PROTOCOL

A Prospective Study of Capsaicin in Subjects with Clinically Localized Prostate Cancer undergoing Active Surveillance or Radical Prostatectomy

(CAPSAICIN Trial)

Principal Investigator:
Dr. Laurence Klotz, Department of Urology, Sunnybrook Health Sciences Centre, MG 408, 2075 Bayview Avenue, Toronto, ON M4N 3M5 Canada

Scientific Advisor:
Dr. Vasundara Venkateswaran, Division of Urology, Department of Surgery, University of Toronto, S-118B, Bayview Avenue, Toronto, ON M4N 3M5, Canada

Primary Contact:
Natalie Venier, PhD Candidate, Division of Urology, Department of Surgery, University of Toronto, S 118B, 2075 Bayview Avenue, Toronto, ON M4N 3M5, Canada

The following Amendment(s) and Administrative Change(s) have been made to this protocol since the date of preparation:

<table>
<thead>
<tr>
<th>Date of Submission</th>
<th>Date of Amendment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>July 15, 2013</td>
</tr>
<tr>
<td>2</td>
<td>September 5, 2013</td>
</tr>
<tr>
<td>3</td>
<td>June 20, 2014</td>
</tr>
</tbody>
</table>
### Investigator Agreement Page

<table>
<thead>
<tr>
<th>Principal Investigator</th>
<th>Primary Scientific Advisor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dr. Laurence Klotz</td>
<td>Dr. Vasundara Venkeswaran</td>
</tr>
<tr>
<td>Sunnybrook Health Sciences Centre</td>
<td>2075 Bayview Avenue</td>
</tr>
<tr>
<td>MG408 – 2075, Bayview Avenue</td>
<td>S-118B, 2075 Bayview Avenue</td>
</tr>
<tr>
<td>Toronto, ON, Canada, M4N 3M5</td>
<td>Toronto, ON, Canada, M4N 3M5</td>
</tr>
</tbody>
</table>

**Date of issue:**
- June 15, 2012
- September 26, 2013
- June 20, 2014

**Purposes:**
- Final Protocol
- Version 2 – Updated Protocol
- Version 3 – Updated Documentation

**Sponsor:**
Investigator Initiated Trial
Sunnybrook Research Institute

**Purpose:**
The purpose of the study is to assess the effect of daily therapy with capsaicin in men on surveillance for favourable risk prostate cancer AND in men undergoing radical prostatectomy.

---

**Dr. Laurence Klotz**

_________________________  ______________________
Signature                  Date
TABLE OF CONTENTS

ABBREVIATIONS

PROTOCOL SUMMARY

1.0 BACKGROUND
  1.1 Prostate Cancer
  1.2 Active Surveillance
  1.3 Chemoprevention
  1.4 Capsaicin: Pre-clinical studies
  1.5 TRP-V1 and TRP-V6

2.0 HYPOTHESIS

3.0 OBJECTIVES
  3.1 Primary
  3.2 Secondary

4.0 ENDPOINTS
  4.1 Primary
  4.2 Secondary
  4.3 Safety and Tolerability
  4.4 Pharmacodynamic

5.0 STUDY DESIGN
  5.1 Overall Study Design and Plan
  5.2 Number of subjects
  5.3 Selection of Study Population
    5.3.1 Inclusion Criteria
    5.3.2 Exclusion Criteria

6.0 STUDY ASSESSMENTS AND PROCEDURES
  6.1 Demographic and Baseline Assessments
  6.2 Safety
    6.2.1 Medical History, Concomitants Medications, Physical Examination
    6.2.2 Physician’s Assessments and Vital Signs
    6.2.3 Clinical Laboratory Assessments
      6.2.3.1 Hematology, Clinical Chemistry and Cholesterol
      6.2.3.2 Prostate Specific Antigen (PSA) and Testosterone (T)
  6.3 Efficacy
    6.3.1 Prostate Cancer Biomarkers
    6.3.2 PSA Kinetics
    6.3.3 hs-CRP and c-CRP
    6.3.4 Safety and tolerability of Capsaicin daily therapy
    6.3.5 Pharmacodynamics

7.0 STUDY TREATMENT
  7.1 Active Surveillance
    7.1.1 Central Pathology
  7.2 Capsaicin
    7.2.1 Description of Study Medication
    7.2.2 Dosage Rationale and Administration
7.2.3 Packaging and Labeling
7.2.4 Handling and Storage
7.2.5 Product Accountability
7.2.6 Assessment of Compliance

8.0 CONCOMITANT MEDICATIONS AND NON-DRUG THERAPIES
8.1 Permitted Medications
8.2 Prohibited Medications
8.3 Non-Drug Therapies

9.0 SUBJECT COMPLETION AND WITHDRAWAL
9.1 Subject Completion
9.2 Subject Withdrawal
  9.2.1 Subject Withdrawal from Study
    9.2.1.1 End of Study Assessments
  9.2.2 Subject Withdrawal from Investigational Product

10.0 ADVERSE EVENTS (AE) AND SERIOUS ADVERSE EVENTS (SAE)
10.1 Definition of an Adverse Event
10.2 Definition of a Serious Adverse Event
   10.2.1 Disease-Related Events or Outcomes Not Qualifying as SAEs
10.3 Lack of Efficacy
10.4 Clinical Laboratory Abnormalities and Other Abnormal Assessments as AEs and SAEs
10.5 Time Period, Frequency and Method of Detecting AEs and SAEs
10.6 Recording of AEs and SAEs
10.7 Evaluating AEs and SAEs
   10.7.1 Assessment of Intensity
   10.7.2 Assessment of Causality
10.8 Follow-Up of AEs and SAEs
10.9 Prompt Reporting of SAEs
   10.9.1 Timeframes for Submitting SAE Reports
10.10 Post Study AEs and SAEs

11.0 DATA ANALYSIS AND STATISTICAL CONSIDERATIONS
11.1 Hypothesis
11.2 Treatment Comparisons of Interest
   11.2.1 Primary Comparison of Interest
   11.2.2 Other Comparisons of Interest
11.3 Interim Analysis
11.4 Sample Size Considerations
11.5 Analysis Populations
11.6 General Considerations for Data Analysis
11.7 Efficacy Analysis
   11.7.1 Primary Analysis
   11.7.2 Secondary Analysis
11.8 Safety Analysis
   11.8.1 Extent of Exposure
   11.8.2 Adverse Events
11.8.3. Hematology, Clinical Chemistry and Cholesterol Evaluations
11.8.4. Serum PSA
11.8.5. Testosterone

12.0 STUDY ADMINISTRATION

12.1 Regulatory and Ethical Considerations
   12.1.1 Regulatory Authority Approval
   12.1.2 Ethical Conduct of the Study and Ethics Approval
   12.1.3 Informed Consent
   12.1.4 Investigator Reporting Requirements

12.2 Study Monitoring
12.3 Quality Assurance
12.4 Study and Site Closure
12.5 Records Retention
12.6 Provision of Study Results and Information to Investigators
12.7 Data Management
12.8 Independent Data Monitoring Committee

REFERENCES

APPENDICES

   Appendix 1: Schedule of Assessments
   Appendix 2: Eastern Cooperative Oncology Group Performance (ECOG) Performance Scale
ABBREVIATIONS

AS  Active Surveillance
AE  Adverse Event
ALT Alanine Aminotransferase
AST Aspartate Aminotransferase
CAP Capsaicin supplement
CK  Creatinine kinase
CS  Clinically Significant
CRF Case Report Form
c-CRP cardiac C-Reactive Protein
DRE Digital Rectal Examination
DT  Doubling Time
ECOG Eastern Cooperative Oncology Group
GCP Good Clinical Practice
GLMM General Linear Mixed Model
hs-CRP High Sensitivity C-Reactive Protein
HDL High Density Lipoprotein
ITT Intent to Treat
LDL Low Density Lipoprotein
LHRH Luteinizing hormone releasing Hormone
Markers: ki67: a cell proliferation marker for growth of tumor cells.
     p27: tumor suppressor gene marker; predictor for tumor grade
NCI CTCAE National Cancer Institute Common Terminology Criteria for Adverse Events
OCC Odette Cancer Centre
PM  Product Monograph
PSA Prostate Specific Antigen
PIN Prostatic Intraepithelial Neoplasia
REB Research Ethics Board
SAE Serious Adverse Event
SHSC Sunnybrook Health Sciences Centre
T  Testosterone
TRP-V1 Transient Receptor Potential – Vanilloid 1 Receptor
TRUS Transrectal ultrasound
VLDL Very Low Density Lipoprotein
PROTOCOL SUMMARY

Rationale
A large body of evidence supports the role of dietary factors in prostate cancer development and progression. Most of this evidence suggests that diet high in fat including red meat and low in micronutrients and other anti-oxidants, increases the risk of disease. We are interested in the therapeutic potential of the dietary agent, capsaicin. Capsaicin is the active compound in chili peppers, and related plants. Pre-clinical studies have found that capsaicin has potent growth inhibitory and pro-apoptotic effects. It is thought that consumption of a capsaicin supplement may have a clinical benefit for subjects with localized prostate cancer who have chosen to be managed by active surveillance or improve surgical outcome of patients undergoing radical prostatectomy.

