A Phase II Randomized Controlled Trial of a Supplement Containing Quercetin, Bromelain, Rye Flower Pollen, and Papain on Reducing the Severity of Radiation-Induced Prostatitis

HCI# 129154

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LIST OF ABBREVIATIONS

Abbreviation or Term[1]	Definition/Explanation
AE	Adverse event
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
ANOVA	Analysis of variance
APTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
AV	Atrioventricular
β-HCG	Beta-human chorionic gonadotropin
BID	Twice daily
BLQ	Below limit of quantification
BMI	Body mass index
BP	Blood pressure
BUN	Blood urea nitrogen
Ca^{++}	Calcium
CBC	Complete blood count
CFR	Code of Federal Regulations
CHF	Congestive heart failure
CI	Confidence interval
Cl-	Chloride
CL_{cr}	Creatinine clearance
C_{max}	Maximum observed concentration
C_{min}	Trough observed concentration
CNS	Central nervous system
CR	Complete response
CRF	Case report form
CT	Computed tomography
CTCAE	Common Toxicity Criteria for Adverse Events
CV	Coefficient of variation
CYP	Cytochrome P450
D/C	Discontinue

Abbreviation or Term[1]	Definition/Explanation
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
DLT	Dose Limiting Toxicity
ECG	Electrocardiogram
Eg	Exempli Gratia (for example)
FACS	Fluorescence-Activated Cell Sorting
FDA	Food and Drug Administration
FDG-PET	Fluorodeoxyglucose (FDG)-positron emission tomography (PET)
GCP	Good Clinical Practice
GFR	Glomerular filtration rate
GGT	Gamma-glutamyltransferase
GLP	Good laboratory practice
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCO_3^-	Bicarbonate
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HR	Heart rate
hr	Hour or hours
IC_{50}	Half maximal inhibitory concentration
i.e.	Id est (that is)
IEC	Independent ethics committee
IND	Investigational New Drug
INR	International normalized ratio
IRB	Institutional review board
IU	International unit
IV	Intravenous, intravenously
LDH	Lactate dehydrogenase
LLQ	The lower limit of quantitation
MedDRA	Medical Dictionary for Drug Regulatory Activities
MID	minimal important difference

Abbreviation or Term[1]	Definition/Explanation
MRI	Magnetic resonance imaging
MRSD	The maximum recommended starting dose
MTD	Maximum tolerated dose
NOAEL	No-observed-adverse-effect level
NOEL	No-observed-effect-level
PCORI	the Patient-Centered Outcomes Research Institute
PD	Pharmacodynamic(s)
PFS	Progression-Free Survival
PK	Pharmacokinetic(s)
PRO	Patient Reported Outcome
PO	Per os (administered by mouth)
PR	Partial response
PT	Prothrombin time
PTT	Partial thromboplastin time
QC	Quality control
RBC	Red blood cell
QD	Once-daily
QOL	Quality of Life
QTc	QT interval corrected
QTcF	QT interval corrected using Fredericia equation
SAE	Serious adverse event
SD	Standard deviation or stable disease
$T_{1/2}$	Terminal elimination half-life
T_3	Triiodothyronine
T_4	Thyroxine
T_{max}	Time of maximum observed concentration
TID	Three times daily
TSH	Thyroid-stimulating hormone
ULN	The upper limit of normal
ULQ	The upper limit of quantitation
UV	Ultraviolet

Abbreviation or Term[1]	Definition/Explanation
WBC	White blood cell
WOCBP	Women of childbearing potential
WONCBP	Women of nonchildbearing potential

[1] All of these abbreviations may or may not be used in the protocol.

PROTOCOL SIGNATURE

I confirm that I have read this protocol, and I will conduct the study as outlined herein and according to the ethical principles stated in the latest version of the Declaration of Helsinki, the applicable ICH guidelines for good clinical practice, and the applicable laws and regulations of the federal government. I will promptly submit the protocol to the IRB for review and approval. Once the protocol has been approved by the IRB, I understand that any modifications made during the course of the study must first be approved by the IRB prior to implementation except when such modification is made to remove an immediate hazard to the subject.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this study. I will discuss this material with them to ensure that they are fully informed regarding the study treatment, the conduct of the study, and the obligations of confidentiality.

Note: This document is signed electronically through submission and approval by the Principal Investigator in the University of Utah IRB Electronic Research Integrity and Compliance Administration (ERICA) system.

