Statistical Analysis Plan

SOTIO

Protocol: SP005

EUDRACT: 2012-002814-38 / IND 015255

Treatment: DCVAC/PCa

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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Contents

Abbreviations

ACE	Angiotensin Converting Enzyme
AE	Adverse Event
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
ARP	All Randomized Patients
AST	Aspartate Aminotransferase
aPTT	Activated Partial Thromboplastin Time
ATC	Anatomical Therapeutic Chemical Classification
BDRM	Blind Data Review Meeting
CBC	Complete Blood Count
CI	Confidence Interval
Cl^-	Chloride
CRP	C-Reactive Protein
CSR	Clinical Study Report
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTP	Concurrent Treatment Period
DCVAC/PCa	Autologous Active Cellular Immunotherapy Consisting of Dendritic Cells For Prostate Cancer Treatment
DSUR	Development Safety Update Report
ECG	Electrocardiogram
ECOG PS	Eastern Cooperative Oncology Group Performance Status
eCRF	Electronic Case Report Form
EQ-5D	Euro Quality of Life 5 Dimensions
EOT	End of Treatment
EOS	End of Study
EWB	Emotional Well-Being
FACT-G	Functional Assessment of Cancer Therapy – General
FACT-P	Functional Assessment of Cancer Therapy – Prostate
FWB	Functional Well-Being
GnRH/LHRH	Gonadotropin Releasing Hormone/ Luteinizing Hormone-Releasing Hormone
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HEENT	Head, Eyes, Ears, Nose, Throat
HIV	Human Immunodeficiency Virus
HLOQ	Higher Limit Of Quantification
HPF	High Power Field
HR	Hazard Ratio
HTLV	human T-lymphotropic virus
iDMC	Independent Data Monitoring Committee
IMP	Investigational Medicinal Product
IRF	Image Review Facility

ITT	Intent-to-Treat
IWRS	Interactive Web Response System
K^+	Potassium
LDH	Lactate Dehydrogenase
LLOQ	Lower Limit Of Quantification
MBP	Maintenance Boosting Period
mCRPC	Metastatic Castration Resistant Prostate Cancer
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic Resonance Imaging
NA	Not Applicable
NA^+	Sodium
OR	Odds Ratio
OS	Overall Survival
PCS	Prostate Cancer Scale
PD	Progression Disease
PE	Physical Examination
PH	Proportional Hazards
PP	Per Protocol
PSA	Prostate-Specific Antigen
PCWG	Prostate Cancer Working Group
PWB	Physical Well-Being
QoL	Quality of Life
RBC	Red Blood Cells
rPFS	Radiographic Progression Free Survival
SAE	Serious Adverse Event
SAF	Safety Population
SAR	Serious Adverse Reaction
SAP	Statistical Analysis Plan
SD	Standard Deviation
SRE	Skeletal Related Events
SWB	Social/Family Well-Being
TE	Treatment-Emergent
TOI	Trial Outcome Index
TSH	Thyroid Stimulating Hormone
WBC	White Blood Cells
WHO	World Health Organization

DOCUMENT VERSION	DATE	RESON FOR CHANGES
Version 4.0	16DEC2013	
Version 5.0	28MAR2018	According final protocol version 7.0 08MAR2018 Interim analysis removed.
Version 6.0		Leukapheresis and Manufacturing failure population added. ITT non-US patients population added. Exposure to second line replaced by exposure to next line. Rescue Medication removed since not collected in eCRF. Analysis of time to the requirement of next line treatment as a continuous variable was replaced by analysis as time to event analysis. Added KM estimates at 3 months, 6 months, 9 months, 12 months, 18 months,24 months, 36 months, 48 months and 60 months. Added survival analysis using model including time-dependent covariate in case of non-proportional hazard model. OR using logit model replaced by RR using log binomial model. Adverse event counted once (with the highest severity) if recorded in several episodes due to change of severity. Evaluation of different methodologies used for determination of PSA levels added.

		Implementation of FDA Type B Preliminary Meeting Responses dated 18th October 2019 (FDA Reference: CRMTS # 12042, file 15255.85.87_20191018_Preliminary Responses.pdf) - Definition of cut-off for the primary analysis added. - Censoring of leukapheresis and manufacturing failures on Day 1 (i.e. day of randomization) in the primary overall survival (OS) analysis has not been endorsed by FDA, this type of analysis can be used as sensitivity. Primary analysis will include all ITT patients without censoring of leukapheresis and manufacturing failures on Day 1. - Subgroup analyses of OS added - Subgroup analysis of OS and AEs before and after Poly (I:C) used for manufacturing of DCVAC/OvCa added. - Sensitivity analysis of PFS and check of assumptions for using Hochberg method a fixed sequential testing added. Further updates: Cox model for main analyses stratified on stratification factors instead of adjusted on stratification factors to be in line with study protocol. Sensitivity analysis for rPFS with censoring patient with interval between two assessments longer than 24 weeks will be planned. Sensitivity analysis for PSA progression with censoring patient with interval between two evaluation longer than 24 weeks will be planned.

		EQ-5D-5L, calculation updated with EQ-5D-5L algorithm instead of EQ-5D-3L Update of TEAE definition where also AEs after end of reporting period will be counted as TEAE. Last contact date for OS analysis was clarified in section 4.6.1
Version 7.0	13DEC2019	Final Version before Unblinding

1 Introduction

This document presents the statistical analysis plan (SAP) for Sotio, Protocol No. 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".

This analysis plan is based on the final protocol version 7.0 08MAR2018.

The SAP provides the description of the analysis for final analyses.

Because of practical reasons the SAP will not be finalized before DB lock. However, the SAP will be finalized (including all appendices/attachments) and signed before unblinding of the study. The process of unblinding is described in SP005_unblinding plan Version 1_final_5Dec2019.pdf.

2 Study Objectives

Primary:

The primary objective is to show superiority of treatment with Autologous Active Cellular Immunotherapy Consisting of Dendritic Cells For Prostate Cancer Treatment (DCVAC/PCa) in addition to Standard of Care chemotherapy (docetaxel plus prednisone) over placebo in addition to Standard of Care chemotherapy (docetaxel plus prednisone) in men with metastatic castration resistant prostate cancer (mCRPC) as measured by overall survival (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 (PSA) 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 SRE.

Exploratory Objective:

Treatment group comparison for the following measures:

- Proportion of patients 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.

2.1 Primary Endpoints

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

2.2 Secondary Endpoints

The definitions of secondary endpoints are based on the prostate cancer working group (PCWG2) guidelines[1]:

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

Other Secondary efficacy endpoints:

- Time to radiographic progression or SRE
- Proportion of patients with SRE.

Definitions

Assessment of Bone Lesions

Progressive disease on bone scan is considered when a minimum of two new lesions are 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, Progressive Disease (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[2] 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.

PSA progression

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.

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.

2.3 Safety Endpoints

Safety endpoints will include but are not limited to incidence of adverse events (AEs), clinically significant laboratory abnormalities, change in vital signs and change in Eastern Cooperative Oncology Group Performance Status (ECOG PS).

2.4 Exploratory Endpoints

Patient reported outcomes will include evaluation of QoL using Functional Assessment of Cancer Therapy - Prostate (FACT-P) questionnaire and Euro Quality of Life 5 Dimensions (EQ-5D) collected in non-US patients only.

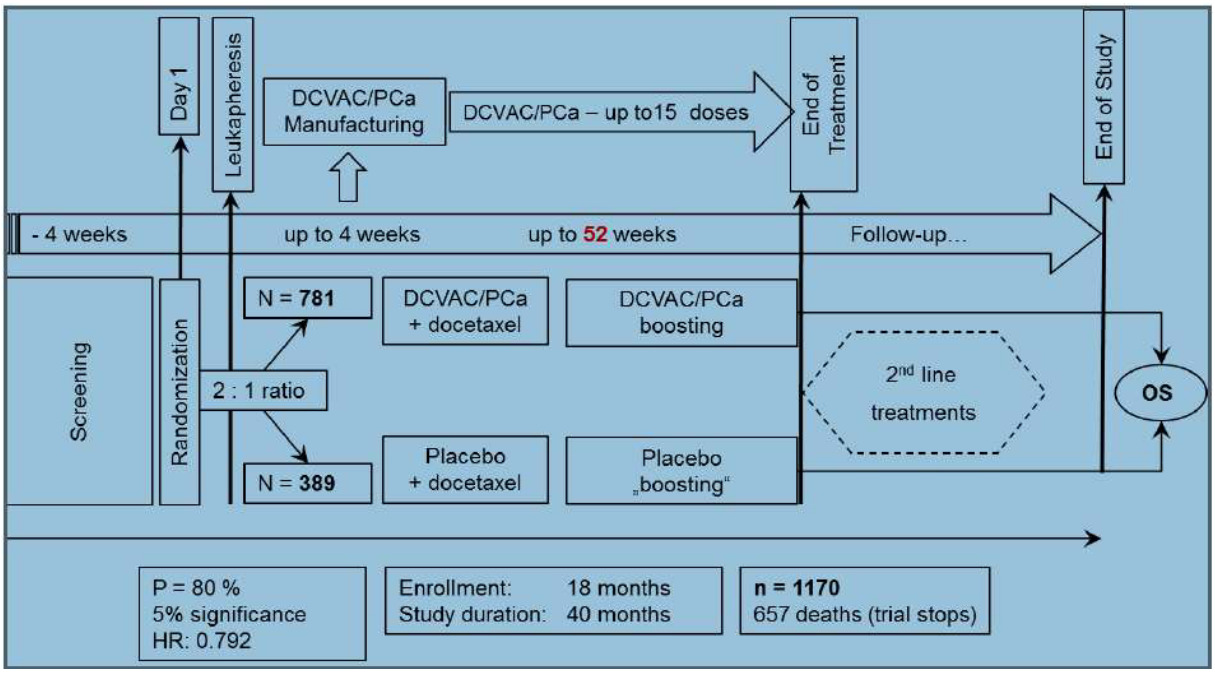
Proportion of patients requiring second line treatment introduction and time to second line treatment introduction will be evaluated.

Exploratory studies for potential biomarkers will be performed to search for parameters that would indicate the biological effect of trial treatment or identify patients profiting from it and will be included in a separate document/analysis.

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

3 Study Design

Figure 1: DCVAC/PCa Phase III study design



Abbreviations: DCVAC/Pac= Autologous active cellular immunotherapy consisting of dendritic cells for prostate cancer treatment; HR=Hazard Ratio; N=number of patients; OS=overall survival; P=Power

3.1 Discussion of Study Design

This is a randomized, double blind, placebo controlled, multi-center, international, parallel-group phase III study. Patients 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).

The sample size is established as 1170 patients, and final analysis is planned after 657 deaths have occurred.
An enrollment period of approximately 18 months and total study duration of approximately 40 months are expected 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.

3.2 Study Treatment

Patients who comply with all inclusion/exclusion criteria at screening (up to 28 days) will participate in this study.

During the concurrent treatment period (CTP), 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 to 15 of chemotherapy cycle).

During the Maintenance Boosting period (MBP), 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. CTP).

3.3 Study Schedule

3.3.1 Screening Period

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

3.3.2 Randomization Visit

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

3.3.3 Leukapheresis Evaluation and Leukapheresis Timeline

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

3.3.4 Concurrent Treatment Period (CTP)

During the CTP, patients will receive Standard of Care chemotherapy with docetaxel plus prednisone plus DCVAC/PCa or placebo every 21 days (every 3-week cycle). Patients will begin the study receiving first line chemotherapy (docetaxel and prednisone) and DCVAC/PCa or placebo treatment will be added after the second cycle of docetaxel.

The CTP ends when the first line Standard of Care chemotherapy has been completed or discontinued for any reason.

3.3.5 Maintenance Boosting Period (MBP)

During the MBP patients will continue to receive DCVAC/PCa or placebo every 28 days (every 4-week cycle) 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 or placebo administration must be discontinued in this case. The MBP ends when the DCVAC/PCa or placebo treatment has been discontinued for any reason.

3.3.6 End of Treatment

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

3.3.7 Follow-up Period

During the Follow-up period patients will be off the DCVAC/PCa or placebo treatment but may continue Standard of Care therapy. Follow-up for toxicities and follow-up for survival are described in Section 6.11 and 6.12 of the protocol.
Patients are followed until refusal, death or study closure. See Section 6.13 of the protocol for the reasons patients are considered to be prematurely withdrawn from the study.

3.3.8 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 patient has a documented date of death.

