STATISTICAL ANALYSIS PLAN (SAP)

Phase IIa Dose Escalation Trial of NanoPac Focal Therapy for Prostate Cancer in Subjects Undergoing Radical Prostatectomy

Protocol Number:	NANOPAC-2016-02	**Study Phase**	IIa
Trial Design:	Open-label, Single Dose, 3+3 Dose Escalation Study with both Dose-Escalation and Dose Confirmation Phases		
Medication/dosage:	Nanopac (Sterile Nanoparticulate Paclitaxel) at concentrations of 6, 10, 15 mg/mL in an injection volume of up to 20% of the lobe of the prostate containing the dominant lesion		
Population	Subjects with prostate cancer scheduled for radical prostatectomy		
Study/Treatment duration:	Study duration will be up to 12 months. For each subject, the participation duration is approximately 9 weeks. Additional follow-up may occur.		

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Version: final

Date: 13-Nov-2018

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Date of Final Protocol (including all amendments) 08-Aug-2017

Date of Final Plan: 13-Nov-2018

I have reviewed the Statistical Analysis Plan. My signature below confirms my agreement with the contents and intent of this document.

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LIST OF ABBREVIATIONS AND TERMS

Abbreviations

Abbreviation	Definition
AE	Adverse Event
APR	Analysis Programming Requirements - detailed programming specifications required to convert the EDC data into analysis/presentation data sets.
ATC	Anatomical Therapeutic Chemical Classification System
BMI	Body Mass Index
CI	Confidence Interval
CRF	Case Report Form
CRO	Contract Research Organization
DLC	Data Logic Check- A combination of programmed and visual checks based on the CRF, protocol, and sponsor input, designed to identify incomplete or illogical data.
DMP	Data Management Plan - details of how data are managed throughout the trial
DSMB	Data Safety Monitoring Board
ECOG	Eastern Cooperative Oncology Group
EDC	Electronic Data Capture
I-PSS	International Prostate Symptom Score
LLOQ	Lower Limit of Quantitation
MedDRA	Medical Dictionary for Regulatory Activities (coding for AEs)
mpMRI	Multiparametric MRI
NIH	National Institutes of Health

Abbreviation	Definition
PI-RADS	Prostate Imaging Reporting And Data System
PK	Pharmacokinetics
PSA	Prostate-Specific Antigen
PT	Preferred Term (from MedDRA coding dictionary)
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SDLC	Systems Development Lifecycle
SHIM	Sexual Health Inventory for Men Questionnaire
SOC	System Organ Class (from MedDRA coding dictionary)
SOP	Standard Operating Procedure
TEAE	Treatment Emergent Adverse Event
WHODD	World Health Organization Drug Dictionary

Definition of Terms

Term	Definition
McDougall	McDougall Scientific Ltd - CRO contracted to perform the data management, statistical programming and analysis functions
NanoPac	Sterile Nanoparticulate Paclitaxel. The investigatational product.

1 BACKGROUND

This Phase IIa trial will be open-label and dose rising, with an expanded cohort at the dose of NanoPac determined to have the best tolerability and safety profile. Subjects with prostate cancer scheduled for prostatectomy will have NanoPac injected under image guidance directly into the lobe of the prostate with the dominant lesion four weeks prior to prostatectomy. The study will include a dose escalation phase and a dose confirmation phase.

In the dose escalation phase, NanoPac concentrations of 6, 10, and 15 mg/mL in an injection volume of up to 20% of the lobe of the prostate containing the dominant lesion will be studied in cohorts of three, with cohorts enrolled sequentially starting at the lowest concentration. Following Data Safety Monitoring Board (DSMB) review of the cohort data the next cohort may begin enrolling, an additional three at the current dose may be enrolled, or if the first dose does not provide adequate safety and tolerability the study may be halted. The dose determined to be the most suitable for further evaluation will be defined as the highest dose with an acceptable safety and tolerability profile as determined by the DSMB.

After the most suitable dose is found, additional subjects will be enrolled to provide a cohort of 12 subjects at that dose level.

2 OBJECTIVES

2.1 Primary Objective

The primary objective of this study is to evaluate the safety and tolerability of NanoPac injected directly into the lobe of the prostate containing the dominant lesion in patients diagnosed with prostate cancer.