STUDY SUMMARY

Title	A Phase II Randomized Controlled Trial of a Supplement Containing Quercetin, Bromelain, Rye Flower Pollen, and Papain on Reducing the Severity of Radiation-Induced Prostatitis
Short Title	Q-Urol
Protocol Identifiers (IRB – internal)	129154
Phase	Phase II
Design	An asymmetric two-sided group sequential design will be used with an interim analysis for efficacy and futility.
Study Duration	Up to three years.
Study Center(s)	Huntsman Cancer Institute
Objectives	**Primary Objective:** To assess the difference in prostatitis symptoms in men with localized prostate cancer following brachytherapy taking Q-Urol relative to placebo. **Secondary Objectives:** • To assess Health-Related Quality of Life (HRQOL) in the urologic, rectal, sexual, hormonal, mental and overall physical domains of men receiving either placebo or supplement after definitive brachytherapy. • To assess if the Q-Urol has any significant impact on serum biomarkers of inflammation relative to placebo. • To access if the addition of Q-Urol introduces any additional toxicity relative to placebo.
Number of Subjects	Up to 140, 70 per arm.
Diagnosis and Main Eligibility Criteria	**Key Inclusion Criteria:** • Male subjects aged ≥ 18 years. • Histologically proven prostate adenocarcinoma who have selected treatment with brachytherapy with or without external beam radiation, with or without androgen deprivation therapy. • Fluent in speaking and reading English. • ECOG Performance Status ≤ 1 **Key Exclusion Criteria:** • Baseline AUA symptom scores > 15.

	• Prior diagnosis of chronic prostatitis type II-IV. • The subject has received systemic therapy intended for the treatment of prostatitis (including herbal supplements) ≤ 14 days of starting study treatment. • The subject has received a fluoroquinolone antibiotic (e.g. ciprofloxacin, norfloxacin, ofloxacin levofloxacin, etc.) ≤ 3 days of starting study treatment. • The subject is actively on anti-inflammatory medications for other medical conditions, unless approved by PI. • The subject has undergone transurethral resection of the prostate (TURP).
Study Product, Dose, Route, Regimen	Q-Urol (proprietary blend 375 mg plus 37.5 mg calcium) two capsules taken twice daily.
Duration of administration	Six weeks after brachytherapy placement.
Reference therapy	Standard of care supportive therapy after brachytherapy placement.
Statistical Methodology	There are two planned analyses of the primary endpoint variable, an interim analysis at N1 = 21 patients per groups and a final analysis at N = 70 patients per group. Two sample *t*-tests will be used for both the analysis. A single interim analysis is planned after N1= 21 subjects per group have outcome data. The interim and final analysis will compare the treatment and control means using nominal *t* statistics (control minus treatment). If the *t* statistic has a value less than -1.16 at the interim analysis the trial will be terminated for futility. If the *t* statistic has a value greater than 2.85 at the interim analysis the trial will be terminated for efficacy. If the study is not terminated for efficacy or futility at the interim analysis an additional N2 = 49 patients per group will be accrued for a total of N = 70 patients per group. If the interim analysis is done at the planned sample size (21 patients per group) the treatment will be deemed efficacious at the final analysis if the *t* statistic has a nominal value greater than 1.67. In addition to formal testing for a difference between groups, the mean change between groups and the mean change within each group together will be reported together with 95% confidence intervals.

