial as planned).
- To continue the trial with modification (e.g. ethical to continue the study but recommend an amendment to the protocol or incorporate an additional safety interim analysis before the next scheduled analysis).
- To halt enrollment pending discussions with SOTIO.
- To stop the trial (e.g. serious safety concerns precluding further study treatment).

If the study is recommended to continue by the IDMC, no details about the results of the current analysis will be revealed until the end of the study.

9 DATA REVIEW AND DATA MANAGEMENT

9.1 Site Monitoring

Before study initiation, at a Site Initiation Visit (SIV) or at an Investigator's meeting, SOTIO personnel (or designated CRO) will review the protocol and eCRFs with the Investigators and their staff. During the study, the field monitor will visit the site regularly to check the completeness of patient records, the accuracy of entries on the eCRFs, the adherence to the protocol and to Good Clinical Practice (GCP), the progress of enrollment, and to ensure that study drug is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the field monitor during these visits.

The Investigator must maintain source documents for each patient in the study recruited at the relevant site, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data, and the results of any other tests or assessments. All information on eCRFs must be traceable to these source documents in the patient's file. The Investigator must also keep the original ICF signed by the patient (a second signed copy original is given to the patient).

The Investigator must give the monitor access to all relevant source documents to confirm their consistency with the eCRF entries. SOTIO monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria, documentation of SAEs, and the recording of data that will be used for all primary and safety variables. Additional checks of the consistency of the source data with the eCRFs are performed according to the study-specific monitoring plan. No information in source documents about the identity of the subjects will be disclosed.

9.2 Data Collection

For studies using EDC, the designated Investigator site staff will enter the data required by the protocol into the eCRF using fully validated software that conforms to 21 CFR Part 11 and EMA/INS/GCP/454280/2010 requirements. Designated Investigator site staff will not be given access to the EDC system until they have been trained. Automatic validation programs check for data discrepancies in the eCRFs and, by generating appropriate error messages, allow modification or verification of the entered data by the Investigator staff before transfer of data to SOTIO (or designated CRO). After database lock, the Investigator will receive a CD-ROM or paper copies of the patient data for archiving at the investigational site.

9.3 Database Management and Quality Control

Data will be entered into the study database by the Investigator/Study Coordinator at each site.

SOTIO personnel (or designated CRO) will review the eCRFs entered by investigational staff for completeness and accuracy and instruct the site personnel to make any required corrections or additions. Queries are sent to the investigational site within the EDC system. Designated Investigator site staff is required to respond to the query and make any necessary changes to the data. If the electronic query system is not used, a paper DQF will be faxed to the site. Site

personnel will complete and sign the faxed copy and fax it back to SOTIO Data Management personnel (or designated CRO) who will make the correction to the database if required. In addition the signed original and resolved DQFs must also be sent to SOTIO Data Management (or designated CRO). Copies of the resolved DQF are kept with the CRFs at the Investigator site.

Concomitant medications entered into the database will be coded using the World Health Organization (WHO) Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system. Medical history/current medical conditions and AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) terminology. Central laboratory samples and/or data will be processed centrally and the results will be sent electronically to SOTIO (or a designated CRO).

Randomization codes and data about all study drug dispensed to the patient will be tracked using an IVRS/IWRS. The system will be supplied by a vendor(s), who will also manage the database. The database will be sent electronically to SOTIO personnel (or designated CRO).

At the conclusion of the study, the occurrence of any protocol violations will be determined. After these actions have been completed and the database has been declared to be complete and accurate, it will be locked.

10 STATISTICAL METHODS AND DATA ANALYSIS

The details of the statistical analyses to be performed on the collected data will be described in a separate Statistical Analysis Plan. This statistical considerations section is focused on the primary analysis.

10.1 Analysis Populations

There are 4 analysis populations. The definitions and criteria provided hereinafter will be updated and possibly detailed in the Statistical Analysis Plan during the data review.

All Randomized Subjects (ARS)

The ARS is a set of subjects who entered the study and who were randomized. The ARS will be used for a summary of demographic and other baseline characteristics.

Safety Population

The Safety population will comprise all subjects who received first-line chemotherapy and/or at least one dose of treatment with DCVAC/PCa or placebo and will be based on the actual treatment received if this differs from that to which the subject was randomized. This population will be used for the analysis of safety data.

Intent-to-Treat Population (ITT)

The ITT population is a subset of all randomized subjects who had at least one baseline assessment. ITT will be the primary efficacy population.