2.2 Secondary Objectives

The secondary objectives are to describe the pharmacokinetics (PK) of NanoPac injected directly into the lobe of the prostate containing the dominant lesion; and to determine the effect of NanoPac on the tumor within the prostate, the ipsilateral lobe of the prostate, the contralateral lobe of the prostate, and pelvic lymph nodes.

3 STUDY DESIGN AND ENDPOINTS

3.1 Study Design

This is a Phase IIa, open-label, dose-escalation trial with two phases: an initial dose-finding phase following a design similar to traditional 3+3 designs, and a dose confirmation phase with 12 subjects enrolled at the most suitable dose determined in the dose-finding phase.

Dose-finding phase: Patients with prostate cancer undergoing radical prostatectomy will be enrolled in groups of 3 to dose-escalated cohorts of NanoPac at concentrations of 6, 10, 15 mg/mL in an injection volume of up to 20% of the lobe of the prostate containing the dominant lesion. Cohorts will be enrolled sequentially starting at the lowest concentration. Each cohort will have a planned minimum of three subjects. Data from the first three subjects in a cohort will be reviewed and evaluated by the DSMB. The outcome will be to determine whether to a) escalate to the next dose; b) add three additional subjects to the current dose; or c) expand the previous dose by three subjects.

Dose confirmation phase: Once the dose deemed appropriate for expansion and further evaluation has been determined, subjects will be enrolled to that dose to provide a total of 12 subjects dosed at that level. If two doses are similar, subjects will be enrolled to each of the doses; however, the total number of subjects treated will remain 12.

3.2 Primary Endpoint

The primary endpoint will be safety and tolerability, as demonstrated by adverse events (AE), changes in laboratory assessments, physical examination findings, and vital signs.

3.3 Secondary Endpoints

The secondary endpoints will be:

- Concentration of paclitaxel in the systemic circulation post-injection and prior to prostatectomy;
- Presence of paclitaxel in the tumor within the prostate, the ipsilateral lobe of the prostate, the contralateral lobe of the prostate, and pelvic lymph nodes excised during prostatectomy;
- Tumor response (change in image volume on mpMRI; histologic evaluation via biopsy);

- Presence of tumor cells in the tumor within the prostate, the ipsilateral lobe of the prostate, the contralateral lobe of the prostate, and pelvic lymph nodes excised during prostatectomy.

3.4 Study Timeline and Schedule of Events

	Screening Clinic Visit	Day 1[13]	Injection-to-Surgery Interval[13]			Day 29[13] (Prostatectomy Surgery)		Hospital discharge
			Day 8	Day 15	Day 22	48-hour Window	Day of Surgery	
Informed Consent	X							
History[1]	X							
Concomitant therapy	X	X	X	X	X		X	X[9]
Physical Exam	X					X		
ECOG[5]	X					X		
Questionnaires[10]	X					X		
Vital Signs	X	X	X	X	X		X	X
Hematology	X			X			X	
Biochemistry	X			X			X	
Urinalysis	X			X			X	
PSA	X	X	X	X	X		X	
Rectal Swab[8]	X							
PK Samples		X[7]	X	X	X		X	
Radiologic Assessment[2]						X		
Antibiotics[8]		X						
Enema[12]		X						
Bladder Scan		X						
NanoPac[6]		X						
Ejaculate collection			X	X	X	X		
Biopsy[11]							X	
Prostatectomy[4]							X	
Adverse Events[3]		X	X	X	X		X	X[9]
End of Study								X

1 History includes all events before initiation of NanoPac treatment.

[2] Imaging assessment will utilize multiparametric MRI (mpMRI).

[3] Adverse event determination will start immediately following initiation of study treatment.

[4] Procedure will include ultrasound evaluation; following prostatectomy, excised prostate and pelvic lymph nodes will be evaluated to determine paclitaxel levels as well as the concentration of tumor cells.

[5] ECOG Performance Status Scale attached as Appendix A

[6] NanoPac will be administered by direct injection to the lobe of the prostate containing the dominant lesion with the aid of MR-TRUS and MRI

[7] PK Samples on Day 1 will be drawn at 1, 2, 4, and 6 hours post-dose. PK samples on Day 1 will allow for a 10-minute window around the samples.

[8] A rectal swab will be taken and cultured during screening to aid antibiotic prophylaxis. Subject will be provided ciprofloxacin 500 mg to take twice a day for three days (or another antibiotic regimen as determined by the treating physician's discretion if resistant organism found on rectal swab culture) after NanoPac injection.