SCHEMA

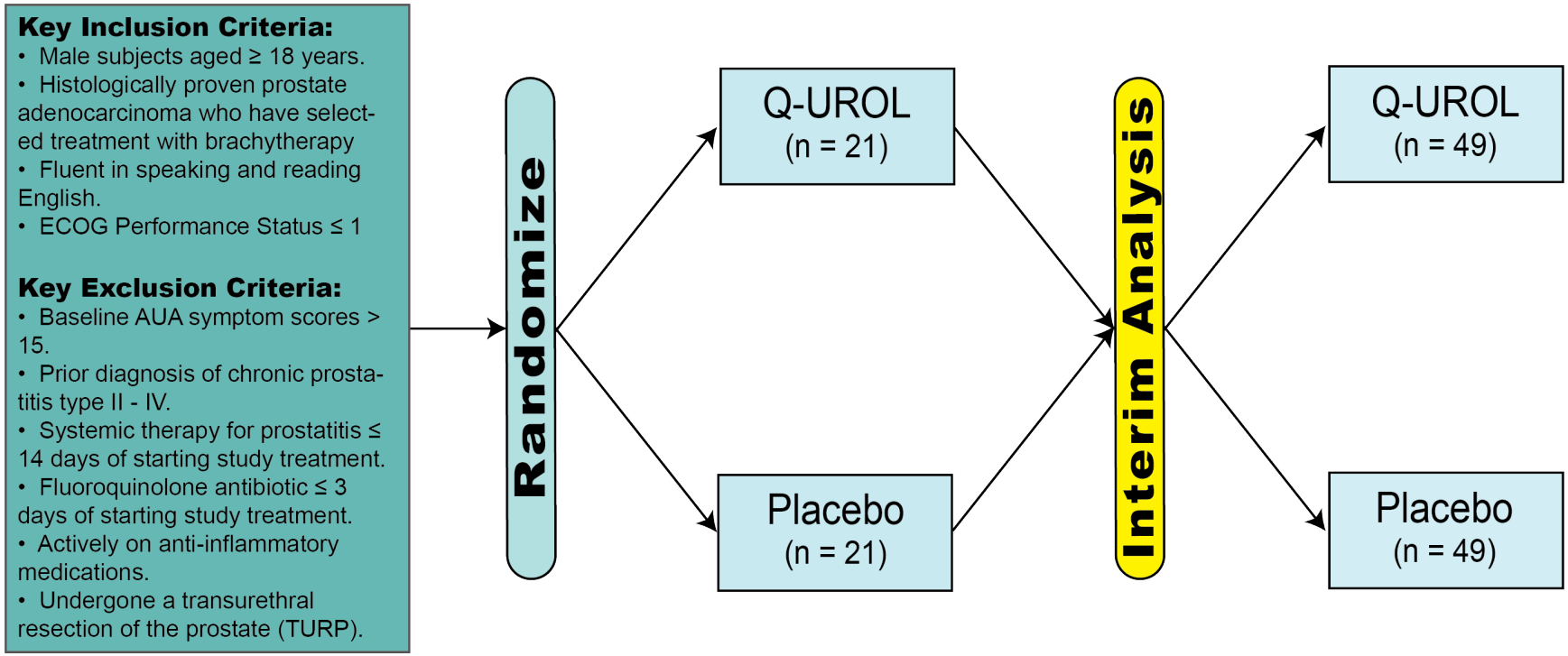

Figure 1 : Study Schema

1 OBJECTIVES

1.1 Primary Objective

1.1.1 To assess the difference in prostatitis symptoms in men with localized prostate cancer following brachytherapy taking Q-Urol relative to placebo.

Primary Endpoint: The mean peak score of the National Institutes of Health-Chronic Prostatitis Symptom Index (NIH-CPSI) measured at six weeks post brachytherapy.

1.2 Secondary Objective(s)

1.2.1 To assess Health-Related Quality of Life (HRQOL) in the urologic, rectal, sexual, hormonal, mental and overall physical domains of men receiving either placebo or supplement after definitive brachytherapy.

Secondary Endpoint: Patient questionnaires administered pre- and post-study therapy: The Expanded Prostate Cancer Index Composite (EPIC), The International Prostate Symptom Score (I-PSS), The Rectal Function Assessment Score (R-FAS), and the Sexual Health Inventory for Men (SHIM).

1.2.2 To assess if the Q-Urol has any significant impact on serum biomarkers of inflammation relative to placebo.

Secondary Endpoint: Inflammation markers pre and post brachytherapy: erythrocyte sedimentation rate, C-reactive protein, and prostate-specific antigen (PSA)

1.2.3 To access if the addition of Q-Urol introduces any additional toxicity relative to placebo.

Secondary Endpoint: Frequency of adverse events (AEs) will be collected and characterized by type, severity (as defined by CTCAE, version 5.0), seriousness, duration, and relationship to study treatment.

1.2.4 To assess the effect on prostatitis-related pain in men with localized prostate cancer following brachytherapy taking Q-Urol relative to placebo.

Secondary Endpoint: The number of days during the 28 days post-brachytherapy that any medication is taken for the treatment of prostate-related pain.