Objective(s)
Primary
• To assess the effect of capsaicin daily therapy on the expression of ki67 and p27 biomarkers in a post-treatment biopsy or prostate specimen from RP.

Secondary
• To assess the effect of therapy with repeat oral dosing of capsaicin two times daily on Prostate Specific Antigen (PSA) kinetics in men on active surveillance for localized prostate cancer
• To assess the effect of therapy with repeat oral dosing of capsaicin two times daily on grade and the presence of prostatic intraepithelial neoplasia (PIN) in a post-treatment biopsy
• To assess the effect of therapy with repeat oral dosing of capsaicin two times daily on the expression of markers of apoptosis, cell cycle, TRP-V1 and TRP-V6
• To assess the safety and tolerability of capsaicin therapy in men on active surveillance (AS) for prostate cancer
• To assess alterations in prostate volume and time to recurrence

Endpoint(s)
Primary
• Determine effect of capsaicin therapy on expression of ki67 and p27 biomarkers in a post-treatment biopsy

Secondary
• Determine effect of capsaicin daily therapy on PSA kinetics in men on active surveillance for localized prostate cancer
• To evaluate the effect of capsaicin daily therapy on grade and the presence of prostatic intraepithelial neoplasia (PIN) in post treatment biopsy
• To assess the effect of capsaicin therapy on the expression of markers of apoptosis, cell cycle, TRP-V1 and TRP-V6

Safety and Tolerability
• Adverse events (AEs)
Clinical laboratory evaluations (PSA, electrolytes, biochemistry, hematology, cholesterol)

**Pharmacodynamic**
- Levels of serum capsaicin (CAP)
- Levels of serum testosterone (T)

**Study Design**
This is a phase II, open label, single centre study to evaluate the efficacy and safety of repeat oral dosing of one CAP capsules twice times daily for 6 months prior to a prostate biopsy in men on active surveillance for localized prostate cancer, as well as 6 weeks prior to radical prostatectomy (RP).

**Study Population**
One hundred men monitored (sixty from active surveillance (AS) and forty patients scheduled to undergo radical prostatectomy) will be eligible for participation. Subjects must satisfy all inclusion and exclusion criteria. A sufficient number will be enrolled to achieve at least 100 completed subjects.

**Inclusion Criteria**
1. Subject is >19 years of age
2. Subject has a histologically documented diagnosis of prostate adenocarcinoma
3. Being monitored by active surveillance (see Table 1) for favourable risk prostate cancer as defined by the following:
   a. Clinical stage T1b, T1c, T2a or T2b at the time of diagnosis
   b. Clinical (diagnostic biopsy) Gleason score \(< 6\)
   c. PSA \(< 10.0 \text{ ng/ml (ug/L)}\)
4. Tumour material from most recent prostate biopsy available with sample (up to 10 unstained slides) collected for determination of ki67 and p27 biomarker expression.
5. Scheduled to have an active surveillance mandated transrectal ultrasound (TRUS) guided biopsy within 6 - 12 months of Day 1 of the study

**Exclusion criteria**
1. Previous malignancy (not including curatively treated basal or squamous cell carcinoma of the skin) within the previous 5 years. (Ta bladder cancer with negative surveillance cystoscopy within the past 2 years may be included.)
2. No previous or current treatment (medical therapy or radical intervention) for prostate cancer excluding biopsy
3. Inability to undergo TRUS biopsy
4. Concurrent administration of the following medications is not permitted during the protocol:
   - 5 α-reductase inhibitors
   - Cytotoxic chemotherapy
   - Immunotherapy
   - Hormonal therapy (megestrol, medroxyprogesterone, cyproterone, diethylstilbestrol, hydrocortisone, etc.)

Version 3: 20 June 2014
Capsaicin and Prostate Cancer

- Non-steroidal anti-androgens (bicalutamide, nilutamide, flutamide, etc.)
- Luteinizing hormone releasing Hormone (LHRH) analogues (leuprolide, goserelin, etc.)
- Ketoconazole
- PC-SPES and any other preparations thought to have endocrine effects
- Medications which inhibit cholesterogenesis (‘statin’ medications, etc.)

5. Eastern Cooperative Oncology Group (ECOG) Performance Status > 2
6. Known or history of liver disease (total bilirubin, alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 2.5 upper limit of normal at screening visit)
7. Subject has a minimum life expectancy of < 5 years
8. Subject is unable to give written and informed consent

Study Assessments and Procedures
Key study assessments include a physical exam including digital rectal examination (DRE), serum PSA, electrolytes, clinical chemistry, hematology, cholesterol (total, low density lipoprotein (LDL) and high density lipoprotein (HDL)), triglyceride, creatinine kinase (CK), high sensitivity C-reactive protein (hs-CRP), cardiac C-reactive protein (c-CRP) and T at screening, month 1, month 3 and every 3 months until the end of study. Physical examination including DRE, serum PSA, electrolytes, clinical chemistry, cholesterol (total, LDL and HDL), triglyceride, CK, hs-CRP, c-CRP, T and transrectal ultrasound (TRUS) guided biopsy within 6 – 12 months of Day 1 for Active Surveillance (AS) and 6-8 weeks before radical prostatectomy.

See Appendix 1: Schedule of Assessments

Efficacy Evaluations
- Effect of capsaicin therapy on expression of prostate cancer biomarkers
- Effect of capsaicin therapy on PSA kinetics
- Effect of capsaicin therapy on surgical outcome.
- Effect of capsaicin therapy on the expression of high sensitivity C-reactive protein (hs-CRP) and cardiac C-reactive protein (CRP)

Safety Evaluations
- Medical history
- Concomitant medications
- Physical examination including digital rectal examination (DRE)
- Physician’s assessment and vital signs
- Clinical laboratory evaluations (serum hematology, chemistry, cholesterol)
- Total PSA
- Adverse event assessments

Statistical Analysis Plan
PSA kinetics will be analyzed using the General Linear Mixed Method (GLMM).

Investigational Product
The investigational product that will be used in this study will consist of Cayenne by Naturesway containing 450.0mg of Capsicum annuum in one soft gelatin capsule by Enzymatic Therapy (Canada) Inc (NPN# 80013036)
1. BACKGROUND

1.1 Prostate cancer
Prostate cancer (PCa) is the most common non-skin cancer in North America. In 2009, more than 192,000 men will be diagnosed with PCa, and more than 27,000 men will die from the disease. It is estimated that there are more than 2 million American men currently living with PCa\(^1\). The etiology of PCa is unknown, although several factors, including age, race, lifestyle and hormones, are thought to play a role\(^2\).

In most cases, PCa is a relatively slow-growing cancer. This means that it usually takes a number of years for the disease to become large enough to be detectable, and even longer for it to spread beyond the prostate. A small percentage of patients, however, experience more rapidly growing, aggressive forms of PCa. Unfortunately, it is difficult to ascertain slow-growing from aggressive cancer, and this complicates treatment decisions\(^1\).