[9] AE and concomitant medications at the 24-hour follow-up which are not considered due to the prostatectomy surgery will be followed; those considered due to the prostatectomy surgery (such as pain, nausea etc.) will not be captured nor followed

[10] Questionnaires include Sexual Health Inventory for Men (SHIM), International Prostate Symptom Score (I-PSS), and National Institutes of Health (NIH) Prostatitis Symptoms

[11] Biopsy will be performed immediately prior to prostatectomy under the same anesthesia.

[12] The evening prior to dosing or on the morning of dosing (12 hours prior to procedure) the subject will receive an enema to assist with the visualization when the imaging is performed.

[13] The day of NanoPac injection (Day 1) will be scheduled relative to prostatectomy, with NanoPac injection occurring four weeks (28 days) prior to the day planned for prostatectomy. However, a window of plus or minus 2 days (28 days prior to prostatectomy, plus or minus two days) is permitted for the Day 1/NanoPac injection visit. All subsequent study visits (Days 8, 15, and 22) will be scheduled relative to the day of NanoPac injection (NOT prostatectomy), with a window of plus or minus one day permitted. Because of the window around the day of injection, prostatectomy may actually fall anywhere between Day 27 and Day 31.

4 DATA MANAGEMENT

4.1 Data Collection and Database Construction

Most data will be collected at the sites via an electronic data capture (EDC) system. The study-specific application will be developed based on the protocol requirements and following the full Systems Development Lifecycle (SDLC). The development and management of the trial application, including security and account administration, will adhere to the Standard Operating Procedures (SOPs) at McDougall. All participants will be trained in the use of the application, and the training documented prior to each site being initiated.

The application design will, where appropriate, provide choice fields in the form of checkboxes, buttons and lists to aid in ensuring high quality standardized data collection. In addition Data Logic Checks (or data Edit Checks) will be built into the application based on variable attributes (e.g. value ranges), system logic (e.g. sequential visit dates) and variable logic (e.g. onset date must be before cessation date). Visual review and data responses will be overseen by a trained data manager.

The database will be locked when all the expected data has been entered into the application, all query responses have been received and validated, the designated data has been noted as monitored in the system and each investigator has signed off the casebook for each of their study subjects. The data coding must be accepted by the Sponsor and any Serious Adverse Events (SAEs) reconciled with the pharmacovigilance data base working with the Medical Monitor.

According to study design, following central lab data will not be entered into EDC system. They will be provided as external data:

- Concentration of paclitaxel in serum
- Presence of paclitaxel in prostate tissue
- Presence of paclitaxel in ejaculate

Sections 4.3 and 4.4 provide more details about these data.

The data management processes are outlined in the project specific Data Management Plan (DMP); this and all related documentation are on file at McDougall and are identified by the project code NA02NAE.

All programming will be performed in SAS version 9.4 or higher.

4.2 Coding

Adverse Events and medical history will be coded in MedDRA version 20.0 and signed off by US Biotest, Inc. All concomitant medications will be coded using WHO Drug Dictionary version March 1, 2017. All coding will be reviewed and signed off prior to data base lock.

4.3 Pharmacokinetics (PK) Data

The PK analysis of plasma paclitaxel concentration will be performed by Covance Madison Laboratories Bioanalytical (BA) Group. The concentration data will be provided to McDougall in Excel data sheets to be read into SAS system for descriptive summaries.

4.4 Presence of Paclitaxel in Ejaculate and Tumor Cells

The presence of paclitaxel in ejaculate will be assessed by Frontage Laboratories, Inc., and will be provided to McDougall in Excel spreadsheet for analysis.

The presence of paclitaxel in the tumor within the prostate, the ipsilateral lobe of the prostate, the contralateral lobe of the prostate, and pelvic lymph nodes excised during prostatectomy will be assessed by Frontage Laboratories, Inc. The results will be provided to McDougall in Excel data sheets to be read into SAS system for analysis.

5 CHANGE TO ANALYSIS AS OUTLINED IN THE PROTOCOL

Ejaculate are collected at Days 8, 15, 22, and within 48 hours before prostatectomy. According to section 10.4.3 of the Protocol, the ejaculate paclitaxel concentration data will be tabulated as mean values for each of the dose groups. In 2018, Sponsor confirmed that central lab (Frontage Laboratories, Inc.) will only check the presence (yes/no) of paclitaxel in ejaculate, and not provide the paclitaxel concentration. Therefore, only paclitaxel presence (yes/no) will be listed and tabulated as percentage by cohort.