ITT subjects will be analyzed according to their randomized study medication.

According to Section 6.10 patients will be withdrawn from treatment, or not receive treatment, due to:

- Emergency unblinding of treatment assignment when investigator or patient are unblinded.
- Protocol violation requiring patient withdrawal as assessed by the Investigator or Sponsor.
- Patient unable to tolerate the leukapheresis procedure.
- Failure to produce DCVAC/PCa or placebo in the Sponsors manufacturing facilities.
- Patients having a serious allergic reaction to DCVAC/PCa or placebo must be withdrawn from the treatment phase of the study.

Patients with emergency unblinding and patients with protocol violations will be included in the ITT population and analyzed accordingly. Patients who have not started DCVAC/PCa or placebo treatment due to leukapheresis or manufacturing failure will also be included in the ITT population, however censored on Day 1 for the analysis of time to event endpoints, including the primary analysis of OS.

Per Protocol Population (PP)
The PP population is a subset of the ITT and includes all subjects who are characterized by following criteria:

- All subjects who have at least one post baseline assessment.
- All subjects who do not have any major protocol violations that would affect the endpoints being assessed.
- All subjects randomized to a treatment who received at least eight doses of DCVAC/PCa or placebo.
- Any other criterion as deemed appropriate will be listed in the Statistical Analysis Plan.

The major protocol violations and detailed reasons for excluding subjects from per protocol set will be fully defined and documented before breaking the blind of the specific trial. PP population will be analyzed according to their actual study medication. The PP population is the secondary efficacy population.

10.1.1 Patient Demographics and other Baseline Characteristics
Summary statistics of demographics, history and stage of prostate cancer, medical history, and other baseline characteristics will be presented by treatment group. A separate summary will be provided for patients with leukapheresis or manufacturing failure.

10.1.2 Treatments
Subjects who have received a different dose of a study medication than that planned in the study protocol will be listed including information on all doses actually received.

Concomitant medications will be coded using the current WHO Drug Dictionary. The number and percentage of subjects who used concomitant medications will be presented by Anatomic Therapeutic Class (ATC) levels 1 and 2 and by treatment group.

10.2 Primary Efficacy Analysis

10.2.1 Primary Efficacy Endpoint
Survival time, defined as the time from randomization until death due to any cause, is the primary endpoint. The primary efficacy analysis will be done with the ITT population.

10.2.2 Statistical Hypothesis, Model and Method of Analysis
The primary endpoint in this study is OS.

The primary hypothesis testing is to demonstrate that the treatment with DCVAC/PCa in addition to Standard of Care chemotherapy (docetaxel plus prednisone) is statistically significantly different from the treatment of Standard of Care chemotherapy (docetaxel plus prednisone) versus the null hypothesis of no difference between two treatment arms.

The primary efficacy analysis is a stratified log-rank test. Assuming an exponential distribution, a total of 657 deaths is required with approximately 80% power to detect a hazard ratio of 0.792 in favor of the DCVAC/PCa group (median survival of 24 months for the DCVAC/PCa group, 19 months for the control group) using a 2-sided log-rank test at a 5% overall significance level (i.e. alpha of 0.05). A total of 1170 patients will be enrolled in a 2:1 ratio (i.e., DCVAC/PCa vs. placebo equal to 2:1), an enrollment period of approximately 18 months, and total study duration of approximately 40 months to observe the required event-driven timeframe of 657 total events for the final analysis. If the anticipated 657 events are not attained during the trial timeline, the study could be prolonged by SOTIO.

Patients will be randomized in a 2:1 ratio, stratified by region (US vs other), prior therapy (abiraterone or enzalutamide or neither of the two) and ECOG score (0, 1 vs 2).

The overall type I error rate will be controlled at 0.05. At the final analysis, a final p-value of ≤ 0.0455 is required to be considered statistically significant. (East 5.4 software with 'Null' variance was used for total events and statistical significance boundary determination).

A Kaplan-Meier plot of survival by arm will be created. Censored observations will be indicated on the Kaplan-Meier plot. Tabular summaries of the Kaplan-Meier analysis giving the median, quartiles, minimum and maximum will be displayed.

The hazard ratio and its 95% confidence interval will be estimated using the Cox proportional hazard regression model with the same stratification factors as used in the log rank test.