3.3.9 Visit Evaluation Schedule

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 I		
				3 week (21 days) cycles																				4 week (28		
Cycle				1	2		3		4		5		6		7		8		9		10		1	2	3	
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	
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	
Biochemistry (incl. ALP, LDH)	X	X		X	X		X		X		X		X		X		X		X		X		X	X	X	
PSA[3]	X	X							X								X						X			
TSH	X								X								X						X			
Urinalysis	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	
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	
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	
FACT-P questionnaire	X			X			X				X				X				X				X	X	X	
EQ-5D questionnaire (only in Europe)	X						X								X[18]								X[18]			
Samples for research[6]		X											X													

Study period	Screening	Randomization	Leukapheresis	Concurrent Treatment Period*																		Maintenance I		
				3 week (21 days) cycles																		4 week (28		
Cycle				1	2		3		4		5		6		7		8		9		10		1	2	3
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
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
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
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
Disease assessment[14] CT(MRI[13])/bone scan	X[15]								X								X						X		
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
Survival Follow-up[17]																									

*The first line chemotherapy may be discontinued early if patient refuses or has intolerance. Patients are then eligible to continue in the Maintenar DCVAC/PCa or placebo as monotherapy in 4 weeks intervals.

†When patients finish or stop receiving DCVAC/PCa or placebo, they complete the End of Treatment procedures within 30 days after the last d 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 aph

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

[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

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

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

[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

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

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

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

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

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

3.4 Concomitant Medication

3.4.1 Prior Medications

A prior medication is defined as any medication that was being taken prior to the first dose of study treatment (stop date of medication < min (start of first line Standard of Care chemotherapy, first date of study medication).

3.4.2 Concomitant Medications

A concomitant medication is defined as any medication taken on or after the first dose of study treatment (stop date of medication ≥ min (start of first line Standard of Care chemotherapy, first date of study medication).

3.4.3 Post Medications

A post medication is defined as any medication taken after the end of study treatment (start date of medication ≥ max (end date of first line Standard of Care chemotherapy, end date of study medication)).

3.4.4 Prohibited Medications

Prohibited medications include:

- Systemic immuno-suppressive therapy, including systemic corticosteroids at doses greater than 40mg 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 gonadotropin releasing hormone/ luteinizing hormone-releasing hormone (GnRH/LHRH) agonists or antagonists for maintaining castrate condition.
- Angiotensin converting enzyme (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.

All other medications (over the counter or prescription only medication) are permitted during this study at the discretion of the Investigator.

The list of considered ATC code have been provided by coding team in an excel file (see Appendix E).

3.5 Study Analysis Populations

After approval of unblinding by the Sponsor

- IWRS provider, company named Endpoints, will send a ASCII Tab Delimited file with the decode of the randomized treatment allocated by the IWRS (planned treatment)
- Sponsor will provide list of patients with information whether placebo or DCVAC/PCa was manufactured and LOT numbers in order to identify protocol deviations in study

treatment administered (against randomization scheme) and in order to have data for treatment arms for safety analysis.

Details of unblinding process are described in SP005_unblinding plan Version 1_final_5Dec2019.pdf.

3.5.1 All Randomized Patients (ARP)

The ARP is a set of patients who entered the study and who were randomized.

3.5.2 Leukapheresis or manufacturing failure

Patients with leukapheresis or manufacturing failure will be defined as patients who have not started DCVAC/PCa or placebo treatment due to leukapheresis (Unable to tolerate leukapheresis procedure in End Of Treatment or End Of Study forms of the eCRF) or manufacturing failure (failure to produce in End Of Study form of the eCRF).
In order to identify all leukapheresis and manufacturing failure, a listing of patients with other reasons including "Leuk" and "Prod" will be provided for data review. Final conclusions and the list of leukapheresis and production failures is included in Appendix F.

In summary:

- 21 patients with reason for study/study drug discontinuation: UNABLE TO TOLERATE LEUKAPHERESIS PROCEDURE. Those patients will be labeled as „Leukapheresis Failures" in disposition table.
- 119 patients with reason for study/study drug discontinuation: FAILURE TO PRODUCE STUDY TREATMENT. Those patients will be labeled as „Manufacturing Failures" in disposition table.
- 7 patients considered as production failures: 5 patients (SP005C129B004-CZE, SP005C217B001-HUN, SP005C395B001-ESP, SP005C677B011-USA, SP005C390B010-ESP) there was no intention to produce DCVAC because of active hepatitis. Patient SP005C485B007-SRB with reason for study drug discontinuation: The cells were dead as they were stuck at the airport, so production wasn't started. Patient SP005C646B005-USA with reason for study drug discontinuation: Produced IP thawed prior to dispensation to the site. Those patients will be labeled as „Considered as production failures" in disposition table.
- 147 patients in total

3.5.3 Safety Population (SAF)

The SAF will be comprised of all patients 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 patient was randomized. This population will be used for the analysis of safety data.

3.5.4 Intent-to-Treat Population (ITT)

The ITT population is a subset of all randomized patients who had at least one baseline assessment. No efficacy baseline assessment will be checked as the primary endpoint is the overall survival; therefore, ITT population consists of all (alive) patients at time of randomization = all randomized patients. ITT will be the primary efficacy population.

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

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

- Emergency unblinding of treatment assignment when investigator or patient are unblinded (see section 6.14 of the protocol).
- 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."

Patients with emergency unblinding and patients with protocol violations will be included in the ITT population and analyzed accordingly. Patients with leukapheresis or manufacturing failure will also be included in the ITT population and their time to event data will be included into the primary analysis. Leukapheresis or manufacturing failure will be censored on Day 1 in sensitivity analysis (see section 4.6.3).

3.5.5 ITT Population of non-US Patients (ITT non-US)

The reduced ITT population is defined as all non-US patients in the ITT population. This will be used only for summaries of EQ-5D.

3.5.6 Per Protocol Population (PP)

The PP population is a subset of the ITT and includes all patients who are characterized by following criteria:

- All patients who have at least one post baseline efficacy assessment.
- All patients who do not have any major protocol violations that would affect the endpoints being assessed.
- All patients randomized to a treatment who received at least eight dose of DCVAC/PCa or placebo.
- Any other criterion as deemed appropriate (as described in Section4.10.1).

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

3.5.7 Leukapheresis Population (LP)

In order to evaluate leukapheresis related AEs the LP will be used. The LP will include all patients who underwent or even started the procedure (i.e. have completed date of leukapheresis).

3.6 Withdrawn Patients

Patients who discontinue either DCVAC/PCa or placebo treatment, enter the follow-up phase of the study. If applicable, patients continue on 2nd line antineoplastic therapies for prostate

cancer and then other therapies. All randomized patients remain in the study and are followed until ICF withdrawal, death or study closure for survival data regardless their future treatment and /or participation in different clinical trials.
Patients 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 electronic case report form (eCRF) and notify the interactive web response system (IWRS).

Patients **must** be withdrawn from the study prematurely for one of the following reasons:
- Informed consent withdrawn for continued study participation.
- Death.

3.7 Randomization

At Randomization visit, all eligible patients are centrally randomized in a 2:1 DCVAC/PCa to placebo allocation ratio via IWRS. The randomization schedule is computer generated and is stratified by:
- Region (US or other)
- Prior therapy (abiraterone, enzalutamide or neither of the two)*
- ECOG status (0 - 1 or 2).

*According to the Interactive Response Technology System (IRT) Site User Guide version 4, these patients were to be randomized within stratum enzalutamide.

3.8 Blinding

Patients, investigational site staff, personnel performing the assessments and monitoring, personnel performing leukapheresis, and data analysts are blinded to the identity of the study treatment from the time of randomization until study unblinding, 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 (any unblinded information will be kept in a secure manner not accessible to anybody else than the independent unblinded statistician).
   - 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, for regulatory reporting purposes and at the conclusion of the study.

3.9 Sample Size

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.
- Patients 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 (HR) 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 was planned to 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.

4 Statistical Methodology

4.1 Planned Analyses

Disposition outputs are generated based on all patients, demographic and baseline outputs based on the ARP (if not equal to ITT), ITT , PP and leukapheresis and manufacturing failures populations, efficacy outputs are generated using the ITT and as sensitivity analysis, PP Population (according to section 4.6), and safety outputs will be generated using the Safety Population. Leukapheresis population will be used for AEs related to leukapheresis.

Summary statistics will be presented for continuous variables, by way of n, missing, mean, standard deviation (SD), median, Q1, Q3, minimum and maximum; by way of group frequencies and percentages for categories of categorical variables. Percentages will be calculated using the total patients per randomized treatment group, except for outputs on the Safety Population, where percentages are based on the total patients per actual treatment group.

For analysis of categorical safety variable per visit percentage will be equal to the number in a given category of the variable divided by the total number of non missing data. A data will be considered missing if there are no available data at the visit. Patients withdraw from the study before the particular visit will be not counted at this visit at all.

In addition, p-values and 95% confidence intervals will be presented as described in each section below.

Summary of Kaplan Meier curves will be done by showing median, 25th and 75th percentiles.

Baseline value is considered the last assessment resulting in a non-missing value before or on day of the randomization. In analyses showing a change from baseline (i.e. post-baseline – baseline), a missing baseline results leads to a missing change from baseline.

If mean values are plotted then the figure will be present also variability.

In addition to outputs generated by visit as recorded in eCRF (CTP cycles, MBP cycles etc.) outputs reflecting more the real chronology in order to avoid mixing patients in MBP cycles who have different number of CPT cycles might be needed to be provided in addition.

All data will be listed.

4.2 Disposition of Patients

Frequencies are presented for the number of patients screened and number of screen failures for the overall population. For the overall population and randomized study arm: number of randomized patients, patients started the leukapheresis, leukapheresis failures, manufacturing failures, number of patients started first line Docetaxel plus prednisone therapy, started DCVAC/PCa or placebo therapy, started boosting period, started second line therapy, number of patients in the ITT, PP and Safety Populations*, number of patients completed the study, number of patients early-terminated the study and reasons for study discontinuation, and number of patient early-terminated but with survival follow-up .
*for Safety population it will be noted (in footnote of the table) for how many patients was manufactured another IMP than that one assigned by randomization (with reference to corresponding listing of programmable protocol deviations).

Information on completion and discontinuation of DCVAC/PCa or placebo will be summarized showing the number of patients started DCVAC/PCa or placebo therapy, number of patients

completed DCVAC/PCa or placebo therapy, number of patients discontinued during the CTP and the reasons for discontinuation, number of patients discontinued during the MBP and the reasons for discontinuation, number of patients discontinued during CTP or MBP and the reasons for discontinuation and the number of patients discontinued the standard of care. This information is presented for all patients in the All Randomised Population.

The reason for discontinuation of the standard of care therapy will be as per reported in eCRF. The exception is only the following: If the reason for discontinuation of first line standard of care is "Other" and the number of cycle is at least 10 cycles, the patient will be counted as completed the treatment.

The number and percentage of patients randomized in each region and country will be presented. In the footnote of the table will be stated patients changed site or moved to another country during the study based on batch cleaning tracker.

The number of screen failures per country is presented.

4.3 Baseline and Demographic Characteristics

All baseline and demographic characteristics will be presented for the ARP (if not equal to ITT), ITT Population, PP population and patients with leukapheresis or manufacturing failure.

4.3.1 Demographics

Race, ethnicity, age (years), age group 1 (< 60, 60 to 69 and ≥ 70 years), age group 2 (<65, ≥ 65 years), weight (kg), region (US and other country) will be summarized.

4.3.2 Baseline Characteristics

Summary statistics for Fact-P QoL and EQ5D Score at baseline, ECOG score at baseline, ECOG category (0,1,2, missing and 0 or 1 vs 2), prior therapy (abiraterone, enzalutamide, both abiraterone and enzalutamide used prior the study, or neither of the two), PSA (ng/L) at baseline, Hemoglobin (g/L) at baseline, Albumin (g/L) at baseline, Alkaline phosphatase (ALP) (IU/L) at baseline, lactate dehydrogenase (LDH) (IU/L) at baseline,LDH > Upper Limit (Yes/No), disease site at baseline, use of certain treatments as recorded on Previous Prostate Cancer Therapy Form (Sipuleucel-T, Abiraterone, Enzalutamide, both Abirateron and Enzulatamide) and use of opioids (Yes/No) (ATC code= N02A) recorded as prior medication in the Concomitant Medication Form and Previous Prostate Cancer Therapy Form will be presented.
It was checked whether the distribution of the laboratory baseline characteristics is symmetric (i.e. median and mean are close to each other and median is in the middle between Q1 and Q3) using pooled data. Based on this check distribution of alkaline phosphatase and lactate dehydrogenase is considered as asymmetric and therefore, geometric means will be presented in addition of arithmetic mean.
Disease site is defined as approximate anatomical location of the disease lesion or lesions in terms of single metastasis or multiple metastases. Disease site corresponds with larger anatomical areas covered by the central reading for lymph nodes (LSLOC contains "Lymph Node" or equal to "Other, Nodal"), soft tissue lesions (LSLOC in "Brain/Bone/Lung, Left (Right)/Lungs, Bilateral/Chest Wall/Kidney, Left (Right) Kidneys, Bilateral/Skin/Soft

Tissue/Adrenal Gland, Left/(Right)/Adrenal Glands, Bilateral/Pleural Effusion/Ascites/Neck/Back/Mediastinal/Pleura/Pericardium/Diaphragm/Paraspinal/Abdominal Wall/Peritoneum/Retroperitoneum/Mesentery/Colon/Rectum/Pelvis/Breast, Left (Right)/Breasts, Bilateral/Muscle/Subcutaneous/Skull/Cervical Spine/Thoracic Spine/Lumbar Spine/Pelvic Bone/Eye/Orbit/Nose/Nasopharynx/Oropharynx/Sinus/Extremity/Urinary Bladder/Rib(s), Left (Right, Bilateral)/Pancreas/Small Bowel/Stomach/Liver/Spleen/Other, Extranodal")bone lesions (if not in lymph nodes and soft tissue lesions categories and LSLOC contains "Bone". Further, disease site at baseline will be categorized as follows: at least one lesion in liver (regardless the rest), at least one lesion in lungs or other visceral lesions (and not liver lesion), lymph node(s) only, bone lesion(s) only, bone lesions and lymph nodes only, none lesion. Data from central reading will be used for identification of categories defined above.