According to the Protocol, besides the summaries of TEAEs for whole study period, the TEAEs also need to be summarized for different time frames. After considering the short study period between study treatment and prostatectomy, in October 2018, Sponsor waived the analyses of TEAE by time frames.

6 STATISTICAL METHODS

Descriptive summaries of continuous data will consist of the mean, standard deviation, median, minimum, and maximum. Categorical data will be summarized with frequencies and percentages. All data will be listed by subject and treatment. This study was not powered for inference, and so no inferential analyses will be included.

6.1 Sample Size

There is no formal sample size calculation for this Phase IIa dose escalation safety study. However, to provide a reference for the ongoing safety review of each cohort and the possible expansion of a cohort with safety concerns, nQuery Advisor (Version 6) employing the procedure "confidence interval for the probability of observing a rare event" determined that, for an event with an occurrence rate of 0.33, the probability of detecting it with 3 subjects is 69.9% vs 91.0% for 6 subjects, and for an event rate of 0.05 the probability of detecting the event was 14.3% and 26.5% for 3 and 6 subjects respectively. The rationale to expand the final cohort to 12 subjects, from either 3 or 6 subjects, was based on the "reasonable gain" in detection rate that each additional subject would provide in this early phase exploratory trial.

6.2 Missing Data

Data will be presented as observed. No imputation will be performed for missing data.

6.3 Calculated Outcomes

The following are key endpoints derived from data captured at the sites via the EDC system. Complete documentation of the calculations and data manipulation required to go from the CRF database to the analysis database are contained in the companion document - the study Analysis Programming Requirements (APR).

Endpoint	Calculation	Comment
Baseline value	Value reported prior to treatment injection	If multiple values collected prior to treatment initiation, non-missing value closest to the date/time of treatment injection is considered baseline
Change from Baseline	Value collected at time point (Visit) – Baseline value	
Time in Trial (days)	Study completion/withdrawal date – date of informed consent date + 1 day	

Treatment Emergent Adverse Event (TEAE)	= no if onset date/time AE is before the date/time of NanoPac injection = yes otherwise	According to conservative rule, all AEs that cannot be determined as started before NanoPac injection will be considered as TEAE
Age (years)	= Informed Consent Year – Birthdate Year, if consent date was on or after birthday, = Informed Consent Year – Birthdate Year – 1, if consent date was before birthday	
Total Score of I-PSS	= Sum of the scores of all questions, if all questions are answered, = Null, if at least one question is not answered	1-7: Mild 8-19: Moderate 20-35: Severe
Total Score of SHIM	= Sum of the scores of all questions, if all questions are answered, = Null, if at least one question is not answered	1-7: Severe ED 8-11: Moderate ED 12-16: Mild to Moderate ED 17-21: Mild ED

NIH Prostatitis Symptoms	Pain Score = sum of the scores of Q1 to Q4; Urinary Symptoms Score = sum of the scores of Q5 and Q6; Quality of Life Impact Score = sum of the scores of Q7 to Q9. If one question is not answered, the score of that question's domain is set to Null.	
Primary Lesion Volume (2 dimensions measured)	If the lesion had two dimensions measured: Set length = the longer dimension, width = the short dimension, and then Volume = $(\pi/6)*length*(width)^2$ If only one dimension was measured, lesion volume will be set to missing.	Only 2 dimensions of the primary lesion were measured. The ellipsoid formula is used to calculate the lesion volume after using width to impute height
Primary Lesion Volume (1 dimension only)	Volume = $(\pi/6)*(length)^3$ Where length is the longer (or only) dimension recorded in EDC	Only one dimension of the primary lesion is used for calculation. The other two dimensions are imputed for the calculation.

6.4 Analysis Population

All enrolled subjects who receive NanoPac injection will be the analysis population for all outcome analyses.

6.5 Interim Analysis/ Data Monitoring

No interim analysis is planned for this trial. The safety data (e.g., Adverse Events, dose limiting toxicities, vital signs, laboratory values, etc.) will be reviewed on an ongoing basis

throughout the study by the Data Safety Monitoring Board (DSMB), to evaluate the risk for the subjects and to make dosing recommendations.
The trial statistician will provide safety report to DSMB for each cohort of the dose-finding phase after the first 3 subjects of the cohort complete the study. If additional 3 subjects are enrolled to the same dose level, the safety report will be provided again for all 6 subjects of the cohort.