Prostate cancer may not cause any signs or symptoms, especially in the early stages. However, if the tumour makes the prostate larger than normal, it can cause it to press on the urethra, making urination painful or more difficult, and possibly cause more frequent urination. An enlarged prostate may also be a result of a common non-cancerous condition called benign prostatic hyperplasia (BPH). Blood tests for PSA, imaging studies including trans-rectal ultrasound (TRUS), and prostate biopsy are usually required for PCa diagnosis\(^3\). Four standard methods are used in the treatment of PCa. They are active surveillance, surgery, radiation therapy, and hormone therapy\(^2\).

1.2 Active Surveillance
Over the last two decades, age-adjusted incidence rates of prostate cancer have risen dramatically\(^4\). This is primarily due to the widespread use of PSA as a screening test for prostate cancer. PSA screening results in the diagnosis of life threatening prostate cancer at a point where it is more amenable to cure. It also results in the diagnosis of many prostate cancers that might previously have remained undiagnosed.

Patients with intermediate to high risk localized PCa (defined as Gleason score 7 or greater, or PSA > 10, or T2b-T4 cancer) who have greater than a 5-10 year life expectancy warrant definitive local therapy in most cases. However, favourable risk patients (defined as a Gleason score of 6 or less, and PSA ≤ 10, and T1c or T2a, are at relatively low risk of dying of PCa, even if they live 20 or more years. In these patients, the approach of active surveillance is an attractive alternative to immediate radical treatment\(^5\).

Early PCa detection and treatment programs presume that treatment with radical prostatectomy or radiotherapy prolongs survival in subjects with clinically localized PCa. This is not convincingly supported by results from the literature. These studies demonstrate that the therapeutic approach of active surveillance with selective delayed intervention for favourable risk disease appears to offer survival and PCa mortality comparable to that of radical treatment (surgery or radiation)\(^5\). The Active Surveillance program involves proactive testing to follow the disease. Standard care consists of regular follow-up appointments with blood work, physical exams, TRUS and biopsies.
1.3 Prostate Cancer and Chemoprevention

Chemopreventive agents are natural or pharmaceutical compounds used to prevent the development (primary chemoprevention) or delay the progression (secondary chemoprevention) of disease. Prostate cancer represents an ideal tumour system for studying chemopreventive agents, due to its prolonged developmental phase and subsequent, commonly slow, progression. Thus, an extended window of opportunity exists for administration of both primary (pre-tumour development) and secondary (post-diagnosis) chemoprevention.

The use of dietary agents for the chemoprevention of prostate cancer has been intensely investigated. While many agents have shown promising results in the pre-clinical arena, none have been successfully translated into chemopreventive strategies that are routinely implemented in clinical practice. Potential explanations as to why micronutrients often fail to successful translation into clinic include: 1) lack of knowledge regarding optimum onset and required duration of intervention, 2) impaired bioavailability of the active component(s) present in the compound and 3) lack of biologically plausible mechanisms of action. Thus, potential successful chemopreventive agents are dietary agents (non-toxic), which are readily absorbed/metabolized to active compounds and target specific pathways related to tumour development/progression. The focus of the present review is to examine the chemopreventive potential of capsaicin and explore its potential translation into clinical trials for prostate cancer.

1.4 Capsaicin and Prostate Cancer

Capsaicin (trans-8-methyl-N-vanillyl-6-nonenamide) is the natural compound found in the Capsicum sp. plants and is responsible for the burning sensation experienced on the contact of red and chili peppers. Capsaicin is widely consumed as a food additive throughout the world, particularly in areas with a low incidence of prostate cancer, such as, South East Asia. It displays both analgesic and anti-inflammatory properties and has been widely used topically for treatment of various chronic pain syndromes. More recently capsaicin has been demonstrated to have anti-carcinogenic properties in several cancers, including PCa. Capsaicin promotes apoptosis in PCa cells in vitro by generating reactive oxygen species, dissipation of the mitochondrial inner transmembrane potential and downstream activation of the caspase-3 pathway. Capsaicin also demonstrates efficacy in vivo by suppressing the growth of prostatic tumor xenografts in nude mice. Recent preliminary studies carried out by our group, have shown that capsaicin can reduce the growth of prostate cancer xenografts which is enhanced with radiation. A recent case study reported by Jankovic et al., describes a 78 year old PCa patient who experienced significant improvement in his PSA levels upon consuming capsaicin daily. Cessation of the capsaicin was followed by a sharp increase in his PSA levels (challenge/re-challenge effect) and PSA trends showed a dose-response relationship.

1.5 Transient Receptor Potential Vanilloid (TRPV)-1 and -6
The vanilloid receptors belong to the family of transient receptor potential (TRP) cation selective channels which modulate intracellular calcium concentrations. Up-regulation of TRPV-1 and TRPV-6 expression in PCa tissue is well-documented in the literature\textsuperscript{13-18}. The expression of TRPV-6 mRNA is low or undetectable in healthy and benign prostate tissue, whereas studies of PCa tissue show increasing expression of TRPV-6 mRNA with increasing tumour grade\textsuperscript{14-18}. The clear correlation with increasing degrees of malignancy and the expression of the samples suggests that TRPV-1 and TRPV-6 may serve as prognostic factors and possibly therapeutic targets for PCa\textsuperscript{13, 15, 19}.

Many of capsaicin’s proliferative and apoptotic effects are reported to be partly TRPV-1 and/or -6 mediated\textsuperscript{20-22}. Numerous investigations have been conducted assessing the role of capsaicin and TRPV-1 in cell proliferation, but results remain conflicting. Recently, TRPV-6 protein has been shown to control PCa cell proliferation via calcium-dependent pathways\textsuperscript{22}. More recent literature has found that capsaicin-induced apoptosis may be mediated by TRPV-6 receptors in cancer cells\textsuperscript{20}. Although the relationship between these two vanilloid receptors remains unclear they represent promising targets for capsaicin interventions.

\textit{In summary, capsaicin has been promoted as a safe and effective supplement metabolism regulator, it has been described as an appetite suppressant aiding in weight loss. Capsaicin has the potential to slow prostate cancer growth by inhibiting cell growth and proliferation, and promoting apoptosis in prostate cancer cells in vitro and in vivo models. There is a strong rationale for the use of capsaicin in patients being managed with active surveillance for localized, low risk, prostate cancer or as an adjunct to conventional therapies. To date, no human studies utilizing capsaicin in this setting have been reported.}

2.0 HYPOTHESIS

That, the administration of CAP in men on surveillance for favourable risk prostate cancer alters the expression of proliferation and cell cycle regulatory genes associated with disease progression.

3.0 OBJECTIVES

3.1 Primary Objectives

- To assess the effect of capsaicin daily therapy on the expression of ki67 and p27 biomarkers in a post-treatment biopsy and prostatectomy specimens.

3.2 Secondary

- To assess the effect of therapy with repeat oral dosing of CAP two times daily on PSA kinetics in men on active surveillance for localized prostate cancer
• To assess the effect of therapy with repeat oral dosing of CAP two times daily on grade and the presence of prostatic intraepithelial neoplasia (PIN) in post-treatment biopsy
• To assess the effect of therapy with repeat oral dosing of CAP three times daily on the expression of hs-CRP and c-CRP in serum
• To assess the safety and tolerability of CAP therapy in men on active surveillance for prostate cancer

4.0 ENDPOINTS

4.1 Primary

• Determine effect of capsaicin therapy on expression of ki67 and p27 biomarkers in a post-treatment biopsy tissue compared to baseline expression in the active surveillance population or in patients undergoing radical prostatectomy (RP).

4.2 Secondary

• Determine effect of capsaicin daily therapy on PSA kinetics in men on active surveillance for localized prostate cancer
• To evaluate the effect of capsaicin daily therapy on grade and the presence of prostatic intraepithelial neoplasia (PIN) in post treatment biopsy compared to pre-treatment biopsy
• To assess the effect of capsaicin therapy on the expression of high sensitivity hs-CRP and c-CRP compared to baseline expression

4.3 Safety and Tolerability

• Adverse events (AEs)
• Clinical laboratory evaluations (PSA, electrolytes, biochemistry, hematology, cholesterol)

4.4 Pharmacodynamic

• Levels of serum testosterone (T)

5.0 STUDY DESIGN

5.1 Overall Study Design and Plan

This is a prospective, phase II, open label, single centre study. Sixty subjects being managed by active surveillance for localized prostate cancer and forty men scheduled to undergo RP will be asked to participate.