4.3.3 Disease History and medical history

Summary statistics for history of SRE, disease history (Gleason score (8 to 10, <8), PSA level at initial diagnosis (median, 25^{th} – 75^{th} percentile), number of missing PSA values (number of ≥ 5 ng/mL, number of < 5 ng/mL), years from adenocarcinoma prostate diagnosis (date of randomization – date of diagnosis + 1)/365.25 in years), Clinical Stage at Diagnosis (I, II, III, IV), measurable disease and previous prostate cancer therapy (yes/no) will be presented.

Medical history will be summarized by SOC and preferred term (PT), by treatment group and overall (active conditions only) and all medical history will be presented in a data listing.

Medical history coded using MedDRA version 22.1.

4.4 Exposure

All exposure tables are presented by treatment and overall for all patients in the Safety population, ITT population and PP population.

Duration of exposure is defined as the (date of last dosing – date of first dosing + 1).

4.4.1 Exposure to DCVAC/PCa or placebo

Exposure to DCVAC/PCa or placebo during the CTP and MBP separately and CTP+MBP combined will be analyzed descriptively by number of doses analyzed as continuous and as categorical variable, duration (months) and duration (days).

4.4.2 Exposure to first line Standard of Care chemotherapy

Exposure to Docetaxel will be summarized by number of doses received analyzed as continuous and as categorical variable, number of patients completed the 10^{th} cycle, duration (days), duration (months), frequencies of the cycle numbers in which dose was modified, and the cycle numbers where Docetaxel exposure was discontinued.

4.4.3 Exposure to next line therapies

Frequencies of the patients per type of Second Line Therapies and Third Line Therapies (if applicable) will be presented.
Type of Chemotherapy refers to the Preferred Term from WHO Drug Dictionary B2 Enhanced March 2014 or newer.

4.5 Prior and Concomitant Medication

Medications are coded using the World Health Organization (WHO) drug dictionary, dated March 2014 during the study and upgraded prior to database lock to the latest version available at that time (WHODD Global B3 Sep 2019).

The name, duration of use and indication, and whether not the medication was given for an AE/serious AE (SAE) for all concomitant medications taken on or after the date of informed consent through the end of study visit will be documented on the eCRF. Prior and concomitant medications will be classified into the default anatomical therapeutic chemical classification system (ATC) code provided by the system. The ATC levels 1 and 2 and preferred term will be used for the data listing. Prior and concomitant medications will be summarized by ATC level 1 and 2, and preferred term as well as presented in a data listing. For the table summary, a patient will only be presented once for each level of summarization.

In the case of missing start and stop dates, all available date information will be used to determine whether or not the medication was taken before the first dose of study medication or start of first line chemo (which occurs first). The worst case will be applied, the lowest date for the start date and the highest date for the end date. If both start and stop date are unknown then consider as concomitant medication.

Prior and concomitant medications will be summarized for the safety population; however, all medications will be in a data listing.

Prohibited medications (see Section 3.4.4) are identified in appendix E and will be flagged in the listings.

Prior, concomitant and post medications will be flagged in the listings.

4.5.1 Prior Medication

Prior medications are summarized by ATC levels 1 and 2, and preferred terms by treatment.

4.5.2 Concomitant Medication

Concomitant medications are summarized by ATC levels 1 and 2, and preferred terms by treatment.

4.5.3 Post-treatment Medication

Post-treatment medications are summarized by ATC levels 1 and 2, and preferred terms by treatment.

4.6 Efficacy / Primary and Secondary Analysis

4.6.1 Primary Endpoint

Overall survival is defined as the time from randomization until death due to any cause: (date of death-date of randomization +1)/30.4375 (expressed in months).

Date of death will be taken from raw dataset DS

The date of randomization will be the date from IWRS data (IWRS database received by the Data Management department).

If only the day is missing, max(RFPENDTC*, 01MMMYYYY) will be considered as the date of death. If month is missing, max(RFPENDTC*, 01JANYYYY) will be considered as the date of death.

* in SDTM terminology, it is a date when a subject ended participation or follow-up in a trial and it equals to the last known date for this subject.

Cut-off definition and rules for censoring: The primary efficacy analysis of OS was planned when the target number of 657 death events is reached. The analysis was originally planned using ITT where leukapheresis and manufacturing failures will be censored on Day 1 (i.e., day of randomization).

Cut-off date is defined as date when the 657th patient in this analysis set died, i.e. died leukapheresis and manufacturing failures will not be counted for determination of cut-off. This date was determined as 30-MAY-2019 using clean data after DB lock and before unblinding.

If there is evidence that patients is alive after cut-off date (as evident from survival visit data or imaging assessment date, laboratory assessment date, concomitant medication/adverse event start date or end date (if end date is not due to death), date physical examination date, exposure 1st, 2nd, 3rd line therapy, vital sign assessment date is after cut-off date), then the patient will be censored at cut-off date. Otherwise, the patient will be censored at the date of the last contact.

The last contact will be identified as latest date out of: last contact date recorded in the survival status form of the eCRF. imaging/tumor assessment date, laboratory assessment date, concomitant medication/adverse event start date or end date (if end date is not due to death), date physical examination date, start of end date of 1st, 2nd, 3rd line therapy, vital sign assessment.

In analysis without application of the cut-off (see section 4.6.3), alive patients will be censored at date of last contact.

The SAS codes for the inferential statistics are listed in Section 4.15.

Assuming a positive outcome of the study, the Sponsor plans to follow patients up for survival for an additional 2 years after the conduct of the final analysis or until 80% of study patients have died (whichever comes first). Detail of this analysis will be described separately, if needed.

4.6.2 Method of Analysis for Primary Outcome

The primary efficacy analysis is a stratified log-rank test based on the ITT population.

Comparisons between treatments will be performed by means of the Log-rank test, stratified by region (US vs Other), prior therapy (abiraterone or not and enzalutamide or not) and, ECOG Score (0-1 vs. 2) at baseline (consider the value at baseline entered in the eCRF and not in the IWRS). Median, quartiles obtained using the Kaplan-Meier method will be presented for each treatment group. The number of patients in study at the beginning, the cumulative number and percentage of deaths at the end of the study period, The Kaplan-Meier estimates of survival at 3 months, 6 months, 9 months, 12 months, 18 months, 24 months, 36 months, 48 months and 60 months (in percentage) will also be tabulated by treatment group.

Estimates for the survivor function of each treatment group obtained using the Kaplan-Meier method will be displayed graphically.

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 treatment group for the Log-rank test and Cox PH model are derived as follows:

- Treatment represents study treatment according to randomization scheme, DCVAC/PCa coded as 1, placebo as 2;

The stratification factors for the Log-rank test and Cox PH model are derived as follows:

- Region = 1 for the US, 0 for any other country.
- Prior1 (1/0) is 1 when abiraterone is used as prior therapy.
- Prior2 (1/0) is 1 when enzalutamide is used as prior therapy;
- ECOG score at baseline (0-1 or 2).

Abiraterone and enzalutamide will be in Previous Prostate Cancer Therapy form from the eCRF, stratification factors of ECOG and US vs. non-US patients will be also derived using eCRF data.

If baseline value of ECOG is missing that value from randomization visit will be taken for stratification factor ECOG.

Proportional Hazards assumptions are investigated by adding a treatment group – time or factor – time interaction:

If proportional hazards cannot be fulfilled (p-value interaction ≤ 0.10), the hazard ratio related to covariate will be the function of time.

The adjusted hazard ratio and its two-sided 95% confidence interval will be presented.

In case of non-proportional hazard, a stratification and/or time dependent model will be done in addition to Cox model described above.

4.6.3 Sensitivity and Subgroup Analyses

1. Unstratified Log-Rank test and Cox model not adjusted for stratification factors . The same analyses as in previous section with only treatment in the model.
2. To analyze the effects of imbalance in the baseline characteristics adjusting for various covariates in the Cox proportional hazard regression model will be performed. In addition to treatment, the 3 stratification factors, the following prognostic factors will be included in the model simultaneously: age group (< 65 years vs. ≥ 65 years) (1/0), baseline PSA (values will be log transformed prior to inclusion, if any values = 0 then all values will have 1 added prior to transformation to allow all values to be included after transformation), baseline LDH (> ULN vs. <= ULN)) (1/0), baseline ALP (values will be log transformed prior to inclusion), baseline albumin, baseline hemoglobin, Gleason score 2-7 vs. 8-10) at initial diagnosis (1/0), opioid use (1/0) (ATC code= N02A), disease site (at least one lesion in liver (regardless the rest), at least one lesion in lungs or other visceral lesions (and not liver lesion), bone lesions and lymph nodes only, lymph node(s) only* + bone lesion(s) only* + none lesion). If another characteristic is imbalanced between treatment group sensitivity analysis adjusted for this characteristics in addition will be also performed. This will be done on the ITT population.

   * patients with only bone lesion(s) or only lymph lesion(s) or without lesions at baseline will be grouped together for covariate and subgroup analysis.

3. To assess the effect of the second line therapy on overall survival, the time from randomization (i.e. **date of first secondary therapy – date of randomization + 1)/30.4375** is added as time-dependent covariate to the primary Cox model (see section 4.7.2).[4]
4. A separate summary of survival data will be provided for patients with leukapheresis or manufacturing failure.
5. A sensitivity analysis with censoring leukapheresis or manufacturing failure on Day 1 (in total 147 patients, see section 3.5.2 for details). Inclusion of leukapheresis and manufacturing failures (i.e. patients who did not received IMP; therefore, it can be expected that their survival will be closed to control arm) into the primary analysis can decrease effect of study drug showed by the analysis. This sensitivity analysis will provide estimate of study drug effect if proportion of leukapheresis and manufacturing failures would be minimize.
6. Analysis without application of the cut-off date. This analysis will not be considered as the primary analysis.
7. Main analysis (as described in section 0) will be conducted for each country and in addition results will be displayed in forest plot presenting HR and its 95% CI for each country and overall. Effect of the country will be evaluated and if further evaluation of OS is needed OS will be analyzed using Cox model with adjustment to country and treatment-by-country interaction (if not feasible to include all countries into the analysis because of low number of patients in both treatment arm, it will be considered to make this sensitivity analysis using subgroup where this analysis is feasible).

The primary endpoint OS will also be analyzed using the PP population to analyze sensitivity of the results to protocol deviations. The 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 on the ITT population.

If applicable, HR and its 95% confidence interval will be tabulated for covariates as well as for the treatment.
The following subgroup analyses will be performed for exploratory purposes:

1. Subgroups per stratification groups: US patients, non-US patients, abiraterone as prior therapy, enzalutamide as prior therapy, abiraterone and enzalutamide used as prior therapy neither of the two used as prior therapy, ECOG at baseline 0-1, ECOG at baseline 2
2. Subgroups by age (< 65 years vs. ≥ 65 years)
3. Subgroups per disease site at baseline as defined above
4. On 25NOV2015 new Poly (I:C) has been started to used for manufacturing and starting 11MAY2016 only new Poly (I:C) was used. Between 25NOV2015 and 11MAY2016 about 9 patients have manufactured DCVAC/PCa using the new Poly (I:C), list of those patients will be provided by manufacturing to statistician after unblinding and presented in footnote of corresponding tables. Subgroup analysis of patients before vs. after this change will be performed using only patients who received at least one dose of IMP (the subgroup analysis will be done also for AEs). Further, comparison of OS of patients whom DCVAC/PCa was manufactured before vs. after this change will be preformed

using patients who received at least one dose of DCVAC/PCa and using patients in per protocol.