2 BACKGROUND

2.1 Prostate Cancer and Brachytherapy Induced Prostatitis

Prostate cancer is the most commonly diagnosed cancer in men with an estimated 174,650 new cases and 31,620 deaths projected in 2019.[1] At diagnosis, approximately 85% of men

will have disease localized to the prostate, and most will elect to have either surgical therapy or radiation treatment with curative intent.

Brachytherapy (seed implant), either alone or combined with external beam radiation therapy, is an established care standard for localized prostate cancer. The physical trauma of the procedure and the continuing exposure of the prostate tissue, neurovascular bundles, bladder neck, and anterior rectal wall over the ensuing 3-6 months to radiation and its effects results in an inflammatory state with symptoms identical to chronic prostatitis type IIIA or IIIB. Virtually 100% of subjects will experience these uncomfortable symptoms, with severity typically peaking around weeks 4-6 post-implant, before gradually improving over the ensuing 6-12 months. Like chronic prostatitis, the mainstay of comfort therapy for these subjects is the use of alpha-blockers, NSAIDs, steroids, anticholinergics, antidiarrheals, and phosphodiesterase inhibitors.

Prostatitis symptoms can result in significant distress, pain, nocturia related-fatigue, loss of work and productivity. Improving the side-effect profile of brachytherapy without adding a significant risk of other toxicities or a decrease in oncologic efficacy is highly desirable.

2.2 Rationale for Q-Urol

Q-Urol is a commercially available supplement whose key active ingredient is Quercetin.

Quercetin has been shown to have the following biological properties:

- A potent free radical scavenger[2] and antioxidant.[3]
- An anti-inflammatory agent, which reduces inflammation by inhibiting interleukin-6, interleukin 8, tumor necrosis factor, and NF-κB.[4-7]
- In animal models of inflammatory pain, quercetin reduced pain, oxidative stress, and cytokine production.[8]
- Patients with chronic prostatitis who report improvement with quercetin have a reduction in the oxidative stress metabolite F2-isoprostane in their expressed prostatic secretions (EPS). [9]
- Quercetin therapy reduces inflammation as measured by prostaglandin E2 levels in EPS, and increases the levels of prostatic β-endorphins.[10]
- Side effects with quercetin therapy are rare.[11]

We propose that the use of Q-Urol will be an effective therapy at reducing symptom burden and distress following prostate brachytherapy procedures due to radiation-induced prostatitis versus a comparator cohort receiving placebo without adding additional toxicity.

2.3 Clinical Experience

In a prospective, randomized, double-blind, placebo-controlled trial of the bioflavinoid quercetin in men with chronic prostatitis, 20% percent of patients taking a placebo and 67% of patients taking the bioflavonoid had an improvement of symptoms of at least 25% as measured by the NIH chronic prostatitis symptom score. In an unblinded open-label follow up study, 82% of patients who received a formulation of quercetin, bromelain, papain and

zinc (Prosta-Q, Farr labs) had at least a 25% improvement in symptom score[9]. The treatment was well tolerated. Out of 30 patients enrolled on the trial, the only adverse events reported were:

- One patient taking placebo developed a rash that resolved when he stopped taking the capsules.
- One patient taking quercetin developed a headache after the first few doses, which resolved
- One patient taking quercetin noted mild tingling of the extremities after each dose. All these side effects resolved after cessation of therapy.

2.4 **Effect of Antioxidants on Radiation efficacy**

The primary mechanism of antitumor activity from radiation therapy is via the production of chemical radicals perturbing DNA in cancer cells resulting in tumor cell death. Some of the supplements being evaluated in this trial have antioxidant properties, and therefore one could hypothesize that they could produce antitumor activity. In the most exhaustive meta-analysis on the effect of antioxidant use with either chemotherapy or radiotherapy, 49 randomized trials were identified that specifically addressed this concern.[12] The authors determined the following:

" In 17 articles of 49 (approximately 35%) included in this study, effects on patient survival or clinical response during chemotherapy and/or radiotherapy were described. In 7 of 17 RCTs using melatonin supplementation, 4 reported a significantly increased survival rate and 4 reported a significantly increased tumor regression rate. In addition, 1 trial each using vitamin A and multiple vitamins reported a significantly increased survival rate. On the other hand, 2 trials using multiple vitamins reported that there were no significant differences between supplementation and control groups, although the survival rates of the supplementation groups were slightly lower than those of the control groups. Two trials using vitamin E reported that there was no significant difference in clinical response between groups. Also, the RCT using ellagic acid reported that there were no significant differences between groups in survival rate and clinical response. Similarly, a trial using l-arginine supplementation reported a significant increase in the pathological response. On the other hand, a trial using combination supplement (vitamins C and E and selenium) reported that there was no significant difference in clinical response."