All eligible subjects will self-administer the study medication, Cayenne by Naturesway, 450mg, by Enzymatic Therapy (Canada) Inc (NPN# 80013036) (21), one capsules, two times daily for 6 – 12 months (active surveillance) after which they will have an active
surveillance mandated TRUS guided prostate biopsy, or 6-8 weeks after they have been scheduled to undergo RP to manage their prostate cancer.

Subjects who elect to discontinue the study prior to having an event of disease progression completion of biopsy will be included for a subset analysis on the efficacy and safety with shorter duration of CAP treatment.

5.2 Number of subjects

Approximately 60 men who are being managed by active surveillance for localized prostate cancer at Sunnybrook Health Sciences Centre (SHSC) and the Odette Cancer Centre (OCC), Toronto, Canada will be eligible for participation. Subjects must satisfy all inclusion and exclusion criteria. A sufficient number will be enrolled to achieve at least 50 completed subjects.

5.3 Selection of Study Population

5.3.1 Inclusion Criteria

A subject will be eligible for study participation if all of the following criteria are met:

1. Subject is >19 years of age
2. Subject has a histologically documented diagnosis of prostate adenocarcinoma
3. Subject is being managed by active surveillance (see Table 1) for favourable risk prostate cancer as defined by the following:
   a. Clinical stage T1b, T1c, T2a or T2b at the time of diagnosis
   b. Clinical (diagnostic biopsy) Gleason score ≤ 6
   c. PSA ≤ 10.0 ng/ml (ug/L)
   OR
   Subject must be Men scheduled to undergoing radical prostatectomy (RP) in at least 6 weeks prior to commencing study. For this study we aim to minimize this by limiting inclusion to patients with Gleason 7 (4+3) cancers or higher (which tend to be larger volume) with at least 30% involvement of 1 core.

4. Tumour material from most recent prostate biopsy available with sample (up to 10 unstained slides) collected for determination of ki67 and p27 biomarker expression.
5. Subject is scheduled to have an active surveillance mandated transrectal ultrasound (TRUS) guided biopsy within 6 - 12 months of Day 1 of the study. OR Subject is scheduled to have a radical prostatectomy with 6 - 8 weeks of Day 1 of the study.

5.3.2 Exclusion Criteria

A subject will be ineligible for study participation if any of the following criteria are met:
1. Subject has a history of previous malignancy (not including curatively treated basal or squamous cell carcinoma of the skin) within the previous 5 years. (Ta bladder cancer with negative surveillance cystoscopy within the past 2 years may be included.)

2. No previous or current treatment (medical therapy or radical intervention) for prostate cancer excluding biopsy

3. Concurrent administration of the following medications is not permitted during the protocol:
   - 5 α-reductase inhibitors
   - Cytotoxic chemotherapy
   - Immunotherapy
   - Hormonal therapy (megestrol, medroxyprogesterone, cyproterone, diethylstilbestrol, hydrocortisone, etc.)
   - Non-steroidal anti-androgens (bicalutamide, nilutamide, flutamide, etc.)
   - LHRH analogues (leuprolide, goserelin)
   - Ketoconazole
   - PC-SPES and any other preparations thought to have endocrine effects
   - Medications which inhibit cholesterogenesis (‘statin’ medications, etc.)

4. Inability to undergo TRUS biopsy

5. Eastern Cooperative Oncology Group (ECOG) Performance Status > 2

6. Known or history of liver disease (total bilirubin, alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 2.5 upper limit of normal at screening visit)

7. Subject has a minimum life expectancy of < 5 years

8. Subject is unable to give written and informed consent

9. Subject is, in the opinion of the investigator, unable to comply with the requirements of the study protocol or is unsuitable for the study for any reason

6.0 STUDY ASSESSMENTS AND PROCEDURES

Informed consent will be obtained before the subject can participate in the study. The contents and process of obtaining informed consent will be in accordance with all applicable regulatory requirements.

6.1 Demographic and Baseline Assessments

Demographic characteristics to be collected during screening/baseline and recorded in the case report form (CRF) are date of birth, race, height and weight.

A medical history will be obtained, including a review of all major organ systems and a history of alcohol and tobacco use.

The oncological history will include a summary of the subject’s prostate cancer history including histopathological grade, Gleason score, PSA history and all treatments and procedures received (i.e. radiation therapy, surgery and others.)
A complete physical examination and a physician’s assessment will be conducted (including DRE). The following assessments will also be completed: vital signs; ECOG performance status; clinical laboratory parameters including serum chemistry, electrolytes, cholesterol (total, LDL and HDL), triglyceride, CK, hs-CRP, e-CRP, hematology, PSA and testosterone; and concomitant medication(s)

6.2 Safety

See Section 10, Adverse Events and Serious Adverse Events, for a complete description of adverse event assessments.

6.2.1 Medical History, Concomitant Medications, Physical Examination

A medical history will be obtained at screening Visit 1 with particular attention paid to the following:

- A thorough review of body systems, both past or current conditions including use of tobacco and alcohol
- Pharmacotherapy, chronic use of any medication (prescribed and over-the-counter, including phytotherapy / dietary supplements)
- History of any allergies or idiosyncratic reactions to drugs
- Family history of prostate cancer

Concomitant medications and adverse events will be assessed at each clinic visit during the treatment interval, Final/Premature and Safety Follow-up visits. All concomitant medications and the use of dietary / herbal supplements will be recorded in the CRF.

For subjects enrolled in the active surveillance arms, a targeted physical examination will be conducted at Screening (Visit 1) and every 3 months for the duration of the study, Final / Premature Termination Visit and the Safety Follow-up visit. Physical examination, DRE evaluation and bloodwork are not required at visit 2 if completed within 14 days of visit 1.

For subjects scheduled to undergo RP, a targeted physical examination will be conducted one day prior to radical prostatectomy where a physical Physical examination, DRE evaluation and bloodwork.

The physical examination will include measurements of height (visit 1 only), vital signs (blood pressure and pulse), ECOG performance status and weight. For height measurements, subjects should be measured without shoes. Weight will be measured on a calibrated scale.

6.2.2 Physician’s Assessments and Vital Signs

At each clinic visit, the study physician will assess the subject’s continued eligibility and safety.
Vital signs (blood pressure followed by heart rate) will be assessed every 3 months during the treatment interval, Final/Premature Termination and Safety Follow-up visits. The subject must be sitting for at least 5 minutes before measurements are taken. No other procedures will be performed during this 5 minute stabilization period. Heart rate will be measured for 30 seconds.

## 6.2.3 Clinical Laboratory Assessments

Subjects will be asked to fast for all clinical laboratory samples. All samples throughout the study will be collected prior to undergoing any clinical procedures. In order to determine each subject’s eligibility to participate in the study, the results of the screening clinical laboratory tests must be assessed by the principal investigator or designee prior to study drug administration.

Any abnormal assessments that are deemed clinically significant (CS) will be recorded as adverse events (AEs) or serious adverse events (SAEs), if they meet the definition of an AE, as defined in Section 10.1 or SAE, as defined in Section 10.2. All clinically significant changes from baseline will be followed until resolution or stabilization as determined by the principal investigator or designee.

Blood samples for hematological, biochemical, cholesterol (total, LDL, HDL), triglyceride, hs-CRP, e-CRP, T and PSA will be analyzed by local accredited laboratories.

<table>
<thead>
<tr>
<th>Laboratory Assessment</th>
<th>Visit Frequency (AS/RP)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematology</td>
<td>Visits 1, month 1, month 3 &amp; every 3 months/Visit 1, Visit 2 (day prior to RP)</td>
</tr>
<tr>
<td>Clinical Chemistry</td>
<td>Visits 1, month 1, month 3 &amp; every 3 months Visit 1, Visit 2 (day prior to RP)</td>
</tr>
<tr>
<td>Serum Cholesterol</td>
<td>Visits 1, month 1, month 3 &amp; every 3 months Visit 1, Visit 2 (day prior to RP)</td>
</tr>
<tr>
<td>PSA / T</td>
<td>Visits 1, every 3 months Visit 1, Visit 2 (day prior to RP)</td>
</tr>
<tr>
<td>Capsaicin analysis</td>
<td>Visits 1, month 1, month 3 &amp; every 3 months Visit 1, Visit 2 (day prior to RP)</td>
</tr>
</tbody>
</table>

In the Active Surveillance Arm (AS), laboratory evaluations are not required at visit 2 if completed within 14 days of visit 1.