5. Further, internal consistency with regard to previous prostate cancer therapy and subsequent therapy/therapies will be explored via the subgroups as defined in the following table. The subgroups were defined according to mode of therapy action.

<table>
<tr><th>Group of patients by previous therapy*</th><th>Grouping of patients by subsequent anti-cancer therapy*</th></tr>
<tr><td><u>Orchiectomy</u>
[assuming 10-15% of patients]</td><td>Patients treated with I or II
[assuming 25 - 30% of patients]</td></tr>
<tr><td>Patients treated with I. only
[assuming 35-40% of patients]</td><td>Patients treated with chemotherapy
[assuming 25 – 30% of patients]

WHODD ATC code and preferred name used for programming:
<table><tr><th>Preferred name</th><th>ATC</th></tr><tr><td>CABAZITAXEL;CARBOPLATIN</td><td>L01XY</td></tr><tr><td>CABOZANTINIB</td><td>L01XE</td></tr><tr><td>CAPECITABINE</td><td>L01BC</td></tr><tr><td>CARBOPLATIN</td><td>L01XA</td></tr><tr><td>CARBOPLATIN;DOCETAXEL</td><td>L01XY</td></tr><tr><td>CARBOPLATIN;ETOPOSIDE</td><td>L01XY</td></tr><tr><td>CARBOPLATIN;GEMCITABINE</td><td>L01XY</td></tr><tr><td>CARBOPLATIN;PACLITAXEL</td><td>L01XY</td></tr><tr><td>CISPLATIN</td><td>L01XA</td></tr><tr><td>CISPLATIN;GEMCITABINE</td><td>L01XY</td></tr><tr><td>COMBINATIONS OF ANTINEOPLASTIC AGENTS</td><td>L01XY</td></tr><tr><td>CYCLOPHOSPHAMIDE</td><td>L01AA</td></tr><tr><td>DOCETAXEL</td><td>L01CD</td></tr><tr><td>DOXORUBICIN HYDROCHLORIDE</td><td>L01DB</td></tr><tr><td>EPIRUBICIN</td><td>L01DB</td></tr><tr><td>ETOPOSIDE</td><td>L01CB</td></tr><tr><td>FLUOROURACIL</td><td>L01BC</td></tr><tr><td>FLUOROURACIL;FOLINIC ACID</td><td>L01BC</td></tr><tr><td>FLUOROURACIL;OXALIPLATIN</td><td>L01XY</td></tr><tr><td>GEMCITABINE</td><td>L01BC</td></tr><tr><td>IRINOTECAN</td><td>L01XX</td></tr><tr><td>MITOXANTRONE</td><td>L01DB</td></tr><tr><td>MITOXANTRONE HYDROCHLORIDE</td><td>L01DB</td></tr><tr><td>OXALIPLATIN</td><td>L01XA</td></tr><tr><td>PACLITAXEL</td><td>L01CD</td></tr><tr><td>VINCRISTINE</td><td>L01CA</td></tr><tr><td>VINORELBINE</td><td>L01CA</td></tr><tr><td>VINORELBINE TARTRATE</td><td>L01CA</td></tr><tr><td>VISCUM ALBUM</td><td>L01CW</td></tr><tr><td>ESTRAMUSTINE</td><td>L01XX</td></tr><tr><td>ESTRAMUSTINE PHOSPHATE</td><td>L01XX</td></tr><tr><td>ESTRAMUSTINE PHOSPHATE SODIUM</td><td>L01XX</td></tr><tr><td>LAPATINIB</td><td>L01XE</td></tr><tr><td>ONAPRISTONE</td><td>L01XX</td></tr><tr><td>PANOBINOSTAT</td><td>L01XX</td></tr><tr><td>TASQUINIMOD</td><td>L01XX</td></tr></table></td></tr>
<tr><td>Patients treated with I. and (II. and/or III.)
[assuming 30-35% of patients]</td><td>Patients treated with PARPi
[assuming <2% of patients]

WHODD ATC code or preferred name used for programming:
<table><tr><th>Preferred name</th><th>ATC</th></tr><tr><td>Niraparib</td><td>L01XX</td></tr><tr><td>Rucaparib</td><td>L01XX</td></tr></table></td></tr>
</table>

<table>
<tr><td></td><td>
<table>
<tr><td>Talazoparib</td><td>L01XX</td></tr>
<tr><td>Olaparib</td><td>L01XX</td></tr>
</table>
</td></tr>
<tr><td>Patients treated with II. and/or III.
[assuming 5-10% of patients]</td><td>Not received any subsequent therapy [assuming about 35 % of patients]</td></tr>
<tr><td>Immunotherapy (including CPIs)
[assuming <10% of patients]

WHODD ATC code or preferred name used for programming:
<table>
<tr><th>Preferred name</th><th>ATC</th></tr>
<tr><td>Interleukins</td><td>L03AC</td></tr>
<tr><td>Sipuleucel-T</td><td>L03AX</td></tr>
<tr><td>Rilimogene</td><td>L03AX</td></tr>
<tr><td>Mycophenolat mofetil</td><td>L04AA</td></tr>
<tr><td>Etanercept</td><td>L04AB</td></tr>
<tr><td>Hydrochloroquine sulfate</td><td>L04AX</td></tr>
<tr><td>Methotrexate sodium</td><td>L04AX</td></tr>
<tr><td>Atezolizumab</td><td>L01XC</td></tr>
<tr><td>Ipilimumab</td><td>L01XC</td></tr>
<tr><td>Nivolumab</td><td>L01XC</td></tr>
<tr><td>Pembrolizumab</td><td>L01XC</td></tr>
</table>
</td><td>Patients treated with alpha emitters (assuming 5 – 10% of patients)

WHODD ATC code and preferred name used for programming:
<table>
<tr><th>Preferred name</th><th>ATC</th></tr>
<tr><td>Radium</td><td>V03A</td></tr>
<tr><td>RADIUM RA 223 DICHLORIDE</td><td>V10XX</td></tr>
</table>
</td></tr>
<tr><td></td><td>Anti-angiogenics and IGF blockers

WHODD ATC code or preferred name used for programming:
<table>
<tr><th>Preferred name</th><th>ATC</th></tr>
<tr><td>AFLIBERCEPT</td><td>S01LA</td></tr>
<tr><td>BEVACIZUMAB</td><td>L01XC</td></tr>
<tr><td>XENTUZUMAB</td><td>L01XC</td></tr>
</table>
</td></tr>
</table>

**I., II., III. are compounds used for chemical castration (for previous and subsequent therapy):*

I. ***Nonsteroidal antiandrogens***

WHODD ATC code and preferred name used for programming:

Preferred name	**ATC**
Apalutamid	L02BB
Bicalutamide	L02BB
Enzalutamide	L02BB
Flutamide	L02BB
Nilutamide	L02BB

II. ***Androgen synthesis inhibitors***

WHODD ATC code and preferred name used for programming:

Preferred name	**ATC**
Abiraterone	L02BX
Abiraterone acetate	L02BX
Abiratero;Prednisolone	L02BX
Seviteronel	L02BX
Orteronel	L02BX
Finasteride	G04CB
Dutasteride	G04CB
Dutasteride; Tamsulosin hydrochloride	G04CA
Ketoconazole	J02AB

III. ***Antigonadotropins*** *(GnRH agonists, GnRH antagonists)*

WHODD ATC code and preferred name used for programming:

Preferred name	**ATC**
Degarelix	L02BX
Degarelix acetate	L02BX
Abarelix	L02BX
Buserelin	L02AE

Buserelin acetate	L02AE
Goserelin	L02AE
Goserelin acetate	L02AE
Histrelin	L02AE
Histrelin acetate	L02AE
Leuprorelin	L02AE
Leuprorelin acetate	L02AE
Triptorelin	L02AE
Triptorelin acetate	L02AE
Triptorelin embonate	L02AE

One drug can have more ATC codes depending on the indications; therefore, the subgroup of patients needs to be identified via combination of ATC code and preferred name as listed above.

Group of patients by previous therapy will be identified via medications recorded in eCRF forms "Previous Prostate Cancer Therapy" and "Concomitant Medication" (as per definition of Prior Medication in section 3.4.1).

Grouping of patients by subsequent anti-cancer therapy will be identified via medications recorded in eCRF forms "Concomitant Medication" and "Second Line Standard of Care Therapy" (next line therapy includes medications started on day of last first line Standard of Care chemotherapy or later).

Analysis as described in section 4.6.2 will be performed for each subgroup defined above (exception will be only that stratification factor redundant to use will not be used in subgroup analysis [1.]). In addition will be displayed in tables and forest plot presenting HR and its 95% CI for each subgroup and overall for the primary analysis.

Analysis of OS by subgroups of prior therapy, by subgroups of subsequent therapy, by subgroups per the sequence of previous and subsequent therapy (if feasible depending on the number of patients per subgroup) will be performed. If further evaluation of OS is needed, OS will be analyzed using a Cox model with adjustment for the type of prior and subsequent therapy.

The subgroup of patients treated with poly(ADP-ribose) polymerase inhibitors (PARPi) as subsequent therapy is assumed to have a smaller number of patients than needed for a robust subgroup analysis. This subgroup is planned to be described only (number of patients by treatment arm and OS).

4.6.4 Secondary Endpoints

Key secondary endpoints are:

- rPFS
- Time to PSA progression
- Time to first SRE.

The 3 key secondary endpoints are analyzed for both ITT and PP populations.

Other secondary endpoints are:

- Time to radiographic progression or SRE
- Proportion of patients with SRE.

These secondary endpoints are analyzed for the ITT population.

4.6.5 Methods of Analysis for Secondary Outcomes

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 method will be used to test time to PSA progression and time to SRE in parallel. This will be done as follows:

No imputation of missing data will be done. For the 3 key secondary endpoints (time to rPFS, time to PSA progression and time to SRE), the last date of documented disease status will be used if the event had not been documented at the time of the analysis or patients had withdrawn the study prior to determination of progression. Such patients will be censored.

As the Hochberg procedure is considered more powerful compared to other methods, this increase of power comes with at the cost of having to make the assumption of independent p-values. Assumptions for using Hochberg method a fixed sequential testing will be checked as follows:
Three scatterplots of rPFS time vs. PSA progression time, rPFS time vs. SRE time and PSA progression time versus SRE time will be computed.
If positively correlated data would be predominately in the +/+ and -/- quadrants, and negative would be in the +/- and -/+ quadrant.
In these plots, patients with events in both, events in neither, and event in one but not the other endpoint will be distinguish by four types of symbols.
Only events will be considered and not the censored data.
Contingency tables with counts of patients with radiological progression vs. PSA progression, radiological progression vs. SRE, PSA progression vs SRE will be also produced.

4.6.5.1 rPFS (Radiographic progression)

This is defined as (**min(date of radiographic progression of bone lesions, date of radiographic progression of soft tissue lesions, date of death) – date of randomization + 1)/30.4375** (expressed in months).

Image Review Facility (IRF) will be used to assess primary rPFS. The detailed rules for radiographic progression are specified in the protocol (Section 7.3.2.4).

Date of radiographic progression of bone lesions will be identified by selecting ADJACPT=”Y” and DOPBL.
Date of radiographic progression of soft tissue lesions will be identified by selecting ADJACPT=”Y” and DOPSTL.

The visit labels from central reading data will be remapped in order to transform the data to SDTM structure which use the visit labels from eCRF data. The remapping will be performed via merging of central reading data and eCRF data by Patient Id and date of CT scan.

rPFS will be analyzed for both ITT and PP populations using the same statistical methods as described as for the primary endpoint.

The date of progression is assigned based on the time of first evidence of radiographic disease progression regardless of violations or discontinuation of study drug. Patients lost to follow up, completed or withdrawn will be censored at the last disease assessment. In case a patient has

no sufficient data to assess radiographic disease progression (post-baseline) and no death observed will be censored at Day 1.

The main reason leading to the determination of rPFS will be tabulated. For patients without rPFS, the main reason for censoring is tabulated as well.

Sensitivity analyses:

1. Unstratified Log-Rank test and unadjusted Cox model will be computed as sensitivity analyses. Further sensitivity analyses specified in the section 4.6.3 will be performed only if imbalance in baseline characteristics is observed.
2. Sensitivity analysis including start of subsequent anti-cancer therapy as an event.
3. If the proportion of patients with an unscheduled assessment of disease progression (i.e. assessment inbetween scheduled assessment) is imbalanced between the treatment arms, then a sensitivity analysis using only scheduled assessments will be performed.
4. If the proportion of patients with disease progression observed after two or more missing/not-evaluable assessments is imbalanced between the treatment arms, then a sensitivity analysis where the patients will be censored at the date of the last assessment before the gap of two or more missing/not-evaluable assessments will be performed.
5. According to conclusions during BDRM (see document Analysis Set Specification v1.0 dated on 9DEC2019 including minutes from blind data review meeting and decisions about exclusion of patients from analysis sets) a sensitivity analysis with censoring patient with interval between two assessments longer than 24 weeks will be planned. The censoring will be done at the last assessment preceding the gap > 24 weeks (reference: FDA guidelines, Clinical Trial Endpoints for the Approval of Non-Small Cell Lung Cancer Drugs and Biologics, Table D1)[6].