With regard to toxicity, the same authors determined:

"In total, 19 radiotoxicity prevention trials were investigated, which specifically aimed to reduce toxicities affecting the mucosa, skin, salivary glands, and taste. Four of 19 trials reported no significant differences in toxicity between groups. Antioxidant supplements such as vitamin E, multivitamin combination, polyphenol, and zinc were effective in preventing radiation-induced toxicities in the skin, mucosa, and salivary glands."

Patients currently undergoing radiation therapies for prostate cancer at the Huntsman Cancer Institute at the University of Utah are not currently counselled to stop antioxidants or supplements, but asked about supplementation use. There is also no recommendation by the NCCN or any other prostate cancer treatment guideline that suggests antioxidants, phytochemicals, minerals or other supplements should be discontinued. Given the

overwhelming amount of evidence from the randomized controlled trials in the contemporary Yasueda meta-analysis, and the current care standard of allowing antioxidant therapies during prostate cancer radiation therapy, the use of antioxidants and phytochemicals used in this study is considered safe by the best evidence available.

2.5 Rationale of definition of ½ standard deviation of the mean for clinically significant difference on the Patient-Reported Outcomes Measures:

A ½ standard deviation from the mean at the baseline for each PRO-QOL measure or domain was specified as the minimal clinically important difference (MID), to be consistent with established convention and other PCa PRO-QOL outcome studies.[13-17] Specifically, a ½ standard deviation was defined as the MID on the landmark ProtecT randomized trial which randomized approximately 1800 men to radiation therapy, versus surgery, versus active surveillance using the same PRO forms (EPIC) used in this study. Utilizing this convention will allow the investigators to compare their outcomes not only against the cohorts in this study, but to historical cohorts such as those in ProtecT, as well as studies funded by the Patient-Centered Outcomes Research Institute (PCORI) evaluating QOL in prostate cancer patients receiving radiation therapy.[18, 19]

3 DRUG INFORMATION

3.1 Q-Urol

Q-Urol is an over-the-counter herbal supplement manufactured by Farr Laboratories claiming to have anti-inflammatory effects. It is a combination product composed of quercetin, pollen extract, bromelain, and papain.

3.1.1 Pharmacology

Quercetin is a bioflavonoid found in plants such as onions, berries, green tea, and apples that has antioxidant and anti-inflammatory effects. It is thought to exert its anti-inflammatory effects through mast cell stabilization leading to the inhibition of prostaglandin D_2 formation and the inhibition of the release of histamine, interleukin-8, and TNF.

Rye Flower pollen extract comes from the pollen of rye grass and is often marketed under the name Cernilton. It is been used by men worldwide for the treatment of benign prostatic hyperplasia. Randomized controlled trials have demonstrated some moderate efficacy in the improvement of urological symptoms.[20, 21] While the mechanism of action is not well understood, it is thought that the efficacy is related to anti-androgenic effects. Rye flower pollen may also act on α-adrenergic receptors to relax the sphincter muscles or by increasing bladder contraction by relaxing urethral smooth muscle tone. Bromelain is a mixture of enzymes found in the fruit and stem of the pineapple plant. Only a small amount of research has been done with bromelain in nasal swelling, inflammation, and the removal of dead skin after burns. Evidence does support its efficacy for relieving acute nasal and sinus inflammation symptoms when used in combination with standard of care medications.[22] It is thought to exert its anti-

inflammatory action by reducing leukocyte migration and through inhibition of COX2 expression.[23, 24] However, those sensitive or allergic to pineapples should not take bromelain.

Papain is a protease isolated from papaya that mediates the hydrolysis of proteins. It is a common ingredient in many products, including toothpaste, contact lens cleaners, meat tenderizers, and meat products However, little research has been done to fully assess its efficacy as an anti-inflammatory. Caution should be taken when used concurrently with warfarin.