### 6.2.3.1 Hematology, Clinical Chemistry and Cholesterol
The following tests will be performed:

<table>
<thead>
<tr>
<th>Hematology</th>
<th>Clinical Chemistry</th>
<th>Cholesterol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total RBC Count</td>
<td>Sodium</td>
<td>ALT</td>
</tr>
<tr>
<td>Total WBC Count</td>
<td>Potassium</td>
<td>AST</td>
</tr>
<tr>
<td>Platelet Count</td>
<td>Total protein</td>
<td>ALP</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>Total bilirubin</td>
<td>Creatinine</td>
</tr>
<tr>
<td></td>
<td>Albumin</td>
<td>Creatinine kinase</td>
</tr>
<tr>
<td></td>
<td>Glucose</td>
<td>Urea</td>
</tr>
<tr>
<td></td>
<td>Capsaicin</td>
<td></td>
</tr>
</tbody>
</table>

6.2.3.2 Prostate Specific Antigen (PSA) and Testosterone (T)

PSA and T will be measured at screening, visit 2 (not required at visit 2 if completed within 14 days of visit 1) and every 3 months for the duration of study treatment and at the Final / Premature Termination visits.

A number of clinical situations can cause transient rises in PSA. Therefore, blood samples for evaluating PSA levels must be collected within the study-defined time windows and prior to performing any clinical procedures (including DRE). Although discouraged, if a PSA measurement outside of the study scheduled assessments is necessary, it should be assayed through the same laboratory.

6.3 Efficacy

6.3.1 Prostate Cancer Biomarkers

Subjects will self-administer study medication for 6 - 12 months, after which they will have a TRUS guided prostate biopsy. Histopathology review will be conducted by an uro-pathologist, assessing grade and presence of prostatic intraepithelial neoplasia (PIN) and staining for additional markers of proliferation (Ki-67) and cell cycle regulation (p27).

6.3.2 PSA Kinetics

The subject’s PSA kinetics, including PSA DT, slope and velocity (25) will be calculated based on the serum measurements from baseline until their prostate biopsy as assessed by the local investigator.

6.3.3 hs-CRP and c-CRP

The subject’s serum will be assessed for the expression of hs-CRP and c-CRP during treatment as compared to baseline expression.

6.3.4 Safety and tolerability of Capsaicin daily therapy
In terms of safety, capsicum essential oil and cayenne pepper are listed in the U.S. Food and Drug Administration (FDA) Generally Recognized as Safe (GRAS) list for use as a spice in foods. Further information on safety can be found in a final report on the safety assessment of *Capsicum annuum* extract, *Capsicum annuum* fruit extract, *Capsicum annuum* resin, *Capsicum annuum* fruit powder, *Capsicum frutescens* fruit, *Capsicum frutescens* resin. There is one published case study from Canada that looked a prostate cancer patient taking a habenero chili sauce "containing capsaicin" a couple times a week that found a slowing of PSA doubling time (Jankovic, Loblaw et al. 2010). There have not been any clinical trials specific to cayenne or capsaicin and prostate health, although there is *in vitro* research showing antiproliferative effects of capsaicin against prostate cancer cells.(3,4)

The frequency and severity of the AEs and SAEs for all patients during treatment with CAP will be evaluated.

### 6.3.5 Pharmacodynamics

The effect of study medication on circulating levels of serum PSA and T in the blood will be evaluated at all study visits.

### 7.0 Treatment of Subjects

#### 7.1 Active Surveillance

While participating in the study, all subjects will be monitored according to the active surveillance investigations and schedule as outlined below (Table 1).

**Table 1: Active Surveillance Evaluation Schema**

<table>
<thead>
<tr>
<th>Investigations</th>
<th>Timing from day of decision to undergo AS monitoring</th>
</tr>
</thead>
<tbody>
<tr>
<td>History and Physical Exam including:</td>
<td></td>
</tr>
<tr>
<td>• Physical examination (including DRE)</td>
<td>Q 6 months</td>
</tr>
<tr>
<td>• ECOG Performance status</td>
<td></td>
</tr>
<tr>
<td>Biochemistry</td>
<td></td>
</tr>
<tr>
<td>• Serum PSA</td>
<td>Q 3 months for 2 years then every 6 months</td>
</tr>
<tr>
<td>• Testosterone</td>
<td></td>
</tr>
<tr>
<td>TRUS Guided Biopsy</td>
<td></td>
</tr>
<tr>
<td>Radiology (bone scan, chest x-rays, CTs)</td>
<td></td>
</tr>
<tr>
<td>• As clinically indicated</td>
<td></td>
</tr>
</tbody>
</table>
### Adverse Events

- Adverse events will be recorded and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) Version 4.03

<table>
<thead>
<tr>
<th>Timeframe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Q 6 months for 2 years then every 6 months</td>
</tr>
</tbody>
</table>

### Additional Therapy

- Evaluation of therapy for benign prostatic hyperplasia and anti-androgen/androgen deprivation therapy

<table>
<thead>
<tr>
<th>Timeframe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Q 6 months for 2 years then every 6 months</td>
</tr>
</tbody>
</table>

If during active surveillance, clinical criteria are met for radical intervention, subjects would then be treated at the discretion of their physician. Radical treatment should be considered when one of more of the following occurs:

- **a) Biochemical progression**
  The subject’s PSA doubling time (25) is calculated to be less than 3 years, based on at least three separate measurements over a minimum of six months as assessed by the local investigator.

- **b) Histologic/grade progression**
  The subject is found to have a Gleason pattern 4 or higher (i.e., Gleason 7 or higher) in a TRUS guided biopsy of prostate. The presence of a minor secondary element of Gleason pattern of 4 is consistent with a decision to continue surveillance based on physician discretion.

- **c) Clinical progression**
  - **Local progression** - Local progression of prostate cancer resulting in urinary retention, gross hematuria or hydronephrosis.
  - **Distant metastasis** - As defined by radiology, cytology or histology at sites remote from the prostate and regional lymph nodes

- **d) Patient’s choice**
  Subjects who do not meet the criteria for biochemical, histologic/grade or clinical progression, but who are uncomfortable remaining on active surveillance, will be free to elect definitive therapy at any time.

- **e) Clinical judgment**
  A clinical decision to proceed with radical intervention based on reasons other than the above pre-specified protocol criteria.

#### 7.1.1 Biopsy Review

Tumour material from the most recent pre-treatment and post-treatment prostate biopsies will be reviewed by the study site uro-pathologist.
7.2 Capsaicin Supplement: Cayenne by Naturesway Supplement

7.2.1 Description of Study Medication

The medication for this study will be supplied by Dr. Laurence Klotz. The product, commercially available as Cayenne by Naturesway, (Nature’s Way Products, Inc, Green Bay, WI, USA). It is in a capsule form and contains 450mg of Cayenne pepper (fruit) and well as gelatin filler. Each capsule contains 0.25% of the active ingredient capsaicin (100,000 H.U). Capsaicin has been shown to reduce serum total cholesterol, triglycerides, very low-density lipoprotein (VLDL), and low-density lipoprotein (LDL), and increasing high-density lipoprotein (HDL), lower blood pressure, and help prevent clotting and hardening of arteries\textsuperscript{27, 28}.

When consumed orally, capsaicin may improve digestion by increasing the digestive fluids in the stomach and by combating bacteria that could cause infection\textsuperscript{27, 28}. Capsaicin has also been reported to act as potent antioxidant and anti-inflammatory agent\textsuperscript{27, 28}.

Physical, chemical and pharmaceutical properties and characteristics of Cayenne by Naturesway, (Nature’s Way Products, Inc, Green Bay, WI, USA) are listed in the product monograph (PM).

The study medication will be supplied in 175 cc white bottles of 60 capsules.