4.6.5.2 Time to PSA progression

PSA progression occurs if the following condition is met: PSA value ≥ min (nadir, baseline) + 2 AND PSA value ≥ min (nadir, baseline) x 1.25, where PSA levels are measured in ng/mL. In order conclude that the patient progressed the PSA progression needs to be confirmed by a second consecutive PSA value obtained at least 3 weeks later. Time to PSA is progression is calculated as (date of confirmed PSA progression – date of randomization + 1)/30.4375.

Time to PSA progression will be analyzed for both ITT and PP populations using the same statistical methods as described as for the primary endpoint.

Only unstratified Log-Rank test and unadjusted Cox model will be computed as sensitivity analyses. Further sensitivity analyses specified in the section 4.6.3 will be performed only if imbalance in baseline characteristics is observed.

The date of the first increase will be used as the date of the failure occurrence. If a failure is not observed during the study, then the time to PSA progression will be censored at the date of last post-baseline PSA evaluation in case of lost-to-follow-up, completion or discontinuation.

Similarly as for time to rPFS, if no post-baseline data is available to determine PSA progression, the patient is censored at Day 1.

In case of no post-baseline data, patient will be censored at Day 1.

Evaluation of different methodologies used for determination of PSA levels.

Different methodology for determination of PSA level have been unintentionally used in EU and in US.

- EU: PSA testing is done on Cobas e602.
- US: PSA testing is done on the Centaur.

Therefore, PSA levels can be analysed only separately for EU and US. Comparison of PSA levels between treatment arms is not objective of the study, the objective is comparison of time to PSA progression. Because PSA progression is defined in terms of increase from nadir/baseline there is not expected the effect of those different methods to time to PSA progression evaluation. Moreover, US vs. non-US is stratification factor, therefore both occurred in treatment arms with the same proportion; therefore, there is not expected effect to comparison of treatment arms in time to PSA progression.

In order to show that expectation of no bias due to different methods used the following exploration was performed:
Linear correlation was calculated between both methods as following:

- 40 serum samples were splitted into 2 aliquots, the aliquots were kept in frozen conditions at -70°C, ship in frozen conditions also.
- No spiked materials nor recombinant protein were used.
- The testing was performed the same day to be on the same Freeze/thaw cycle at both sites.
- Method X is Cobas and method Y is centaur xp.

Correlation coefficient formula:

$$r = \frac{n(\Sigma xy) - (\Sigma x)(\Sigma y)}{\sqrt{\left[n\Sigma x^2 - (\Sigma x)^2\right]\left[n\Sigma y^2 - (\Sigma y)^2\right]}}$$

with:
N = number of values or elements in the set
X = first score
Y = second score
ΣXY = sum of the product of both scores
ΣX = sum of first scores
ΣY = sum of second scores
ΣX2 = sum of squares of first set of scores
ΣY2 = sum of squares of second set of scores

The result is a coefficient of correlation using the software Ep evaluator between both methods of 0.9897 (see appendix D)

In order to explore potential effect of the two methods on the study results the following exploration was performed:

- Simulation of results with US method ; time to PSA progression was calculated applying the conversion factor 0.9897 to the EU patients, and
- Simulation of results with EU method; time to PSA progression was calculated applying the conversion factor 1.0104 (1/0.9897) to the US patients.

Because the differences were negligible it was concluded that the study results of time to PSA progression are not affected.

According to conclusions during BDRM (see document Analysis Set Specification v1.0 dated on 9DEC2019 including minutes from blind data review meeting and decisions about exclusion of patients from analysis sets) a sensitivity analysis with censoring patient with

interval between two assessments longer than 24 weeks will be planned. The censoring will be done at the last assessment preceding the gap > 24 weeks (reference: FDA guidelines , Clinical Trial Endpoints for the Approval of Non-Small Cell Lung Cancer Drugs and Biologics, Table D1) [6].

4.6.5.3 Time to first Skeletal Related Event (SRE)

This is defined as (**date of first skeletal related events the time – date of randomization + 1)/30.4375** (expressed in months).

All SRE will be in the SRE form of the eCRF.

Time to first SRE will be for both ITT and PP populations using the same statistical methods as described as for the primary endpoint.

Only unstratified Log-Rank test and unadjusted Cox model will be computed as sensitivity analyses. Further sensitivity analyses specified in the section 4.6.3 will be performed only if imbalance in baseline characteristics is observed.

SRE is any radiation therapy to bone, pathologic bone fracture, spinal cord compression, surgery to bone or change in antineoplastic therapy to treat bone pain. SRE is assessed by the Investigator during each clinical visit.

The date of first occurrence of an event meeting the definition of SRE, will be used as the date of the failure occurrence. If there is no evidence of occurrence, the patient will be censored at date of last SRE assessment (in case the patient is lost-to-follow-up, completed or discontinued the study). If there is no post-baseline data, the patient is censored at Day 1.

In case of incomplete date of first occurrence of SRE, the similar rule as for the incomplete onset date of Adverse Event will be applied and missing day will be completed by last day in the month.

4.6.5.4 Other Secondary efficacy endpoints:

Time to radiographic progression or SRE is defined as **(min(date of first skeletal related events the time, date of first radiographic progression) – date of randomization + 1)/30.4375** (expressed in months).

If there are no post-baseline available, the patient will be censored at Day 1.

Otherwise, if there is no evidence of the event occurrence, the patient will be censored at the first date between the last date of PSA assessment and the last date of SRE assessment (if the patient is lost-to-follow-up, completed or discontinued the study).

It will be for both ITT and PP populations using the same statistical methods as described as for the primary endpoint.

The proportion of patients with SRE will be summarized by treatment group, and analyzed by means of a log binomial model, adjusted for stratification factors as in previous statistical models. P-values and Risk Ratio (RR) with 95% confidence interval for covariates will be tabulated, as well as for treatment.

Response represents the binary variable (patient with SRE/ Patient without SRE) for each patient. Probability of "Patient with SRE" will be modeled. It will be for both ITT and PP populations.

4.7 Exploratory Analyses

4.7.1 Quality of Life (QoL)

4.7.1.1 FACT-P Scores

The evaluation of the results from the FACT-P questionnaire will be summarized for the ITT population. Summary statistics [FACT-P, Functional Assessment of Cancer Therapy – General (FACT-G), Trial Outcome Index (TOI), Prostate Cancer Scale (PCS), subscales Physical Well-Being (PWB), Social/family Well-Being (SWB), Emotional Well-Being (EWB) and Functional Well-Being (FWB)] and changes from baseline are presented by visit for each treatment group. A manual for computations and missing values handling is summarized in section 4.11 and shown in Appendix A.

Mean values and changes from baseline and associated 95% CI in FACT-P, FACT-G, TOI, PCS, PWB, SWB, EWB and FWB for each treatment group will also be plotted over time.

The individual FACT-P items will also be presented in a data listing.

4.7.1.2 EQ-5D scores

The evaluation of the results (index and VAS) from the EQ-5D questionnaire (except for patients in the US where the EQ5D is not performed) and the changes from baseline will be summarized by visit using a reduced version of the ITT (i.e. the ITT population with patients in the US excluded). See Appendix B for missing values and Appendix C for the algorithm of EQ-5D scores.

Mean values and changes from baseline in index and VAS for each treatment group will also be plotted over time.

4.7.2 Next Line Treatment

The number and proportion of patients requiring next line treatment (second line treatment, third line treatment) will be summarized for the ITT in section 4.4.2. Patients without information on next line treatment will be considered as missing. Time to the requirement of next line treatment from randomization, defined as ((start date of next line treatment) – date of randomization+ 1)/30.4375 (expressed in months), will be analyzed using ITT population. Median, quartiles obtained using the Kaplan-Meier method will be presented for each treatment group. Patients lost to follow up, completed or discontinued the study will be censored at the date of first line discontinuation.

Kaplan-Meier curves will also be computed.

Duration of next line therapy (expressed in days and in months) will be calculated by summing the duration of the second line therapy and the duration of the third line therapy. The analysis

will be repeated for the following next line treatments: abiraterone, cabazitaxel, docetaxel, enzalutamide, mitoxantrone, radium-223.

If there will be substantial number of patients with recorded next-line therapy in Concomitant medication Form sensitivity analysis (time-to-event data analysis only) using also data from Concomitant Medication form will be performed. For selection of next line therapy=subsequent therapy from Concomitant Medication will be used ATC codes and preferred names defined in section 4.6.3., next line therapy includes medications started on day of last first line Standard of Care chemotherapy or later. The following rule will be applied: If the start date of Concomitant Medication is missing or partially missing, it will not be imputed and taken into account then.

4.8 Safety Analysis

4.8.1 Adverse Events

An AE is considered treatment-emergent (TE) when the onset date of the event falls on or after the earliest start date of chemotherapy or study treatment i.e. min(start date first line Standard of Care chemotherapy, start date DCVAC/PCa or placebo) or when the AE worsens (increase in severity) on or after the earliest start date of chemotherapy or study treatment.
Disease progression related events will be recorded as AEs but will not be recorded as SAEs even if fatal.

In case of missing (onset date is assumed to be the start date of treatment*) or partial missing onset dates, TE status is assigned using a 4-steps approach:

1. impute the onset date considering the last day of the year/month or the day of AE end (which comes first);
2. if onset date imputed according to step 1 ≤ treatment start date*, then stop. Else go to step 3;
3. impute onset start date as max(onset date imputed considering the first day of the year/month, treatment start date*).
4. If AE end date <treatment start date*then AE will be not considered as TE.

*treatment start date refers to the earliest start date of chemotherapy or study treatment i.e. min(start date first line Standard of Care chemotherapy, start date DCVAC/PCa or placebo)

In addition to treatment-emergent AEs will be defined also IMP-emergent AE as AE with the onset date on or after the first IMP (i.e. DCVAC/PCa or Placebo) administration or AE worsens (increase in severity) on or after the first IMP. In case of missing or incomplete onset date of AE the same rules as described above will be used with only one change: treatment start date refers to the first DCVAC/PCa or placebo administration.

The intensity of each AE will be assessed using National Cancer Institute (NCI) common terminology criteria for adverse events (CTCAE) v4.03 grading.

Missing severity and outcome will be classed as unknown. Missing causality will be regarded as related (if the event is TE and the onset date is not before the procedure of interest).

The duration of an AE will be calculated as follows:

- AE end date – AE onset date + 1 (when both dates are completely known);
- Date of completion/discontinuation – AE onset date + 1 (when the AE onset date is fully known but the AE is not resolved at the end of the trial): in this case the duration will be presented as ">x days" in the listing rather than "x days";
- missing (when the AE onset date is incomplete or unknown, or when the AE has resolved but with an incomplete or unknown end date, or when the AE onset date is > date of completion/discontinuation and the AE is not resolved).

In case an AE changes of intensity, the above rule implies the AE onset date of the first occurrence of this AE, and the stop date (if available) of last intensity change of this AE.

A summary table is presented, showing the number of patients and number of events () , based on the Safety Population, per treatment, for following categories:

- Number of AEs
- Number of AEs leading to study discontinuation
- Number of AEs related to DCVAC/PCa or placebo
- Number of AEs related to Standard Care Therapy
- Number of AEs related to Leukapheresis (based on the LP)
- Injection Site reaction AEs
- Number of AESIs (SAEAESI = "Y in SAE form in the eCRF)
- Number of Skeletal Related Events
- Number of AEs leading to action taken with:
  - Investigation medicinal product (IMP) – presented in categories as per eCRF
  - Chemotherapy– presented in categories as per eCRF
  - Concomitant medication– presented in categories as per eCRF
- AE severity
- AE outcome.

In case of several episodes of the same AE identified by the AE record number (according to variable AECSSPEC), the AE will be counted only once with worst CTC grade, seriousness, causality (the outcome, action taken with IMP/chemoof the last episode will be remained), the SOC and PT of the worst grade or if two records with the same grade the later onset date will be taken from AE record.

A similar summary table is produced on all SAEs.