3.1.2 Clinical Safety

In a prospective, placebo-controlled, randomized trial, 30 patients with category III chronic prostatitis were randomized to receive quercetin/placebo in a 1:1 ratio. [9] Prosta-Q was then administered for 17 additional patients after completion of the randomized portion of the trial. Of the 15 patients randomized to receive quercetin, one experienced a headache after the first few doses and another patient noted mild tingling in the extremities after each dose. Both adverse events resolved on their own upon discontinuation of study therapy.

The group randomized to receive quercetin reported a 35% improvement in the mean NIH symptom score vs. 7.2% reported by the placebo group. However, the 17 patients treated with Prosta-Q reported a mean improvement of 44%.

139 men were treated in a prospective, placebo-controlled, randomized trial of pollen extract in patients with inflammatory chronic prostatitis and chronic pelvic pain syndrome. After 12 weeks of therapy, response (defined as a decrease of the NIH-CPSI total score by at least 25% or at least 6 points) was seen in the pollen extract versus placebo group in 70.6% and 50.0% (p=0.0141). The pollen was well tolerated; two patients reported mild gastrointestinal disorders that caused a short treatment interruption and moderate pain (not otherwise specified) that caused discontinuation of treatment.

4 STUDY DESIGN

4.1 Description

This is a Phase 2, double-blinded, placebo-controlled trial assessing the safety of Q-Urol use after brachytherapy placement in patients with localized prostate cancer. Patients will be randomized in a 1:1 ratio to receive Q-Urol/Placebo twice daily for six weeks after brachytherapy placement. Questionnaires will be administered pre- and post-treatment to assess the change in prostatitis symptoms and quality of life measures. The mean values between groups will be compared.

Once 42 patients (21 to each arm) have been enrolled and treated on the study therapy, enrollment will be placed on hold and an interim analysis conducted. The interim analysis will be conducted for futility and efficacy and will be reviewed by the DSMC. If the analysis is favorable, as defined in the Statistical Analysis section, the trial will open to the enrollment of 98 additional subjects, 49 per arm. However, if the analysis does not demonstrate standards defined in the statistical analysis, the trial will be closed to accrual.

Safety monitoring will be overseen by the DSMC at HCI. See Section 12.4 for safety monitoring plan and early stopping rules.

4.2 Randomization and Blinding

Patients who meet all criteria for enrollment will be randomly assigned to receive Q-Urol (Arm 1) or placebo (Arm 2). Patients will be randomized through the OnCore system in a 1:1 ratio to Arm 1 or Arm 2 and stratified by dose level of brachytherapy used.

To preserve the blind, only the Investigational Drug Services Pharmacy personnel and Data Safety Monitoring Committee (DSMC) at Huntsman Cancer Institute will know treatment assignments. Access to unblinded data/documents will be controlled by the pharmacy to ensure the blind is maintained. Every effort will be made to blind the patient, the investigator, and the study team to the treatment assignment, but the inadvertent unblinding of a patient may occur. If an investigator, site personnel, or patient is inadvertently unblinded, the unblinding will not be sufficient cause for the patient to be discontinued from study treatment or excluded from study analyses. Cases of accidental unblinding will be recorded in the applicable eCRF and evaluated by the DSMC for appropriateness of inclusion in the study analysis.

In the case of an emergency, the treating investigator has the sole responsibility for determining if unblinding of a patient's treatment assignment is warranted. Patient safety must always be the first consideration in making such a determination. If the treating investigator decides that unblinding is warranted, the investigator should contact the investigational pharmacy for treatment assignment.

4.3 Number of Patients

The trial will enroll up to 70 patients to each arm, 140 patients total.

4.4 Number of Study Centers

This will be a single-center trial run at the Huntsman Cancer Institute at the University of Utah.

4.5 Study Duration

The study is projected to last for 3 years from the first patient on to the last patient end of treatment visit.

5 ELIGIBILITY CRITERIA

This eligibility checklist is used to determine patient eligibility and filed with the enrolling investigator's signature in the patient research chart.

Patient No. _____

Patient's Initials: (L,F,M) _____

5.1 Inclusion Criteria

Yes/No (Response of "no" = patient ineligible)

5.1.1 _____ Male subjects aged ≥ 18 years.

5.1.2 _____ Men with histologically proven localized prostate adenocarcinoma, stage I – III (as defined by AJCC 8th edition), who have selected treatment with brachytherapy with or without external beam radiation, with or without androgen deprivation therapy.

5.1.3 _____ Fluent in speaking and reading English.

5.1.4 _____ ECOG Performance Status ≤ 1.