7.2.2 Dosage Rationale and Administration

The dose of capsaicin that inhibits prostate cancer cell growth has not been established. Clinical trials evaluating the efficacy of capsaicin for the treatment of hypercholesterolemia utilized dosages ranging from 600mg (1 capsule) RYR twice daily to a maximum dosage of 2400mg (4 capsules) RYR twice daily [1200mg – 4800mg total daily dose]. Commercial preparations of RYR contain varying concentrations of monacolins with the concentration of monacolin K known to vary from 1.02 mg / capsule to 3.2mg / capsule depending on the strain of yeast or fermentation process used to produce RYR. (17)

Subjects meeting all inclusion and exclusion criteria at visit 1 and who continue to satisfy eligibility criteria at visit 2, will self-administer the study drug orally 1 capsules two time daily at the same time of day for the duration of the study period (6 - 12 months). The dosage was chosen as it is similar to that used in the largest randomized clinical trial of RYR. This dosage was also associated with a low rate of adverse events and was generally tolerated by study participants. (17, 21)

All subjects will return monthly for scheduled clinic visits for assessments and study drug re-supply until the end of the study. The investigator or designee should not make any adjustments to the dosage or frequency of the study medication. If a dose is missed, the subject should be instructed to not make up the dose.
Subjects will be reminded to return all medication to the study centre during scheduled clinic visits. Study staff at the centre will conduct counts of all returned study medication to ensure compliance.

Subjects withdrawn from the study retain their subject number. New subjects will be allocated a new subject number.

7.2.3 Packaging and Labeling

Study medication will be provided in high density, polyethylene, sealed bottles with plastic closures.

The contents of the label will be in accordance with all applicable regulatory requirements.

7.2.4 Handling and Storage

Study medication must be dispensed or administered according to procedures described herein. Only subjects enrolled in the study may receive the study medication, in accordance with all applicable regulatory requirements. Only authorized site staff may supply the study medication.

All study medication is stored in a secure area with access limited to the investigator and authorized site staff and under physical conditions that are consistent with investigational product-specific requirements. Prior to dispensing, all study medication will be kept safely locked and stored at or below 30°C (86°F).

7.2.5 Product Accountability

The investigator is responsible for study drug accountability, reconciliation and record maintenance. In accordance with all applicable regulatory requirements, the investigator or designated site staff will maintain the study drug accountability records throughout the course of the study. This person(s) will document the amount of study drug received from Farr Laboratories, LLC, the amount supplied and/or administered to and returned by subjects.

At each return clinic visit, the subject will return all unused study drug and any empty bottles to the site. Study drug accountability will be performed to document compliance with the dosing regimen. All study drug that is dispensed and returned or wasted/lost will be recorded in the CRF.

The investigator will be responsible for study drug destruction at the end of the trial. Local destruction of the study medication is the preferred procedure for destroying unused (full bottles never dispensed), damaged or used bottles of capsules. Local destruction will be performed in accordance with local site regulations. Proof of
destruction document signed by the person who has completed destruction will be filed in the investigator study binder.

The remaining drug inventory will be destroyed locally by the Urology Research office staff according to applicable regulatory requirements. Proof of destruction document signed by the person who has completed destruction will be filed in the investigator study binder.

7.2.6 Assessment of Compliance

For each subject, the number of capsules dispensed and returned or wasted/lost will be recorded in the CRF at each clinic visit. Compliance will be determined from the number of capsules dispensed, returned and lost/wasted from each bottle dispensed and the ‘total number’ of capsules dispensed, returned and lost/wasted. Capsules that are not returned will be considered to have been taken.

8.0 CONCOMITANT MEDICATIONS AND NON-DRUG THERAPIES

8.1 Permitted Medications

All concomitant medications taken during the study will be recorded in the CRF with indication, dose information and dates of administration. The definition of which medication would be considered outside the routine medical practice is up to the discretion of the investigator. All dietary and herbal supplement usage will be recorded in the CRF.

8.2 Prohibited Medications

Use of the following medications will be prohibited during the study:

- 5 α-reductase inhibitors
- Cytotoxic chemotherapy
- Immunotherapy
- Hormonal therapy (megestrol, medroxyprogesterone, cyproterone, diethylstilbestrol, hydrocortisone, etc.)
- Non-steroidal anti-androgens (bicalutamide, nilutamide, flutamide, etc.)
- LHRH analogues (leuprolide, goserelin, etc.)
- Ketoconazole
- PC-SPES and any other preparations thought to have endocrine effects
- Medications which inhibit cholesterogenesis (‘statin’ medications, etc.)

8.3 Non-Drug Therapies

Any occurrence of prostate-related surgical and/or non-surgical (or minimally invasive) intervention during the conduct of the study will be recorded in the CRF.

9.0 SUBJECT COMPLETION AND WITHDRAWAL
9.1 Subject Completion

A completed subject as defined for efficacy analyses is defined as a subject who has undergone the prostate biopsy at the completion of 6 – 12 months of RYR therapy.

For safety analyses, a completed subject is defined as a subject who has completed all phases of the study.

9.2 Subject Withdrawal

9.2.1. Subject Withdrawal from Study

A subject may discontinue participation in this study at any time at the investigator’s discretion or at the request of the subject.

If a subject discontinues at or before Visit 2, he is not required to complete end of study assessments.

If a subject discontinues after Visit 2 for any reason, the investigator should make every effort to complete the activities bulleted below.

- End of study assessments as outlined in Section 9.2.1.1
- One month follow-up assessments of concomitant medications, adverse events and partner pregnancies.
- Any occurrence of death, prostatic surgical intervention, non-surgical treatment for prostate cancer and any excluded medications taken after study withdrawal should be documented in the CRF and source documents.

Subjects who are discontinued from the study will not be replaced.

In the event that a subject is prematurely discontinued from the study at any time due to an AE, the procedures describe in Section 10 must be followed.

Subjects should be withdrawn from the study for any of the following criteria:

- Non-compliance with the requirements of the study or study medication by either the subject or the investigator.
- Request to discontinue treatment. This request can be made by either the subject or the investigator.
- Develops progressive disease.

9.2.1.1 End of Study Assessments

The end of study assessments comprise an essential safety evaluation that should be completed prior to discharging any subject from the study.
• Concurrent medications
• Adverse events
• Physician assessment
• Physical examination (including DRE)
• Vital signs and heart rate
• Obtain blood samples for hematology, chemistry, cholesterol (total, LDL, HDL and triglyceride), hs-CRP, c-CRP, PSA and T
• Assess drug accountability
• Complete CRF
• Retrieve any study medication

9.2.2 Subject Withdrawal from Study Drug

If the investigational product is permanently discontinued during the course of the study, the subject must be withdrawn from the study and the reason for study drug discontinuation documented in the CRF. Assessments and follow-up will be completed as describe in Section 9.2.1.

10. ADVERSE EVENTS (AE) AND SERIOUS ADVERSE EVENTS (SAE)

The investigator is responsible for the detection and documentation of events meeting the criteria and definition of an AE or SAE as provided in this protocol. During this study, when there is a safety evaluation, the investigator or site staff will be responsible for detecting AEs and SAEs, as detailed in this section of the protocol.

10.1 Definition of an Adverse Event (AE)

An adverse event is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product, whether or not considered causally related to the product.

An undesirable medical condition can be symptoms (e.g. nausea, chest pain), signs (e.g. tachycardia, enlarged liver) or the abnormal results of an investigation (e.g. laboratory findings, electrocardiogram). In clinical studies, an AE can include an undesirable medical condition occurring at any time, including run-in or washout periods, even if no study treatment has been administered.

The pre-defined events as listed below are not required to be reported as either an AE or SAE except when the investigator assesses the event as more severe than expected for the subject’s condition or the event is either life-threatening or fatal.

• Medical or surgical procedure (e.g. endoscopy, appendectomy, etc.); the condition that leads to the procedure is an AE.
• Situations where an untoward medical occurrence did not occur (social and/or convenience admission to hospital).
• Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.
• The disease/disorder being studied, or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the subject’s condition.