Summaries of TEAEs by SOCs and PT will be done for:

- All AEs
- All SAEs
- All AEs leading to study discontinuation
- All AEs leading to permanent discontinuation of IMP

- All AEs leading to permanent discontinuation of chemotherapy
- All fatal AEs
- All AEs related to DCVAC/PCa or placebo
- Skeletal Related AEs
- Injection Site reaction AEs
- AEs of Special-Interest
- AEs related to standard of care chemotherapy
- AEs with grade > 2
- AEs with grade > 2 related to DCVAC/PCa or placebo
- AEs by country
- SAEs by country
- Fatal AEs by country

In addition, frequency table by SOC and PT of

- AE (including non-TEAE) related to leukapheresis will be provided (these are not TEAEs since leukapheresis occurs prior to first dose of study treatment) on leukapheresis population.
- AEs occurred on the day of leukapheresis or on the day after will be provided on leukapheresis population.

A patient with more than one occurrence of the same AE in a particular SOC will be counted only once in the total of those experiencing adverse events in that particular system organ class.

With the exception of leukapheresis related AEs, only TEAEs (commencing after exposure to study treatment) will be included in the adverse and serious adverse event summaries. Non-TE events (other than leukapheresis related AEs) (i.e. starting prior to exposure to first line chemo or study treatment) will be included in the patient listings and flagged but not included in the above summaries.

On 25NOV2015 new Poly (I:C) has been started to used for manufacturing and starting 11MAY2016 only new Poly (I:C) was used. Between 25NOV2015 and 11MAY2016 about 9 patients have manufactured DCVAC/PCa using the new Poly (I:C), list of those patients will be provided by manufacturing to statistician after unblinding and presented in footnote of corresponding tables. Subgroup analysis of AEs before vs. after this change will be performed using only patients who received at least one dose of IMP. The following tables will be provided for this subgroup analysis:

- Summary table as defined above
- All AEs per SOC and PT
- All SAEs per SOC and PT
- AEs with grade > 2 related to DCVAC/PCa or placebo

The tables will have 4 columns presenting the frequencies: DCVAC/PCa arm and Control arm before Poly (I:C) change, DCVAC/PCa arm and Control arm after Poly (I:C) change.

A summary of all deaths will also be provided. The number of deaths, number and percentage of patients with each immediate cause of death (including summary by system organ class and preferred term) and number and percentage of patients with each underlying cause of death (including summary by system organ class and preferred term) will be presented.

AEs coded using MedDRA version 22.1.

4.8.2 Laboratory Findings

Only Central laboratory data will be summarized. The local laboratory data will be listed without any derivation.
Laboratory values will be graded according to the NCI CTCAE 4.03. CTCAE grades will be shown in the laboratory listings. The following parameters will be graded: Activated Partial Thromboplastin Time, Hemoglobin, Leukocytes, Lymphocytes, Neutrophils, Platelets, Alanine Aminotransferase, Albumin, Alkaline Phosphatase, Aspartate Aminotransferase, Bilirubin, Calcium, Creatinine, Glucose, Potassium, Sodium and Urate.

PSA and testosterone samples as well as virology information will also be listed.

The actual laboratory values and changes from baseline for hematology and biochemistry will be summarized for the Safety Population by visit and by treatment group.

The following summaries will include only parameters where CTC grades can be calculated. Some parameters will be included for both high and low grades separately. Low grades will be classed as NA (<LLN)for the corresponding high summary. Similarly, high grades will be classed as NA (>ULN) for the corresponding low summary.

- The number and percentage of patients with each CTC grade (worst case by patient) will be presented for each parameter.
- The number and percentage of patients with at least one grade 1 to 4 result will be presented for each parameter.
- The number and percentage of patients with at least one grade 3 to 4 result will be presented for each parameter.
- The number and percentage of patients with a change from minimum to maximum CTC grade of 1 to 4 will be presented for each parameter.
- The number and percentage of patients with a change from minimum to maximum CTC grade of 3 to 4 will be presented for each parameter.

Shift tables of CTC grades (Low/High) for hematology and biochemistry will be summarized, for the Safety population for:

- Each Study Cycle (baseline versus Study Cycle toxicity grade) and
- Worst Toxicity Grade (baseline versus worst toxicity grade across all visits).

If a patient has multiple test results for a particular test at a particular time point only the scheduled time point will be used. Repeat and unscheduled measurements will not be summarized; however, they will be in the data listings.

All results outside predefined normal ranges will be flagged in the data listings.

Mean values and changes from baseline and associated 95% CI by treatment group will also be plotted over time.

Hematology:

Hematology will be collected every 3 weeks (or Day 1 (-3 days) of each chemotherapy cycle) during the CTP 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. Laboratory changes which are clinically relevant (e.g. interruption or delay of study treatment, lead to clinical symptoms, or require therapeutic intervention) will be reported if they meet the criteria for an AE and will be recorded in the Adverse Events eCRF.

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

Biochemistry:

Biochemistry will be collected every 3 weeks (or Day 1 (-3 days) of each chemotherapy cycle) during the CTP 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.

Thyroid stimulating hormone (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. Laboratory changes which are clinically relevant (e.g. interruption or delay of study treatment, lead to clinical symptoms, or require therapeutic intervention) will be reported if they meet the criteria for an AE and will be recorded in the Adverse Events eCRF.

Biochemistry includes sodium (Na^+), potassium (K^+), chloride (Cl^-), calcium (Ca^{2+}), glucose, aspartate aminotransferase (AST), alanine aminotransferase (ALT), ALP, LDH, bilirubin, creatinine, uric acid, C-reactive protein (CRP), total protein, and albumin.

In case of LLOQ, the value will be replaced by LLOQ/2 for SAS programming .

In case of HLOQ, the value will be replaced by HLOQ+HLOQ/2 for SAS programming.

Identified LLOQ	
Syphilis IgM index (CSYPHMI)	0.9 index
Testosterone (GTESTO)	0.4 nmol/L
Total PSA (GTPSA)	0.074 ug/L
TSH (GTSH)	0.046 mIU/L
ALT (SGPT) (TALT)	4 IU/L
Glucose, Serum (TGLS)	1.1 mmol/L
TSTRON	0.3 nmol/L
TSTRON2	0.3 nmol/L
Total Bilirubine (TTBL)	2 umol/L
CRP (TTCRP)	0.7 mg/L

	Identified HLOQ
PT (GPT)	120.0 sec
PTT (GPTT)	180.0 sec
Total PSA (GTPSA)	5000.000 ug/L
Red Blood Cells (RBC)	7.50 10^12/L
Alkaline Phosphatase (TALP)	3000 IU/L
LDH (TLDH)	2000 IU/L
Uric Acid (TUA)	1249 umol/L

Urine:

Urinalysis including dipstick analysis (pH, protein, glucose, ketones, bilirubin, blood, leucocyte esterase) will be collected every 6 weeks (+/-7 days) during the CTP and every 12 weeks (-14/+7 days) in MBP.

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. Results of these exams will be listed. Laboratory changes which are clinically relevant (e.g. interruption or delay of study treatment, lead to clinical symptoms, or require therapeutic intervention) will be recorded in the Adverse Events eCRF.

Coagulation:

Coagulation parameters [i.e., activated partial thromboplastin time (aPTT) and Quick] will be collected at screening. Coagulation parameters will be presented in a data listing.

4.8.3 Vital Signs

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

Percentage change from baseline is defined as (final visit – baseline)/baseline.

Vital signs assessments includes Body Temperature (degrees C), Systolic Blood Pressure (mmHg), Diastolic Blood Pressure (mmHg), Heart Rate (bpm), and Respiratory Rate (breaths per minute).

All vital signs will be presented in a data listing.

Mean values and changes from baseline and associated 95% CI by each treatment group will also be plotted over time.

4.8.4 Physical Exam, Weight, and 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 injection 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 CTP and at each DCVAC/PCa or placebo administration visit in the MBP and at the End of Treatment Visit.

All physical examination will be presented in a data listing, Body Weight will be tabulated per visit, and as change and percentage change from baseline to final visit.

4.8.5 Performance Status

Results for ECOG will be summarized by treatment and visit.

Shift table for change from baseline will be also computed.

4.9 Adjustment for Covariates

As patients are randomized, stratified by region, prior therapy and ECOG Score at baseline, all statistical analyses, resulting in p-values or confidence intervals, will be stratified as well:

- Region will be 1 if the patient is in the US, and 0 otherwise;
- Prior therapy will consist of 2 dummy variables:
    - Therapy1 is 1 if the prior therapy is abiraterone, and 0 otherwise
    - Therapy2 is 1 if the prior therapy is enzalutamide, and 0 otherwise
- ECOG can be 0,1 or 2, as per eCRF.

Other prognostic factors are used for exploratory purposes, to adjust for a potential imbalance during randomization:

- PSA at baseline (values will be log transformed prior to inclusion, if any values = 0 then all values will have 1 added prior to transformation to allow all values to be included after transformation)
- LDH at baseline (> ULN vs. <= ULN)
- ALP at baseline (Alkaline phosphatase) (numerical in log scale)
- Albumin at baseline (numerical)
- Hemoglobin at baseline (numerical)
- Gleason score (numerical or 2-7 vs. 8-10)
- opioid use (yes/no) ATC code

  ATC3_NAME = OPIOIDS and ATC3_CODE = N02A in Concomitant Medication form from eCRF
- disease site at baseline (as defined in section 4.6.3).

4.9.1 Center Effects

This is a multicenter study, but patients from all centers will be pooled.

A sensibility analysis will explore the country effect (see section 4.6.3).

4.10 Protocol Violations and Protocol Deviations

Major protocol deviations affecting the efficacy analyses may include wrong inclusions, poor compliance and non-permitted concomitant medications. Exact definition of major and minor protocol deviations affecting efficacy is in the Analysis Set Specification v1.0 dated on 9DEC2019 including also minutes from blind data review meeting and decisions about exclusion of patients from analysis sets.. Patients to be excluded from the PP population are listed in file SP005_PP_Population_Exclusion_9Dec2019.xlsx which is attached to the Analysis Set Specification v1.0 dated on 9DEC2019. The information about reasons for exclusion from PP will be converted in SAS dataset.
A listing with Level 2 PD deviation collected on Manual PD log sorted by patients and a listing with programmable PD sorted by patients will be performed. For the protocol deviation PD008, only identified deviations in prohibited medications will be listed with footnote stating that listing was generated and deviations were identified by review of Sponsor as documented in Analysis Set Specification v1.0 dated on 9DEC2019.
Also a table will present count of PDs, count of patient with PD (and %). There will be two categories "Manual PD based on PD log" and "Programmable PD based on eCRF data" with the count for each sub-category.
Frequencies will be presented: for each category and sub-category, for PDs leading to exclusion from PP for each category and sub-category, for PDs leading to exclusion from PP in Total.

4.11 Missing Values

Partial or missing dates of AE onset are imputed as stated in section 4.9.1.

The FACT-P scores can show "NOT DONE" or having a missing score, which are treated both as missing. When there are missing data, if at least 50% of the items are answered, the subscales (Functional Well-Being, Emotional Well-Being, Social/Family Well-Being, Prostate Cancer Subscale) are calculated as [Sum of item scores] x [N of items in subscale] ÷ [N of items answered], and are set to missing when the response rate is less than 50%. The total score is then calculated as the sum of the unweighted subscale scores if the response rate is greater than 80% and missing otherwise.

No other imputations are done.

4.12 Deviations from SAP

Any deviations from the original statistical plan will be described and justified in the final CSR, whether written post interim or final analysis.

4.13 Changes in Conduct or Planned Analyses from the Protocol

According to protocol section 10.3.2.1 "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 of study treatment will be summarized."
In programmable identification of TEAE criterion worsens in frequency will be omitted as cannot be compared with baseline status.

Further, all recorded AEs from the first dose of study treatment will be summarized regardless end of AE reporting period.

As detailed in section *10.1 Analysis populations* of the study protocol, leukapheresis and manufacturing failures are included in the ITT population and will be censored on Day 1 (i.e., day of randomization) in the primary OS analysis. Protocol section *10.2.2 Statistical hypothesis, model and method of analysis* states that separate summary of survival data will be provided for patients with leukapheresis or manufacturing failure. A sensitivity analysis including the survival data of patients with leukapheresis or manufacturing failure (and not censored on Day 1) will be performed to show robustness of the primary analysis. Such sensitivity analysis is more conservative and could potentially show a lower treatment effect. It will be conducted with an intention to show that the results of the primary analysis are robust and their interpretability is not jeopardized.
This way of analysis was not endorsed by FDA according to FDA Type B Preliminary Meeting Responses dated 18th October 2019 (FDA Reference: CRMTS # 12042, file 15255.85.87_20191018_Preliminary Responses.pdf). FDA requests that those subjects who have not received the investigational product (DCVAC/PCa) or placebo treatment due to leukapheresis or manufacturing failure should be followed until event occurrence or discontinuation / drop-out and the actual time to observed event occurrence or discontinuation / drop-out should be included in the primary analysis of OS. FDA states that the originally proposed primary analysis can be performed as a sensitivity analysis.