6.6 Analysis Methods

All calculations and analyses will be performed using SAS version 9.4 or higher under the Windows Server 2012R2 operating system at McDougall Scientific Ltd. in Toronto, Canada. Continuous data will be summarized via PROC MEANS - mean, standard deviation, median, range, and 95% CIs, while categorical data will be presented as counts and percentages (or proportions) via PROC FREQ for the descriptive displays.

All outcomes will be summarized by cohort, i.e., dose level, and visit, if applicable.

No statistical inference will be made for all outcomes.

7 RESULTS

All enrolled and treated subjects will be the analysis population for all analyses. All data collected in EDC will be at a minimum listed.

All summaries will be presented by cohort, i.e., NanoPac concentration level.

The eligibility data of screen failures will be provided in a separate listing.

7.1 Study Subjects

7.1.1 Patient Disposition

All enrolled and treated subjects will be accounted for. A summary of subjects by cohort and by study phase will be provided. All early discontinuations will be summarized by primary reason of discontinuation.

Time in trial will also be summarized.

7.1.2 Demographics and Baseline Characteristics

Demographic (age, sex, ethnicity, and race), baseline body measurements (height, weight, and calculated BMI), and vital signs (blood pressures, heart rate, and body temperature) will be summarized.

7.1.3 Medical History

Medical history will be coded in MedDRA and presented in a by-cohort table by System Organ Class (SOC) and Preferred Term (PT).

7.1.4 NanoPac Administration

NanoPac administration data at study Day 1, including injection date, time, dose level, calculated injection volume, and actual volume (in mL) and dose (in mg) injected, will be listed.

7.1.5 Prostatectomy

Prostatectomy information, including surgery date, time, number of tissue samples and lymph nodes taken/stored for checking paclitaxel levels, will be presented in data listing.

7.2 Primary Outcomes

The primary endpoint will be safety and tolerability, as demonstrated by adverse events (AE), changes in laboratory assessments, physical examination findings, and vital signs.

All primary outcomes will be descriptively summarized. No statistical inference will be made for primary endpoint.

7.2.1 Adverse Events

According to the Protocol, in this study, AE is limited to be events collected at all study visits from the time of NanoPac injection. Therefore, all AEs in the study are Treatment Emergent Adverse Events (TEAEs).

Summaries of AEs will be prepared by treatment group, and include:

- Brief summary of AEs - include the total number of AEs, serious AEs (SAEs), death, and AEs leading to early discontinuation
- AEs by MedDRA System Organ Class (SOC) and Preferred Term (PT)
- AEs by MedDRA SOC, PT, and relationship to NanoPac treatment.
- AEs by MedDRA SOC, PT, and severity.
- SAEs by MedDRA System Organ Class (SOC) and Preferred Term (PT)

All these summaries will include the counts and frequencies of events, and of subjects who had events.

All AEs will be listed by subject. Death and other SAEs will be listed separately.

7.2.2 Laboratory Assessments

Laboratory assessments, including raw assessments at each visit and change from baseline at post-baseline visits, will be summarized by visit and analyte.

Each non-missing lab result's normal/abnormal status (e.g. normal/low/high for quantitative results, and normal/abnormal for qualitative results) will be calculated based on the normal reference ranges provided by the lab. The status will be summarized using shift tables from baseline to each post- baseline time point.

All lab data will be presented in by-subject data listing. Separate listings will be provided for subjects with abnormal lab values which are judged by the investigator to be clinically significant.

Following lab tests are required for the study:

Chemistry: Sodium, potassium, chloride, carbon dioxide, calcium, phosphorus, glucose, blood urea nitrogen, creatinine, alkaline phosphatase, total bilirubin, direct bilirubin, aspartate aminotransferase, alanine aminotransferase, lactate dehydrogenase, total protein, albumin, triglycerides, cholesterol, uric acid and calculated creatinine clearance;

Hematology: Red blood cell count, hemoglobin, hematocrit, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, white blood cell count including differential, reticulocyte count, and platelet count;

Coagulation: Prothrombin time and activated partial thromboplastin time;

Urinalysis: Specific gravity, hydrogen ion concentration, RBC, WBC, protein, glucose, and microscopic analysis.