10.2 Definition of a Serious Adverse Event (SAE)

A serious adverse event is any untoward medical occurrence that occurs during any study phase that, at any dose:

(a) results in death
(b) is life-threatening

The term ‘life-threatening’ in the definition of ‘serious’ refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

(c) requires hospitalisation or prolongation of existing hospitalisation

In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at a hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physicians’ office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfils any other serious criteria, the event is serious. When in doubt as to whether ‘hospitalization’ occurred or was necessary, the AE should be considered serious.

Hospitalization for elective treatment of a pre-existing condition that did not worsen form baseline is not considered an AE.

(d) results in disability / incapacity, or

The term disability means substantial disruption of a person’s ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza and accidental trauma (e.g. sprained ankle) which may interfere or prevent everyday life functions but do not constitute a substantial disruption.

(e) is a congenital abnormality/birth defect

(f) Medical or scientific judgement should be exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be immediately life threatening or result in death or hospitalization but may jeopardise the subject or may require medical or surgical intervention to prevent one of the outcomes listed in the above definition. These should also be considered serious. Examples of such events are invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependence or drug abuse.
10.2.1 Disease-Related Events or Outcomes Not Qualifying as SAEs

An event which is part of the natural course of the disease under study (i.e., disease progression) does not need to be reported as a serious adverse event. Progression of the subject's neoplasia will be recorded in the clinical assessments in the CRF. Death due to progressive disease is not an SAE. However, if the progression of the underlying disease is greater than that which would normally be expected for the subject, or if the investigator considers that there was a causal relationship between treatment with study medication or protocol design/procedures and the disease progression, then this must be reported as an SAE. Any new primary cancer must be reported as an SAE.

10.3 Lack of Efficacy

“Lack of efficacy” will not be reported as an AE. The signs and symptoms or clinical sequelae resulting from lack of efficacy will be reported if they fulfill the AE or SAE definition (including clarifications).

10.4 Clinical Laboratory Abnormalities and Other Abnormal Assessments as AEs and SAEs

Abnormal laboratory findings or other abnormal assessments that are judged by the investigator as clinically significant (CS) will be recorded as AEs or SAEs if they meet the definition of an AE or SAE. Clinically significant abnormal laboratory findings or other abnormal assessments that are detected during the study or are present at baseline and significantly worsen following the start of the study will be reported as AEs or SAEs. However, clinically significant abnormal findings or other abnormal assessments that are associated with the disease being studied, unless judged by the investigator as more severe than expected for the subject’s condition or that are present or detected at the start of the study and do not worsen, will not be reported as AEs or SAEs.

The investigator will exercise his or her medical and scientific judgment in deciding whether an abnormal laboratory finding or other abnormal assessment is clinically significant.

10.5 Time Period, Frequency and Method of Detecting AEs and SAEs

At each clinic visit throughout the study, subjects receiving the study drug will be queried by the principal investigator or designated study personnel for adverse events. Any AEs or SAEs must be documented in the subject's source medical records and on the appropriate page of the CRF from the time consent is signed until completion of the safety follow-up visit. SAEs will be reported on the SAE case report form from the time consent is signed until the safety follow-up visit is completed. AEs will be reported on the AE case report form from the time of screening until the safety follow-up visit is completed.
10.6 Recording AEs and SAEs

When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation relative to the event. The investigator will then record all relevant information regarding an AE/SAE on the CRF.

The investigator will attempt to establish a diagnosis of the event based on signs, symptoms and/or other clinical information. In such cases, the diagnosis should be documented as the AE/SAE and not the individual signs/symptoms.

10.7 Evaluating AEs and SAEs

10.7.1. Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study. Degree of severity and change in severity will be recorded by means of National Cancer Institute, Common Terminology Criteria for Adverse Events (NCI CTCAE), Version 4.03 June 14, 2010. (26)

If the event is not listed in the NCI CTCAE (v.4.03), the assessment will be based on the investigator’s clinical judgment. The intensity of each AE and SAE recorded in the CRF should be assigned to one of the following categories:

**Mild:** An event that is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities.

**Moderate:** An event that is sufficiently discomforting to interfere with normal everyday activities.

**Severe:** An event that prevents normal everyday activities.

An event that is classified as severe should not be confused with a SAE. Severity is a category utilized for rating the intensity of an event; both AEs and SAEs can be assessed as severe.

10.7.2. Assessment of Causality

The investigator is obligated to assess the relationship between the study drug and the occurrence of each AE/SAE. The investigator will use clinical judgment to determine the relationship. Alternative causes and the temporal relationship of the event to the study drug will be considered and investigated. The investigator will also consult the PM and in the determination of his/her assessment.

10.8 Follow-up of AEs and SAEs
After the initial AE/SAE report, the investigator is required to proactively follow each subject and provide further information to the Sunnybrook Health Sciences Centre (SHSC) Research Ethics Board (REB).

All AEs and SAEs documented at a previous visit/contact and are ongoing, will be reviewed at subsequent visits/contacts.

All AEs and SAEs will be followed until resolution, until the condition stabilizes, until the event is otherwise explained or until the subject is lost to follow-up. Once resolved, the appropriate AE/SAE CRF page(s) will be updated. The investigator will ensure that follow-up includes any supplemental investigations as may be indicated to elucidate the nature and/or causality of the AE or SAE.

New or updated information will be recorded on the originally completed SAE CRF, with all changes signed and dated by the investigator or designate. The updated SAE CRF should be resent to the SHSC REB within the time frames outlined in Section 10.9

10.9 Prompt Reporting of SAEs

All SAEs will be promptly reported to the SHSC REB once the investigator determines that the events meet the protocol definition of an SAE.

10.9.1 Timeframes for Submitting SAE Reports

All initial SAEs will be reported to the SHSC REB using the trial specific Serious Adverse Event Form. If the investigator does not have all information regarding as SAE, he will not wait to receive additional information before notifying the SHSC REB of the event and completing the form.

The investigator will always provide an assessment of causality at the time of the initial report as per NCI CTCAE, Version 4.03: June 14, 2010.

Subjects will be followed until the AE has resolved. In the case of an SAE, the subject will be followed until clinical recovery or until the event is judged to be chronic.

Follow-up of SAE’s will be documented on the SAE Form and submitted to the SHSC REB

The site will be responsible for notifying Health Canada Natural Products Directorate (BGTD) in an expedited manner of any SAE considered unexpected and related to protocol treatment as stated in the Drug Directorate Guideline entitled: “Clinical Safety Data Management: Definitions and Standards for Expedited Reporting”, dated 1995.

10.10 Post-study AEs and SAEs

A post-study AE/SAE is defined as any event that occurs outside of the AE/SAE detection period defined in Section 10.5 of the protocol.
If the investigator learns of any SAE at any time after a subject has been discharged from the study, and such event(s) is (are) reasonably related to the study drug, the investigator should promptly notify the SHSC REB in addition to reporting to Health Canada as required.

11. DATA ANALYSIS AND STATISTICAL CONSIDERATIONS

11.1 Hypothesis

That the administration of capsaicin in men on surveillance for favorable risk prostate cancer OR for men scheduled for RP reduces the expression of Ki-67 and increases expression of p27.

The null hypothesis is that the addition of red yeast rice will not alter expression of these proteins.

11.2 Treatment Comparisons of Interest

11.2.1 Primary Comparison of Interest

• To assess the effect of capsaicin daily therapy on the expression of ki67 and p27 biomarkers in a post-treatment biopsy

11.2.2. Other Comparisons of Interest

• To assess the effect of therapy with repeat oral dosing of CAP two times daily on the PSA kinetics in men on active surveillance for localized prostate cancer
• To assess the effect of therapy with repeat oral dosing of CAP two times daily on grade and the presence of prostatic intraepithelial neoplasia (PIN) in the post-treatment biopsy
• To assess the effect of therapy with repeat oral dosing of CAP two times daily on the expression of high sensitivity C-reactive protein (hs-CRP) and cardiac C-reactive protein (c-CRP) as compared to baseline expression
• To assess the safety and tolerability of CAP therapy in men on active surveillance for prostate cancer

A one-sided T-test will be used for these comparisons of interest.

11.3 Interim Analysis

An interim analysis will be conducted after the first 25 subjects have completed 6 months of trial therapy. An early stopping rule will be implemented on the basis of a futility analysis.