4.14 Algorithms/SAS Codes

- **Tables that need descriptive statistics – continuous variables:**

PROC UNIVARIATE DATA=dset NOPRINT;
VAR var1 var2 var3 …varn;
BY byvar; (optional)
OUTPUT OUT=outname
N=n MEAN=mean MIN=min MAX=max MEDIAN=median STD=std;
RUN;

- **Tables that need frequency counts:**

PROC FREQ DATA=dset NOPRINT;
BY byvar; (optional)
*TABLES var1*var2;*
OUTPUT OUT=outname;
RUN;

- **Tables that need Adjusted Log-Rank test:**

PROC LIFETEST data=dataset alpha=.05 outsurv=estim reduceout;
*TIME time*event(0);*
STRATA region prior1 prior2 ECOG / group = treatment;
RUN;

- **Kaplan-Meier curves for treatment:**

PROC LIFETEST data=dataset plots=survival(strata=individual);
*TIME time*event(0);*
STRATA treatment;
RUN;

- **Tables that need Cox Proportional Hazards models:**

PROC PHREG data=dataset;

CLASS treatment region prior1 prior2 ECOG;

*MODEL time*event(0) = treatment / ties=exact;*
STRATA region prior1 prior2 ECOG / group = treatment;

CONTRAST 'a vs b' treatment 1 / estimate=exp;

RUN;

Testing PH assumptions:

PROC PHREG data=dataset;

CLASS treatment region prior1 prior2 ECOG;

*MODEL time*event(0) = treatment / ties=exact;*
STRATA region prior1 prior2 ECOG / group = treatment;

*Treatment_t = treatment*log(time);*

Proportionality_test: test treatment_t

RUN;

Model for time dependent covariate:PROC PHREG data=dataset;
CLASS treatment region prior1 prior2 ECOG;
*MODEL time*event(0) = treatment vartimedependant / ties=exact;*
STRATA region prior1 prior2 ECOG;
CONTRAST 'a vs b' treatment 1 / estimate=exp;
Vartimedependant=var(time>x)*

RUN;
Vartimedependant=var(time>x) will be defined after review the the results of model with interaction and HR curves*

- **Tables that need Logistic Regression:**
PROC GENMOD data = dataset;
CLASS treatment region prior1 prior2 ECOG;
MODEL response = treatment region prior1 prior2 ECOG / dist=bin link=log wald type3;

LSMEANS treatment region prior1 prior2 ECOG / diff exp cl;
RUN;

5 Tables and Listings

5.1 Table Format

All output will be produced using SAS version 9.2 or a later version.

In the top left portion of each table/listing, a *table/listing number* followed by the *title* of the table/listing will be presented. After the title line, optional *sub-title* or *population* information can be presented. Horizontal lines will appear before and after the column heading of the table/listing. *Footnotes* will be put under the main body of text at the bottom of the page.

The *sponsor name*, *protocol number,* programmers User ID, status of the table/listing (i.e. draft or final) and *SAS program name* will appear bottom left in a string and the *page number* will appear on the bottom right corner of each table/listing. The *date and time of creation* of table/listing will appear bottom left under the sponsor name. The source listing number will appear bottom left.

A *landscape layout* is proposed for both table and listing presentations.

The *left* and *right margins* of all tables and listings will be a minimum of 2.1 cm from the left and 1.9cm from the right. The *top and bottom margins* will be a minimum 2.92cm. *Header and footer* will be both 1.27 cm.

There is no special requirement of *font type* and *size*, but an *8-point* font size for tables and *7*or *8-point* for listings is proposed using *Courier New* font. A maximum SAS line size=141 and page size=44 for *8-point* font size, and line size=161 and page size=50 for *7-point* will be used so as to fit on both UK and US paper sizes.

In a listing, in the case that a patient's record has been continued to the next page, an appropriate identification (e.g., the patient ID number) must be presented at the beginning of that page.

A watermark saying 'SOTIO CONFIDENTIAL' will be placed on all outputs produced.

5.2 Conventions

Unless otherwise specified, in summary tables of continuous variables, the minimum and maximum values will be displayed to the same number of decimal places as the raw data, the mean and median will be presented to one extra decimal place compared to the raw data, and the standard deviation will be displayed to two extra decimal places compared to the raw data. Wherever possible data will be decimal aligned.

Unless otherwise specified frequency tabulations will be presented by number and percentage, where the percentage is presented in brackets to 1 decimal place.

The Kaplan-Meier estimates and associated 95% CI will be presented with one decimal place.

P-values, if applicable, will be presented to 3 decimal places. If a p-value is less than 0.05 but is greater than or equal to 0.01, then an asterisk (*) will be added next to this value. If a p-value is less than 0.01 but is greater than or equal to 0.001, then two asterisks (**) will be added next to this value. Finally, if the p-value is less than 0.001 then three asterisks (***) will be added next to this value and it will be presented as <0.001. If the rounded result is a value of 1.000, it will be displayed as >0.999. Any date information in the listing will use the *date9.* format, for example, 07MAY2002. In the listing, a unit associated with a variable will be presented only once within parentheses either below or next to that variable in the heading portion. If a parameter has multiple units, each unit will be displayed only once, as applicable.

All tables will have their source listing referenced in a footnote. Listings should be sorted by treatment group, patient and visit and have the raw data (export from eCRF and external data) and SDTM/ADaM source referenced in a footnote. All tables, listings and figures will be converted into Microsoft Word documents and collated into three complete documents.

5.3 Tables

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As stated in section 4 "In addition to outputs generated by visit as recorded in eCRF (CTP cycles, MBP cycles etc.) outputs reflecting more the real chronology in order to avoid mixing patients in MBP cycles who have different number of CPT cycles might be needed to be provided in addition."

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As stated in section 4 “In addition to outputs generated by visit as recorded in eCRF (CTP cycles, MBP cycles etc.) outputs reflecting more the real chronology in order to avoid mixing patients in MBP cycles who have different number of CPT cycles might be needed to be provided in addition.”

5.6 References

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Appendix A – Quality of Life Guidelines – FACT-P

Instructions:

1. Record answers in "item response" column. If missing, mark with an X
2. Perform reversals as indicated, and sum individual items to obtain a score.
3. Multiply the sum of the item scores by the number of items in the subscale, then divide by the number of items answered. This produces the subscale score.
4. Add subscale scores to derive total scores (TOI, FACT-G & FACT-P).
5. The higher the score, the better the QOL.

Subscale	Item Code	Reverse item?		Item response	Item Score
PHYSICAL WELL-BEING (PWB)	GP1	4	-	_____	=_____
	GP2	4	-	_____	=_____
	GP3	4	-	_____	=_____
	GP4	4	-	_____	=_____
Score range: 0-28	GP5	4	-	_____	=_____
	GP6	4	-	_____	=_____
	GP7	4	-	_____	=_____

Sum individual item scores: _____
Multiply by 7: _____
Divide by number of items answered: _____=**PWB subscale score**

SOCIAL/FAMILY WELL-BEING (SWB)	GS1	0	+	_____	=_____
	GS2	0	+	_____	=_____
	GS3	0	+	_____	=_____
	GS4	0	+	_____	=_____
Score range: 0-28	GS5	0	+	_____	=_____
	GS6	0	+	_____	=_____
	GS7	0	+	_____	=_____

Sum individual item scores: _____
Multiply by 7: _____
Divide by number of items answered: _____=**SWB subscale score**

EMOTIONAL WELL-BEING (EWB)	GE1	4	-	_____	=_____
	GE2	0	+	_____	=_____
	GE3	4	-	_____	=_____
	GE4	4	-	_____	=_____
Score range: 0-24	GE5	4	-	_____	=_____
	GE6	4	-	_____	=_____

Sum individual item scores: _____
Multiply by 6: _____
Divide by number of items answered: _____=**EWB subscale score**

FUNCTIONAL WELL-BEING (FWB)	GF1	0	+	_____	=_____
	GF2	0	+	_____	=_____
	GF3	0	+	_____	=_____
	GF4	0	+	_____	=_____
Score range: 0-28	GF5	0	+	_____	=_____
	GF6	0	+	_____	=_____
	GF7	0	+	_____	=_____

Sum individual item scores: _____
Multiply by 7: _____
Divide by number of items answered: _____=**FWB subscale score**

Subscale	**Item Code**	**Reverse item?**		**Item response**	**Item Score**
PROSTATE	C2	4	-	_____	=_____
CANCER	C6	0	+	_____	=_____
SUBSCALE	P1	4	-	_____	=_____
(PCS)	P2	4	-	_____	=_____
	P3	4	-	_____	=_____
Score range: 0-48	P4	0	+	_____	=_____
	P5	0	+	_____	=_____
	P6	4	-	_____	=_____
	P7	4	-	_____	=_____
	BL2	4	-	_____	=_____
	P8	4	-	_____	=_____
	BL5	0	+	_____	=_____

Sum individual item scores: _____
Multiply by 12: _____
Divide by number of items answered: _____=**PC Subscale score**

To derive a FACT-P Trial Outcome Index (TOI):
Score range: 0-104

_____ + _____ + _____ =_____=**FACT-P TOI**
(**PWB** score) (**FWB** score) (**PCS** score)

To Derive a FACT-G total score:
Score range: 0-108

_____ + _____ + _____ + _____=_____=**FACT-G Total score**
(**PWB** score) (**SWB** score) (**EWB** score) (**FWB** score)

To Derive a FACT-P total score:
Score range: 0-156

_____ + _____ + _____ + _____ + _____ =_____=**FACT-P Total score**
(**PWB** score) (**SWB** score) (**EWB** score) (**FWB** score) (**PCS** score)

Appendix B – Quality of Life Guidelines – EQ-5D

MOBILITY		**Score**
I have no problems in walking about	·	1
I have slight problems in walking about	·	2
I have moderate problems in walking about	·	3
I have severe problems in walking about	·	4
I am unable to walk about	·	5

SELF-CARE		
I have no problems washing or dressing myself	·	1
I have slight problems washing or dressing myself	·	2
I have moderate problems washing or dressing myself	·	3
I have severe problems washing or dressing myself	·	4
I am unable to wash or dress myself	·	5

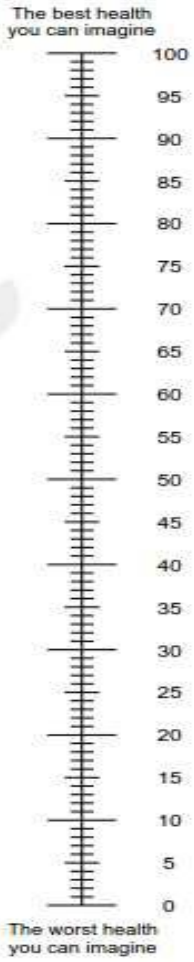
USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*		
I have no problems doing my usual activities	·	1
I have slight problems doing my usual activities	·	2
I have moderate problems doing my usual activities	·	3
I have severe problems doing my usual activities	·	4
I am unable to do my usual activities	·	5

PAIN / DISCOMFORT		
I have no pain or discomfort	·	1
I have slight pain or discomfort	·	2
I have moderate pain or discomfort	·	3
I have severe pain or discomfort	·	4
I have extreme pain or discomfort	·	5

ANXIETY / DEPRESSION		
I am not anxious or depressed	·	1
I am slightly anxious or depressed	·	2
I am moderately anxious or depressed	·	3
I am severely anxious or depressed	·	4
I am extremely anxious or depressed	·	5

- 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 = ☐



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Appendix C: EQ-5D-5L algorithm

Based on manuscript "Valuing health related quality of life. An EQ-5D-5L value set for England"; Nancy J. Devlin | Koonal K. Shah1 | Yan Feng | Brendan Mulhern | Ben van Hout, Wiley, 23Jun2017

The EQ-5D-5L descriptive system comprises the following 5 dimensions: mobility, self-care, usual activities, pain / discomfort and anxiety / depression. Each dimension has 5 levels: no problems, slight problems, moderate problems, severe problems, extreme problems. A unique health state is defined by combining 1 level from each of the 5 dimensions. Each state is referred to in terms of a 5-digit code. No health state value will be calculated if any of the dimensions is missing.
The EQ-5D-5L value set has a higher value for the worst possible health state and substantially fewer worse than dead values. The decrement from the best (11111) to next best health state is smaller in the EQ-5D-5L value set than in the other value sets, as might be expected given differences in number of levels and labelling between the instruments (e.g., 11211 describes "slight" problems performing usual activities in the five-level instrument and "some" problems in the three-level version). Pain/discomfort has the largest overall decrement (defined as the change from Levels 1 to 5), whereas usual activities has the smallest.