The following sensitivity analyses of the primary endpoint will be also performed using the ITT population:

- Unstratified Log rank test and Cox model (No stratification and prognostic factors adjustment).
- To analyze the effects of imbalance in the baseline characteristics and treatment with chemotherapy by adjusting for various covariates in the Cox proportional hazard regression model. In addition to treatment and the 3 stratification factors, the following prognostic factors[16,33] will be included in the model simultaneously: Baseline PSA (values will be log transformed before inclusion, if any values = 0 then all values will have 1 added before transformation to allow for all values to be included after transformation), baseline LDH (> ULN; ≥ ULN) (1/0), baseline ALP (values will be log transformed before inclusion), baseline albumin, baseline hemoglobin, Gleason score 2-7; 8-10) at initial diagnosis (1/0), opioid use (yes; no) (1/0), disease site (will be defined in a separate document). This will be done on the ITT population.

Log transformation of covariates may be used in the model. The adjusted hazard ratio and its two-sided 95% confidence interval will be estimated using the Cox proportional hazard regression model with the covariates.

To assess the effect of the second line therapy on survival, the time from randomization to initiation of the first secondary therapy will be added as time-dependent covariate to the above primary Cox model.

A separate summary of survival data will be provided for patients with leukapheresis or manufacturing failure. A sensitivity analysis including the real survival data of patients with leukapheresis or manufacturing failure as such (and not censored on Day 1), will be performed to show robustness of the primary analysis. Such sensitivity analysis is indeed more conservative and could potentially show lower treatment effect. It will be conducted with an intention to show that the results of the primary analysis are robust enough and their interpretability is not jeopardized.
Additional exploratory analyses may be performed if deemed necessary.

10.2.3 Supportive Analysis

The primary endpoint OS will also be analyzed using the PP population to analyze sensitivity of the results to protocol deviations. Similar statistical methods as described for the primary analysis of OS will be used. The PP analyses for the primary efficacy endpoint will be used to support the primary analysis for OS using the ITT population.

10.3 Secondary Objectives

10.3.1 Secondary Efficacy Endpoints

rPFS will be analyzed for both ITT and PP populations using similar statistical methods as described for the primary endpoint. Similarly, time to PSA progression, time to first skeletal related events and time to radiographic progression or SRE will be also analyzed.

Incidence of skeletal related events (SRE) will be summarized.

Definitions of endpoints reflect recommendations of PCWG2[29] (see section 7.3). For Soft tissue and Bone evaluations there will be Investigator based and IRF results. Both results to be recorded, but the IRF conclusion will be used for ultimate evaluation as specified in the trial specific Imaging Charter. Radiographic assessments by IRF will be considered as the primary analyses.

A fixed sequential testing procedure will be used to test the 3 key secondary endpoints including rPFS, Time to PSA progression, and time to SRE. rPFS will be tested first. Then Hochberg[7] method will be used to test time to PSA progression and time to SRE in parallel. The details will be fully described in the SAP.

No special data imputation algorithms will be used to replace missing data.

For the analysis of OS, the last known date that the patient was alive will be used as the censoring date for those subjects that did not die at the time of analysis. As the period of treatment for any patient will be dependent on its efficacy and toxicity, the duration of follow-

up will vary between subjects. Consequently, there will be no imputation for missing data. For time-to-event endpoints (e.g. time to rPFS, time to PSA progression and time to SRE), the last date of documented disease status will be used if event (progression) had not been documented at the time of the analysis or subjects had withdrawn the study prior to determination of progression; such subjects will be considered censored in the analysis.

10.3.2 Safety

10.3.2.1 Adverse events

AEs will be coded using MedDRA and grouped by System Organ Class. AE severity will be graded according to NCI CTCAE 4.03. An AE is considered treatment-emergent when the onset date of the event falls on or after the earliest start date of chemotherapy or study treatment and when the onset date of the event occurs until 30 days after the last dose given (first line chemo or study treatment) or when the AE worsens (increase in severity and/or frequency) on or after the earliest start date of chemotherapy or study treatment. Only treatment-emergent AEs occurring from the first dose through 30 days after the last dose of study treatment will be summarized.

AEs will be classified according to severity and relationship to study medication.

The number and percentage of subjects who experienced any treatment-emergent: AE, SAE, treatment related AE and treatment related SAEs, will be summarized. The denominator used to calculate incidence percentages consists of subjects in the Safety Population. Incidence of safety complications resulting from leukapheresis will also be reported in the analysis of safety.