11.4 Sample Size Considerations
For this trial, each patient will serve as their own control. For the primary end point, the expression of Ki67 and p27 will be compared between the baseline pre-treatment prostate biopsy and the on study prostate biopsy.

Earlier studies of p27 expression in prostate cancer suggest that approximately 20% of untreated prostate cancers express p27. The study will have an 80% power with alpha 0.05 to detect a difference in strong (4/4) p27 expression between pre-treatment and post-treated tissues of > 20% (i.e., a 100% relative increase, from 20 to 40%, in the rate of p27 expression).

It is expected that 50 subjects will be recruited over a 1 year period by one site.

11.5 Analysis Populations

The primary population of subjects to be used for statistical analysis will be the ‘intent to treat’ (ITT) population which will consist of all subjects who received at least one dose of study treatment.

11.6 General Considerations for Data Analysis

All available data for subjects who prematurely discontinue the study will be included in all analyses. For purposes of data analyses, the baseline value of a particular type of assessment for a given subject will be defined as the latest assessment prior to initiation of the study. Change from baseline for each subject will be computed as post-baseline value – baseline value.

11.7 Efficacy Analysis

11.7.1 Primary Analysis

The analysis of the primary endpoint will be done using the one-sided T-test to determine if treatment with CAP significantly alters the expression of ki67 and p27 biomarkers between the pre-treatment biopsy and post-treatment prostate biopsy/prostate specimen.

11.7.2 Secondary Analysis

The analysis of the secondary endpoints will be done using the one-sided T test to determine if treatment with CAP:

- significantly affects the PSA doubling time (< 12 months or ≥ 12 months at baseline) at the end of therapy
- significantly affects the grade and presence of prostatic intraepithelial neoplasia (PIN) in post treatment biopsy
- significantly affects the expression of high sensitivity C-reactive protein (hs-CRP) and cardiac C-reactive protein (c-CRP) in post treatment serum
11.8 Safety Analyses

11.8.1 Extent of Exposure

Study drug exposure in days will be calculated for each subject as treatment stop date minus treatment start date plus one. Study drug compliance between visits and cumulative study drug compliance will be calculated by dividing the number of study drug capsules used by the total number of study drug capsules prescribed and multiplying the result by 100. Study drug compliance between visits and cumulative study drug compliance will be summarized.

11.8.2 Adverse Events

Adverse events will be coded using the MedDRA coding dictionary. The frequency of events, the frequency of subjects and the percentage of subjects reporting each AE will be summarized by treatment group for all AEs and separately for drug-related AEs. The proportion of subjects reporting at least one AE, at least one drug-related AE, at least one SAE and at least one AE leading to withdrawal will be computed.

The most common AEs are defined as those occurring in at least 5% of the subjects.

Subgroup analyses to assess the effect of age and race on the incidence of AEs will be conducted.

11.8.3 Hematology, Clinical Chemistry and Cholesterol Evaluations

For purposes of statistical analyses the latest laboratory test value prior to the start of the study treatment will be used as the baseline value. Only those laboratory tests with a numeric normal range value and at least one post baseline value will be analyzed statistically.

A laboratory value that is on or within the normal range is considered normal. A laboratory value that is outside the testing laboratory’s normal range is considered an abnormal value. A laboratory value that is above the upper limit of the normal range is considered high abnormal. A laboratory value that is below the lower limit of the normal range is considered low abnormal.

To describe the laboratory values at baseline, the frequency of subjects with an abnormal laboratory value at baseline among subjects with a baseline laboratory value and a post baseline laboratory value will be computed. Among subjects with a normal value at baseline, the frequency of abnormal values, high abnormal values and low abnormal values at any post baseline evaluation will be computed. Among subjects with a normal or low abnormal value at baseline, the frequency of high abnormal values at any post
baseline evaluation will be computed. Among subjects with a normal or high abnormal value at baseline, the frequency of low abnormal values at any post baseline evaluation will be computed.

Differences in laboratory values between baseline and the final scheduled laboratory assessment will be calculated for each laboratory test and summarized.

11.8.4 Serum PSA

Total PSA, change from baseline total PSA and percentage change from baseline total PSA will be summarized using both the last observation carried forward and observed cases approaches at each scheduled post-baseline assessment. Change from baseline total PSA will be compared at each scheduled post-baseline assessment using a GLMM with effects for treatment and baseline total PSA. Statistical analysis of the change from baseline total PSA will be performed using the Student’s exact T-test.

11.8.5 Testosterone

Total T, change from baseline total T and percentage change from baseline total T will be summarized using both the last observation carried forward and observed cases approaches at each scheduled post-baseline assessment.

12.0 STUDY ADMINISTRATION

12.1 Regulatory and Ethical Considerations

12.1.1. Regulatory Authority Approval

The investigator will obtain approval to conduct the study from Health Canada Therapeutic Product Directorate.

12.1.2 Ethical Conduct of the Study and Ethics Approval

This study will be conducted in accordance with ‘good clinical practice’ (GCP) and all applicable regulatory requirements, including where applicable, the 1996 version of the Declaration of Helsinki.

The protocol, the site’s informed consent form and any other information that will be present to potential subjects will be reviewed and approved by the SHSC REB. The investigator agrees to allow the SHSC REB direct access to all relevant regulatory documents and any relevant document(s)/data that are needed for ethical review and approval of the study. Before investigational product and CRFs can be utilized at the site, the investigator will obtain SHSC REB approval of the protocol and approved informed consent form and any other information that the SHSC REB has deemed necessary. Subsequently, the investigator will also obtain SHSC REB approval for any amendments to the protocol or any other documentation before implementation.
Copies of all SHSC REB approvals and correspondence will be filed in the investigator study binders.

12.1.3 Informed Consent

Informed consent will be obtained before the subject can participate in the study. The contents and process of obtaining informed consent will be in accordance with all applicable regulatory requirements.

12.1.4 Investigator Reporting Requirements

The investigator is responsible for reporting SAEs to the SHSC REB and Health Canada in accordance with all applicable regulations. Furthermore, the investigator may be required to provide periodic safety updates on the conduct of the study at his site and notification of study closure to the SHSC REB.

12.2 Study Monitoring

As this is an investigator initiated protocol, no study monitoring will be performed. Site personnel will ensure that:

- Identify any issues and address their resolution
- Data are authentic, accurate and complete
- Safety and rights of subjects are being protected
- Study is conducted in accordance with the currently approved protocol (and any amendments), GCP and all applicable regulatory requirements

12.3 Quality Assurance

Regulatory agencies may conduct a regulatory inspection of the study. Such audits/inspections can occur at any time during or after completion of the study. If an audit or inspection occurs, the investigator and institution agree to allow the auditor/inspector direct access to all relevant documents and to allocate his time and the time of his staff to the auditory/inspector to discuss findings and any relevant issues.

12.4 Study and Site Closure

Upon completion of the study, the investigator will conduct the following activities:

- Data queries
- Accountability, reconciliation and arrangements for unused investigational product
- Review of site study records for completeness

If the study is prematurely discontinued, the investigator has the responsibility to destroy any used/unused clinical supplies as per site destruction policies.
Financial compensation to investigators and/or institutions will be in accordance with the agreement established between the investigator.

12.5 Records Retention

Following closure of the study, the investigator must maintain all site study records in a safe and secure location. The records must be maintained to allow easy and timely retrieval when needed and whenever feasible, to allow any subsequent review of data in conjunction with assessment of the facility, supporting systems and staff.

The minimum retention time will meet the strictest standard applicable to that site for the study as dictated by any institutional requirements or local laws or regulations; otherwise, the retention period will default to 25 years.

12.6 Provision of Study Results and Information to Investigators

When a clinical study report is completed, the investigator will provide the major findings of the study to Dr. Laurence Klotz.

12.7 Data Management

Subject data are collected by the investigator or designee using the CRF. Subject data necessary for analysis and reporting will be entered/transmitted into a database. Clinical data management will be performed in accordance with applicable standards and data cleaning procedures. Database freeze will occur when data management quality control procedures are completed.

12.8 Independent Data Monitoring Committee

This investigator-initiated trial will not have an independent data monitoring committee.
REFERENCES