Table 2 simplifies the presentation of the value set by reporting the coefficients for dimensions/levels after the application of the latent class coefficients. The minimum value is −0.285 (for the worst health state, 55555) with 5.1% of the 3,125 health states described by the EQ-5D-5L being valued as worse than dead. The size of the coefficients in Table 2 reflects the relative weight placed on different sorts of health problems by our sample.
For example, at the worst,

TABLE 2 An EQ-5D-5L value set for England

	Central estimate	Value for health state 23245
Constant	1.000	1.000
Mobility		
Slight	0.058	0.058
Moderate	0.076	
Severe	0.207	
Unable	0.274	
Self-care		
Slight	0.050	
Moderate	0.080	0.080
Severe	0.164	
Unable	0.203	
Usual activities		
Slight	0.050	0.050
Moderate	0.063	
Severe	0.162	
Unable	0.184	
Pain/discomfort		
Slight	0.063	
Moderate	0.084	
Severe	0.276	0.276
Extreme	0.335	
Anxiety/depression		
Slight	0.078	
Moderate	0.104	
Severe	0.285	
Extreme	0.289	0.289
The value for health state 23245	1 − (0.058 + 0.080 + 0.050 + 0.276 + 0.289)	= 0.247

Appendix D: PSA correlation

EP Evaluator®

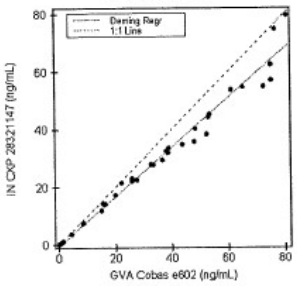
PSA

Covance CLS – Covance, INC

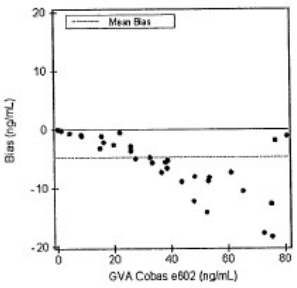
Alternate (Quantitative) Method Comparison

X Method: GVA Cobas e602 **Y Method: IN CXP 28321147**

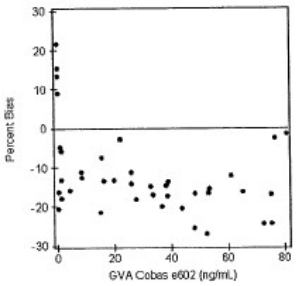
Scatter Plot



Bias



Percent Bias



Regression Analysis

	Deming	Regular
Slope:	0.857 (0.816 to 0.897)	0.849 (0.809 to 0.890)
Intercept:	-0.3890 (-2.0059 to 1.2279)	-0.1602 (-1.7741 to 1.4537)
Std Err Est:	3.2607	3.2547

95% Confidence Intervals are shown in parentheses

Supporting Statistics

Corr Coef (R):	0.9897	SubRange Bounds:	None
Bias:	-4.7624 (-16.9189 %)	Points (Plotted/Total):	40/40
X Mean ± SD:	30.5300 ± 26.1316	Outliers:	Not Tested
Y Mean ± SD:	25.7675 ± 22.4237	Scatter Plot Bounds:	None
Std Dev Diffs:	5.0832		

Experiment Description

	X Method	Y Method
[redacted]	[redacted]	[redacted]
Rep SD:	1	1
Result Ranges:	0.074 to 80.820	0.090 to 79.650
Units:	ng/mL	ng/mL
Reagent	--	--
Calibrators	--	--
Analyst:	GVA	IND
Comment:		

Accepted by: M FLORENT Signature

20 Avril 2018 Date

EP Evaluator 9.4.0.457

INDY IMMUNOLOGY: Centaur/IN-IMM-Centaur Printed: 19 Apr 2018 09:54:47 Page 1

Appendix E: Prohibited Medication


CDG_B3C3_Septem
ber1_2019_Corticost


SDG_B3C3_Septem
ber1_2019_Angioter


SDG_B3C3_Septem
ber1_2019_Anti And


SDG_B3C3_Septem
ber1_2019_Corticost


SDG_B3C3_Septem
ber1_2019_Interfero


SDG_B3C3_Septem
ber1_2019_Interleuk


SDG_B3C3_Septem
ber1_2019_Monoclo


SDG_B3C3_Septem
ber1_2019_Other im


SDG_B3C3_Septem
ber1_2019_Selective


SDG_B3C3_Septem
ber1_2019_Therapeu

SDG_B3C3_Septem
ber1_2019_GnRH an

In SP005_ANALYSIS SET SPECIFICATION_V1_final_9Dec2019.docx are excel files attached above referred as file Medications_20Nov2019_UPDATED LIST.zip

In addition to excel files above, L02BX ATC code of medications (GNRH antagonist) for medications ORTERONEL, SEVITERONEL, ABIRATERONE ACETATE which belongs to group of prohibited medications.

Appendix F: Leukapheresis and Manufacturing failures Population

Screening ID from last screening	Intent-To-Treat Population Flag	Intent-To-Treat Non US Population Flag	Leukapheresis Population	Leuk. or manuf. failure Population Flag	Safety Population Flag	Per-Protocol Population Flag
C030B017	Y	Y	Y	Y	Y	N
C031B010	Y	Y		Y	N	N
C037B003	Y	Y		Y	N	N
C037B004	Y	Y	Y	Y	Y	N
C037B009	Y	Y	Y	Y	Y	N
C037B012	Y	Y		Y	N	N
C040B014	Y	Y		Y	N	N
C060B001	Y	Y	Y	Y	Y	N
C060B002	Y	Y	Y	Y	Y	N
C062B005	Y	Y	Y	Y	Y	N
C062B006	Y	Y	Y	Y	Y	N
C065B009	Y	Y	Y	Y	Y	N
C065B012	Y	Y	Y	Y	Y	N
C071B005	Y	Y	Y	Y	Y	N
C091B002	Y	Y	Y	Y	Y	N
C091B003	Y	Y	Y	Y	Y	N
C095B007	Y	Y	Y	Y	Y	N
C095B011	Y	Y	Y	Y	Y	N
C095B012	Y	Y	Y	Y	Y	N
C099B004	Y	Y	Y	Y	Y	N
C099B007	Y	Y	Y	Y	Y	N

C128B001	Y	Y		Y	N	N
C129B004	Y	Y		Y	N	N
C129B006	Y	Y	Y	Y	N	N
C129B007	Y	Y		Y	Y	N
C129B012	Y	Y	Y	Y	Y	N
C141B005	Y	Y	Y	Y	Y	N
C142B007	Y	Y	Y	Y	Y	N
C142B015	Y	Y	Y	Y	Y	N
C142B024	Y	Y	Y	Y	Y	N
C165B001	Y	Y	Y	Y	Y	N
C169B013	Y	Y	Y	Y	Y	N
C170B003	Y	Y	Y	Y	Y	N
C170B005	Y	Y	Y	Y	Y	N
C174B003	Y	Y	Y	Y	N	N
C177B001	Y	Y	Y	Y	Y	N
C180B012	Y	Y	Y	Y	Y	N
C180B015	Y	Y	Y	Y	Y	N
C183B017	Y	Y	Y	Y	Y	N
C183B018	Y	Y	Y	Y	Y	N
C183B030	Y	Y	Y	Y	Y	N
C185B006	Y	Y		Y	Y	N
C185B011	Y	Y	Y	Y	Y	N
C197B003	Y	Y	Y	Y	Y	N
C197B004	Y	Y	Y	Y	Y	N
C199B012	Y	Y	Y	Y	Y	N
C202B002	Y	Y	Y	Y	Y	N
C205B010	Y	Y		Y	N	N

C211B005	Y	Y	Y	Y	Y	N
C214B009	Y	Y		Y	Y	N
C214B010	Y	Y		Y	N	N
C214B016	Y	Y		Y	Y	N
C217B001	Y	Y		Y	N	N
C217B013	Y	Y		Y	N	N
C217B023	Y	Y		Y	N	N
C217B025	Y	Y	Y	Y	Y	N
C248B008	Y	Y	Y	Y	Y	N
C254B002	Y	Y	Y	Y	Y	N
C259B005	Y	Y	Y	Y	Y	N
C275B005	Y	Y	Y	Y	Y	N
C276B002	Y	Y	Y	Y	Y	N
C276B008	Y	Y		Y	N	N
C284B001	Y	Y	Y	Y	Y	N
C285B004	Y	Y	Y	Y	N	N
C285B009	Y	Y	Y	Y	N	N
C303B003	Y	Y	Y	Y	Y	N
C303B025	Y	Y	Y	Y	Y	N
C311B009	Y	Y	Y	Y	Y	N
C314B002	Y	Y	Y	Y	Y	N
C314B014	Y	Y	Y	Y	Y	N
C314B016	Y	Y	Y	Y	Y	N
C314B018	Y	Y	Y	Y	Y	N
C314B028	Y	Y	Y	Y	Y	N
C314B033	Y	Y	Y	Y	Y	N
C314B040	Y	Y	Y	Y	Y	N
C319B013	Y	Y	Y	Y	Y	N

C319B019	Y	Y	Y	Y	Y	N
C319B023	Y	Y		Y	Y	N
C323B017	Y	Y	Y	Y	Y	N
C332B001	Y	Y	Y	Y	Y	N
C332B013	Y	Y		Y	N	N
C332B017	Y	Y	Y	Y	Y	N
C332B018	Y	Y	Y	Y	Y	N
C334B002	Y	Y	Y	Y	Y	N
C390B003	Y	Y	Y	Y	Y	N
C390B008	Y	Y	Y	Y	Y	N
C390B010	Y	Y		Y	Y	N
C395B001	Y	Y	Y	Y	N	N
C407B005	Y	Y	Y	Y	Y	N
C409B002	Y	Y	Y	Y	Y	N
C409B004	Y	Y	Y	Y	Y	N
C417B001	Y	Y	Y	Y	Y	N
C429B001	Y	Y	Y	Y	Y	N
C451B005	Y	Y	Y	Y	Y	N
C451B009	Y	Y	Y	Y	Y	N
C451B511	Y	Y	Y	Y	Y	N
C455B007	Y	Y	Y	Y	Y	N
C457B009	Y	Y	Y	Y	N	N
C459B002	Y	Y		Y	N	N
C459B005	Y	Y	Y	Y	Y	N
C459B008	Y	Y	Y	Y	Y	N
C463B003	Y	Y	Y	Y	Y	N
C468B007	Y	Y	Y	Y	Y	N
C470B001	Y	Y	Y	Y	Y	N
C470B002	Y	Y	Y	Y	Y	N

C485B005	Y	Y	Y	Y	Y	N
C485B007	Y	Y	Y	Y	Y	N
C485B010	Y	Y	Y	Y	Y	N
C485B012	Y	Y	Y	Y	Y	N
C485B018	Y	Y	Y	Y	Y	N
C485B019	Y	Y	Y	Y	Y	N
C541B006	Y	Y	Y	Y	Y	N
C542B004	Y	Y	Y	Y	Y	N
C601B003	Y	N	Y	Y	Y	N
C605B008	Y	N	Y	Y	N	N
C610B013	Y	N	Y	Y	Y	N
C613B002	Y	N	Y	Y	Y	N
C616B001	Y	N	Y	Y	Y	N
C634B005	Y	N	Y	Y	Y	N
C646B005	Y	N	Y	Y	Y	N
C646B015	Y	N	Y	Y	Y	N
C646B018	Y	N	Y	Y	Y	N
C646B019	Y	N		Y	Y	N
C657B001	Y	N	Y	Y	Y	N
C676B007	Y	N	Y	Y	N	N
C676B014	Y	N	Y	Y	Y	N
C677B002	Y	N	Y	Y	Y	N
C677B006	Y	N	Y	Y	Y	N
C677B008	Y	N	Y	Y	Y	N
C677B011	Y	N	Y	Y	N	N
C680B013	Y	N	Y	Y	Y	N
C683B001	Y	N	Y	Y	Y	N

C690B006	Y	N	Y	Y	Y	N
C690B011	Y	N	Y	Y	Y	N
C692B004	Y	N	Y	Y	Y	N
C694B007	Y	N	Y	Y	N	N
C694B012	Y	N	Y	Y	Y	N
C852B002	Y	Y	Y	Y	Y	N
C853B002	Y	Y		Y	N	N
C859B001	Y	Y	Y	Y	Y	N
C859B005	Y	Y	Y	Y	Y	N
C963B003	Y	Y	Y	Y	Y	N
C980B006	Y	Y	Y	Y	Y	N
C980B015	Y	Y	Y	Y	Y	N
C981B003	Y	Y	Y	Y	Y	N
C981B010	Y	Y	Y	Y	Y	N
C981B021	Y	Y	Y	Y	Y	N