AEs will be grouped by System Organ Class and preferred term and sorted in descending frequency in the overall group. For tables by NCI CTCAE grade, if a patient has more than one AE the maximum grade will be summarized.

Missing values will be treated as missing, except for causality of AEs to study drugs. If causality is missing, the AE will be regarded as related to study drug.

10.3.2.2 Laboratory

Clinical laboratory parameters will be used for individual patient safety monitoring. Laboratory values will be graded according to the NCI CTCAE 4.03. For each patient the baseline value is the value recorded at screening. The actual laboratory values and changes from baseline will be summarized by visit and by treatment.

Laboratory abnormalities will be identified, summarized and presented in shift tables for each Study Cycle (baseline [Cycle 1, Day 1 pre-dose] versus Study Cycle toxicity grade) and by Worst Toxicity Grade (baseline versus worst toxicity grade across all visits).

10.3.2.3 Other safety data

Physical examination findings will be captured at baseline and during the Treatment Period and abnormalities that represent a worsening or change from baseline will be reported as AEs.

Vital signs will be summarized as measured values during the study and as change and percentage change from baseline to final visit.

Body weight will be summarized as change and percentage changes from baseline to final visit.

10.4 Exploratory Endpoints

10.4.1 Quality of Life (QoL)

Patient reported outcomes will include evaluation of QoL using the questionnaires FACT-P and EQ-5D (EQ-5D only in Europe). The QoL questionnaires FACT-P and EQ-5D will be summarized by treatment in accordance with the scoring manuals. Each score will be summarized by visit for the ITT population. Changes from baseline will be summarized and at specified time points of interest by treatment groups.

Missing values related to patient reported outcomes will be treated in accordance with the appropriate scoring manual whenever possible. If it is not possible, the Last Observation Carried Forward (LOCF) imputation technique may be used.

10.4.2 Second Line Treatment

Proportion of subjects requiring second line antineoplastic treatment introduction will be summarized. Time from randomization to second line treatment initiation will be described.

10.5 Pharmacokinetics

Not applicable.

10.6 Immune Response Biomarkers and Gene Expressions

See section 7.10 for description of these exploratory studies.

10.7 Sample Size Calculation

Sample size (in terms of number of deaths) calculation assumptions:

- A median survival of 24 months for the DCVAC/PCa group, 19 months for the control group and an exponential survival.[7,8]
- Subjects were randomized into the study with 2:1 allocation ratio (i.e., DCVAC/PCa: placebo equal to 2:1).
- Assume an exponential survival distribution, then hazard ratio can be calculated as $HR = M_R/M_T$, where M_T and M_R are the median survival times on test and reference, respectively, which results in HR = 0.792 in favor of the DCVAC/PCa group.

- Assuming proportional hazards
- Two-tailed level of significance of 0.05 and 80% power,

Based on the above assumptions, the sample size (in terms of number of deaths) would be 657 events in total.

To reach 657 events required, a total of 1170 patients will be enrolled in a 2:1 ratio (i.e., DCVAC/PCa vs. placebo equal to 2:1) with an expected enrollment period of approximately 18 months, and total study duration of approximately 40 months to observe the required event-driven timeframe of 657 total events for the final analysis. If the anticipated 657 events are not attained during the trial timeline, the study could be prolonged by SOTIO.

Patients will be randomized in a 2:1 ratio, stratified by region (US vs Other), prior therapy (abiraterone or enzalutamide or neither of the two) and ECOG Score (0, 1 vs 2).

The overall type I error rate will be controlled at 0.05.

11 ADMINISTRATIVE PROCEDURES

11.1 Regulatory and Ethical Compliance

This clinical study was designed and shall be implemented and reported in accordance with the protocol, the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including European Directive 2001/20/EC and US Code of Federal Regulations Title 21), and with the ethical principles laid down in the Declaration of Helsinki.

11.2 Insurance

Financial terms will be agreed upon in a separate contract document.

For each participating patient the sponsor has taken out insurance covering the amount determined by respective national laws. All participating subjects will be informed about the existence of the insurance in detail in the patient informed consent. They have the right to review the terms and conditions described therein.