7.2.3 Physical Examination

All abnormal findings from the physical examination after study treatment will be recorded as AEs. The analysis of physical examination will be included in AE summaries. See section 7.2.1.

7.2.4 Vital Signs

Vital Signs (blood pressure, heart rate, temperature, body weight and height) will be summarized for each visit.

Vital Signs' change from baseline values, with the exception of height, will be summarized at all post-dose visits.

Unscheduled vital signs will only be presented in by-subject data listing.

7.2.5 Eastern Cooperative Oncology Group (ECOG)

ECOG scale will be summarized by visit.

7.3 Secondary Outcomes

7.3.1 Plasma Paclitaxel Concentration

PK samples for plasma paclitaxel concentration are collected on Day 1 at pre-injection, 1, 2, 4, and 6 hours post-injection, Day 8, Day 15, Day 22, and on Day 29 pre-surgery.

All numeric paclitaxel concentration data above the Lower Limit of Quantitation (LLOQ), i.e. the detectable limit, will be tabulated by cohort using the arithmetic mean, standard deviation, coefficient of variation, median, and range.

All paclitaxel concentration data (individual subjects and cohort mean) will be visually presented in spaghetti plots.

7.3.2 Ejaculate Paclitaxel Concentration

The presence (yes/no) of paclitaxel in the ejaculate paclitaxel concentration data is assessed at Days 8, 15, 22, and the pre-operative work-up visit. If applicable, the data will be tabulated.

7.3.3 Presence of Paclitaxel in the Prostate

The presence (yes/no) of paclitaxel in the tumor within the prostate, the ipsilateral lobe of the prostate, the contralateral lobe of the prostate, and pelvic lymph nodes excised during prostatectomy will be summarized by cohort.

7.3.4 Tumor Responses

Imaging with multiparametric MRI (mpMRI) is performed within 3 months prior to screening visit and within 48 hours prior to prostatectomy. The tumor image volume on mpMRI (data at two visits and change from screening) will be tabulated by cohort, using calculations based on 2-diemnsion formula and 1-dimension formula as described in section 6.3.

Other mpMRI assessments, i.e. prostate volume, PSA density, type of primary lesion, seminal vesicle Invasion, lymph vascular Invasion, extracapsular extension, and PI-RADS Score, will be summarized. The summaries for the change value of the continuous assessments are also presented. If applicable, the change of lesion type and PI-RADS score will be summarized in the shift tables.

The histological evaluation of the biopsies, taken prior to screening confirming adenocarcinoma and prior to prostatectomy, will be summarized and treated in the same manner as the mpMRI data.

7.3.5 Tumor Cells

The presence of tumor cells and, if tumor is present, the volume of tumor cells (i.e. Proportion Considered as Adenocarcinoma (%) from tumor assessment biopsy), in the tumor within the prostate, the ipsilateral lobe of the prostate, the contralateral lobe of the prostate, and pelvic lymph nodes excised during prostatectomy will be tabulated by cohort.

7.4 Safety Outcomes

All safety analyses will be presented as part of the primary endpoint analysis. See section 7.2.

7.5 Other Outcomes

7.5.1 PSA

Serum PSA is tested at screening, on Day 1 before NanoPac injection, Day 8, Day 15, Day 22 and Day 29. The PSA results of each visit and change from baseline at each post-baseline visit will be summarized by cohort.

PSA data at each visit will also be graphically presented by subject and by cohort.

7.5.2 Questionnaires

Questionnaires include Sexual Health Inventory for Men (SHIM), International Prostate Symptom Score (I-PSS), and National Institutes of Health (NIH) Prostatitis Symptoms. The questionnaire results are collected at screening and at three days before prostatectomy. The total/subtotal scores of each questionnaire (see section 6.3 for calculation), raw at visit and change from baseline, will be summarized by cohort. In addition, I-PSS questions #2 and #4 will also be summarized.

7.5.3 Concomitant Medications

A summary of all concomitant medications taken during the course of the study will be presented in tabular form by therapeutic drug class (ATC Level 2 code) and generic drug name (ATC Level 4 code) using the World Health Organization Drug Dictionary (WHODD).

7.5.4 Concomitant Procedures

All concomitant procedures performed during the study will be listed.

Appendix A: ECOG Performance Scale

Patient performance status will be graded according to the Eastern Cooperative Oncology Group (ECOG) scale* as described below.

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

* As published in Am. J. Clin. Oncol.:
Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982.