11.3 Responsibilities of the Investigator and IRB/IEC

The protocol and the proposed ICF must be reviewed and approved by a properly constituted Institutional Review Board/Independent Ethics Committee (IRB/IEC) before study start. A signed and dated statement that the protocol and informed consent have been approved by the IRB/IEC must be given to SOTIO before study initiation. Prior to study start, the Investigator is required to sign a protocol signature page confirming his agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to SOTIO monitors, auditors, SOTIO Clinical Quality Assurance representatives, designated agents of SOTIO, IRBs/IECs and regulatory authorities as required.

Where applicable by regulatory mandate all subjects participating in this clinical trial will receive from the investigator an alert card, which has been previously agreed by the sponsor and approved by the IRB/IEC, containing as minimum the name of the subject, the investigator contact number and information regarding the medical treatment received.

Blood samples are being collected and stored for research purposes for this study. The sponsor of the trial, the tissue establishments/procurement organization, the manufacturer and the investigator institution should keep their parts of the traceability records for a minimum of 30 years after the expiry date of the product, or longer if required by the terms of the clinical trial authorization or by the agreement with the sponsor. In the case of the tissue establishments, if that period is longer than provided in the Directives referred to in section 3, the sponsor should ensure through contractual agreements that the traceability records are kept for that longer period.

11.4 Informed Consent

Eligible subjects may only be included in the study after providing written (witnessed, where required by law or regulation), IRB/IEC-approved informed consent, or, if incapable of doing

so, after such consent has been provided by a legally acceptable representative of the patient. In cases where the patient's representative gives consent, the patient should be informed about the study to the extent possible given his understanding. If the patient is capable of doing so, he should indicate assent by personally signing and dating the written informed consent document or a separate assent form. Informed consent must be obtained before conducting any study-specific procedures (i.e. all of the procedures described in the protocol). The process of obtaining informed consent should be documented in the patient source documents.

SOTIO will provide to Investigators in a separate document a proposed informed consent form that complies with the ICH GCP guideline and regulatory requirements and is considered appropriate for this study. Any changes to the proposed consent form suggested by the Investigator must be agreed to by SOTIO before submission to the IRB/IEC, and a copy of the approved version must be provided to the SOTIO monitor after IRB/IEC approval.

11.5 Leukapheresis Procedure Informed Consent Form

For the purpose of performing leukapheresis procedure apheresis center **may ask patient to sign a separate not study specific consent form.**

11.6 Amendments to the Protocol

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by SOTIO, Health Authorities where required, and the IRB/IEC. Only amendments that are required for patient safety may be implemented prior to IRB/IEC approval. Notwithstanding the need for approval of formal protocol amendments, the Investigator is expected to take any immediate action required for the safety of any patient included in this study, even if this action represents a deviation from the protocol. In such cases, SOTIO should be notified of this action and the IRB/IEC at the study site should be informed within 10 working days.

11.7 Discontinuation of the Study

SOTIO reserves the right to discontinue this study under the conditions specified in the clinical trial agreement.

11.8 Study Drug Supply and Re-supply, Storage and Tracking/Drug Accountability

Study drugs must be received by a designated person at the study site, handled and stored safely and properly, and kept in a secured location to which only the Investigator and designated assistants have access. Upon receipt, the DCVAC/PCa or placebo should be stored according to the instructions specified on the secondary package labels. Clinical supplies are to be dispensed only in accordance with the protocol.

Medication package labels will comply with the legal requirements of each country.

The Investigator must maintain an accurate record of the shipment and dispensing of study drug in a drug accountability ledger. Drug accountability will be noted by the field monitor during site visits and at the completion of the trial.

At the conclusion of the study, and, as appropriate during the course of the study, the Investigator will return all used and unused study drug, packaging, drug labels, and a copy of the completed drug accountability ledger to the monitor or to the SOTIO address provided in the Investigator folder at each site.

12 PROTOCOL ADHERENCE

Investigators ascertain they will apply due diligence to avoid protocol deviations. Under no circumstances should the Investigator contact SOTIO or its agents, if any, monitoring the trial to request approval of a protocol deviation, as no authorized deviations are permitted. If the Investigator feels a protocol deviation would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by SOTIO and approved by the IRB/IEC and concerned regulatory authorities, it cannot be implemented. All significant protocol deviations will be recorded and reported in the Clinical Study Report.

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14 APPENDICES

14.1 FACT-P Questionnaire

Sample form and background available at: http://www.facit.org/FACITOrg/Questionnaires .

For study purposes official forms will be distributed for completion by subjects.

	EMOTIONAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GE1	I feel sad	0	1	2	3	4
GE2	I am satisfied with how I am coping with my illness	0	1	2	3	4
GE3	I am losing hope in the fight against my illness	0	1	2	3	4
GE4	I feel nervous	0	1	2	3	4
GE5	I worry about dying	0	1	2	3	4
GE6	I worry that my condition will get worse	0	1	2	3	4

	FUNCTIONAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GF1	I am able to work (include work at home)	0	1	2	3	4
GF2	My work (include work at home) is fulfilling	0	1	2	3	4
GF3	I am able to enjoy life	0	1	2	3	4
GF4	I have accepted my illness	0	1	2	3	4
GF5	I am sleeping well	0	1	2	3	4
GF6	I am enjoying the things I usually do for fun	0	1	2	3	4
GF7	I am content with the quality of my life right now	0	1	2	3	4

	ADDITIONAL CONCERNS	Not at all	A little bit	Some-what	Quite a bit	Very much
C2	I am losing weight	0	1	2	3	4
C6	I have a good appetite	0	1	2	3	4
P1	I have aches and pains that bother me	0	1	2	3	4
P2	I have certain parts of my body where I experience pain	0	1	2	3	4
P3	My pain keeps me from doing things I want to do	0	1	2	3	4
P4	I am satisfied with my present comfort level	0	1	2	3	4
P5	I am able to feel like a man	0	1	2	3	4
P6	I have trouble moving my bowels	0	1	2	3	4
P7	I have difficulty urinating	0	1	2	3	4
BL2	I urinate more frequently than usual	0	1	2	3	4
P8	My problems with urinating limit my activities	0	1	2	3	4
BL5	I am able to have and maintain an erection	0	1	2	3	4

	PHYSICAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GP1	I have a lack of energy	0	1	2	3	4
GP2	I have nausea	0	1	2	3	4
GP3	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
GP5	I am bothered by side effects of treatment	0	1	2	3	4
GP6	I feel ill	0	1	2	3	4
GP7	I am forced to spend time in bed	0	1	2	3	4

	SOCIAL/FAMILY WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GS1	I feel close to my friends	0	1	2	3	4
GS2	I get emotional support from my family	0	1	2	3	4
GS3	I get support from my friends	0	1	2	3	4
GS4	My family has accepted my illness	0	1	2	3	4
GS5	I am satisfied with family communication about my illness	0	1	2	3	4
GS6	I feel close to my partner (or the person who is my main support)	0	1	2	3	4
Q1	*Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please mark this box* ☐ *and go to the next section.*					
GS7	I am satisfied with my sex life	0	1	2	3	4

	EMOTIONAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GE1	I feel sad	0	1	2	3	4
GE2	I am satisfied with how I am coping with my illness	0	1	2	3	4
GE3	I am losing hope in the fight against my illness	0	1	2	3	4
GE4	I feel nervous	0	1	2	3	4
GE5	I worry about dying	0	1	2	3	4
GE6	I worry that my condition will get worse	0	1	2	3	4

	FUNCTIONAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GF1	I am able to work (include work at home)	0	1	2	3	4
GF2	My work (include work at home) is fulfilling	0	1	2	3	4
GF3	I am able to enjoy life	0	1	2	3	4
GF4	I have accepted my illness	0	1	2	3	4
GF5	I am sleeping well	0	1	2	3	4
GF6	I am enjoying the things I usually do for fun	0	1	2	3	4
GF7	I am content with the quality of my life right now	0	1	2	3	4

	ADDITIONAL CONCERNS	Not at all	A little bit	Some-what	Quite a bit	Very much
C2	I am losing weight	0	1	2	3	4
C6	I have a good appetite	0	1	2	3	4
P1	I have aches and pains that bother me	0	1	2	3	4
P2	I have certain parts of my body where I experience pain	0	1	2	3	4
P3	My pain keeps me from doing things I want to do	0	1	2	3	4
P4	I am satisfied with my present comfort level	0	1	2	3	4
P5	I am able to feel like a man	0	1	2	3	4
P6	I have trouble moving my bowels	0	1	2	3	4
P7	I have difficulty urinating	0	1	2	3	4
BL2	I urinate more frequently than usual	0	1	2	3	4
P8	My problems with urinating limit my activities	0	1	2	3	4
BL5	I am able to have and maintain an erection	0	1	2	3	4

14.2 EQ-5D Questionnaire

Health Questionnaire

English version for the UK

Under each heading, please tick the ONE box that best describes your health TODAY.

MOBILITY

I have no problems in walking about ❑
I have slight problems in walking about ❑
I have moderate problems in walking about ❑
I have severe problems in walking about ❑
I am unable to walk about ❑

SELF-CARE

I have no problems washing or dressing myself ❑
I have slight problems washing or dressing myself ❑
I have moderate problems washing or dressing myself ❑
I have severe problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ❑
I have slight problems doing my usual activities ❑
I have moderate problems doing my usual activities ❑
I have severe problems doing my usual activities ❑
I am unable to do my usual activities ❑

PAIN / DISCOMFORT

I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

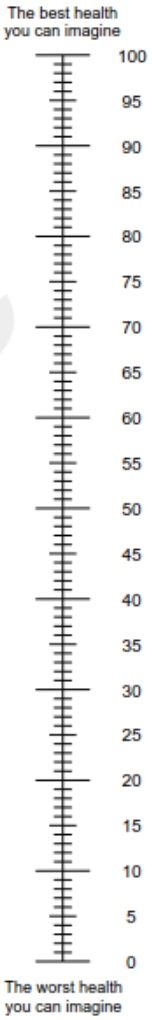
ANXIETY / DEPRESSION

I am not anxious or depressed ❑
I am slightly anxious or depressed ❑
I am moderately anxious or depressed ❑
I am severely anxious or depressed ❑
I am extremely anxious or depressed ❑

2

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



3

14.3 NCI CTCAE

Version 4.03 of the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), dated 14 June 2010, may be viewed and/or downloaded by accessing the following website:

http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf

14.4 Protocol Violations/Deviations

http://www.genome.gov/Pages/Research/Intramural/IRB/Deviation_Violation_examples8-07.pdf

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Protocol Deviations and Violations

Protocol Deviation- A protocol deviation is any change, divergence, or departure from the study design or procedures of a research protocol that is under the Investigator's control and that has not been approved by the IRB. Upon discovery, the Principal Investigator is responsible for reporting protocol deviations to the IRB using the standard reporting form. Any change, divergence, or departure from the study design or procedures of a research protocol that affects the subject's rights, safety, or well-being and/or the completeness, accuracy and reliability of the study data constitutes a protocol violation. Changes or alterations in the conduct of the trial which do not have a major impact on the subject's rights, safety or well-being, or the completeness, accuracy and reliability of the study data are considered minor protocol deviations.

Protocol Violation- A protocol violation is a deviation from the IRB approved protocol that may affect the subject's rights, safety, or well-being and/or the completeness, accuracy and reliability of the study data. If the deviation meets any of the following criteria, it is considered a protocol violation.

Example list is not exhaustive.

I. The deviation has harmed or posed a significant or substantive risk of harm to the research subject.

Examples:

- A research subject received the wrong treatment or incorrect dose.
- A research subject met withdrawal criteria during the study but was not withdrawn.
- A research subject received an excluded concomitant medication.

II. The deviation compromises the scientific integrity of the data collected for the study.

Examples:

- A research subject was enrolled but does not meet the protocol's eligibility criteria.

• Failure to treat research subjects per protocol procedures that specifically relate to primary efficacy outcomes. (if it involves patient safety it meets the first category above)
• Changing the protocol without prior IRB approval.
• Inadvertent loss of samples or data.
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III. The deviation is a willful or knowing breach of human subject protection regulations, policies, or procedures on the part of the Investigator(s).
Examples:
• Failure to obtain informed consent prior to initiation of study-related procedures
• Falsifying research or medical records.
• Performing tests or procedures beyond the individual's professional scope or privilege status (credentialing)

IV. The deviation involves a serious or continuing noncompliance with federal, state, local or institutional human subject protection regulations, policies, or procedures.
Examples:
• Working under an expired professional license or certification
• Failure to follow federal and/or local regulations, and intramural research or CC policies
• Repeated minor deviations.

V. The deviation is inconsistent with the NIH Human Research Protection Program's research, medical, and ethical principles.
Examples:
• A breach of confidentiality.
• Inadequate or improper informed consent procedure.

Minor Protocol Deviation- A minor protocol deviation is any change, divergence, or departure from the study design or procedures of a research protocol that has not been approved by the IRB and which DOES NOT have a major impact on the subject's rights, safety or well-being, or the completeness, accuracy and reliability of the study data.