5.1.5 _____ Adequate organ function as defined as:

- **Hepatic:**
  - Total Bilirubin ≤ 1.5x institutional upper limit of normal (ULN)
  - AST(SGOT)/ALT(SGPT) ≤ 3 × institutional ULN
- **Renal:**
  - Estimated creatinine clearance ≥ 30 mL/min by Cockcroft-Gault formula:
    - Males: $\frac{(140-age)\times weight[kg]}{serum\ creatinine\left[\frac{mg}{dL}\right]\times 72}$

5.1.6 _____ Highly effective contraception for both male subjects and their female partners of childbearing potential throughout the study and at least 5 days after last study treatment administration if the risk of conception exists.

5.1.7 _____ Median life expectancy ≥ 5 years as calculated by the Lee and Shonberg Index (https://eprognosis.ucsf.edu/leeschonberg.php)

5.1.8 _____ Able to provide informed consent and willing to sign an approved consent form that conforms to federal and institutional guidelines.

5.2 Exclusion Criteria

Yes/No (Response of "yes" = patient ineligible)

5.2.1 _____ Baseline AUA symptom scores > 15.

5.2.2 _____ Prior diagnosis of chronic prostatitis type II through IV.

5.2.3 _____ Subject has received systemic therapy intended for the treatment of prostatitis (including herbal supplements) ≤ 14 days of starting study treatment.

5.2.4 _____ Subject has received a fluoroquinolone antibiotic (e.g. ciprofloxacin, norfloxacin, ofloxacin levofloxacin, etc.) ≤ 3 days of starting study treatment.

5.2.5 _____ Subject is actively on anti-inflammatory medications for other medical conditions, unless approved by PI.

5.2.6 _____ Subject has undergone transurethral resection of the prostate (TURP).

5.2.7 _____ Patients with a prior or concurrent malignancy whose natural history or treatment has the potential to interfere with the safety or efficacy assessment of the investigational regimen.

5.2.8 _____ History of irritable bowel syndrome, chronic fatigue syndrome, fibromyalgia, and interstitial cystitis-bladder pain syndrome (IC/BPS).

5.2.9 _____ History of symptomatic hypotension, falls, or syncope

5.2.10 _____ Chronic hypoglycemia requiring hospitalization.

5.2.11 _____ Actively abusing alcohol or drugs

5.2.12 _____ The subject has uncontrolled, significant intercurrent, or recent illness including, but not limited to, the following conditions:

- Congestive heart failure
- Diabetes
- Pulmonary artery hypertension
- Any clinically significant condition that requires therapy with diuretic medications for any indication other than the management of hypertension.
- Other clinically significant disorders that would, in the opinion of the treating investigator, preclude safe study participation.

5.2.13 _____ Known prior severe hypersensitivity to investigational product or any component in its formulations (NCI CTCAE v5.0 Grade ≥ 3).

5.2.14 _____ Known allergy to pineapple or pineapple containing products.

5.2.15 _____ Subjects taking prohibited medications as described in Section 7.3 A washout period of prohibited medications for a period of at least 5 half-lives or as clinically indicated should occur prior to the start of treatment.

I certify that this patient meets all inclusion and exclusion criteria for enrollment onto this study.

Investigator Signature	**Date**	**Time**

5.3 Recruitment Strategies

Potential patients will be identified by Investigators in the setting of their outpatient clinics.

6 STRATIFICATION FACTORS

Patients will be stratified by prior use of alpha-blockers for prostate related condition (yes, no) and the dose of brachytherapy: high dose rate (HDR) or low dose rate (LDR).

7 TREATMENT PLAN

7.1 Administration Schedule

Patients will undergo Low Dose Radiation (LDR) brachytherapy with or without External Beam Radiation Therapy (EBRT) or High Dose Radiation (HDR) brachytherapy with EBRT. When LDR is used as monotherapy the isotope will be PD-103 prescribed at 125 Gy, when used as a combined modality with EBRT, the LDR brachytherapy will precede the EBRT, the isotope used will be PD 103 prescribed at 100Gy. HDR monotherapy will not be performed. The HDR + EBRT regimen will be a single fraction of Iridium-192 prescribed at 15Gy and will precede the EBRT. When EBRT is combined with LDR or HDR, the EBRT will only occur after the completion of the study drug regimen and toxicity evaluations for the primary endpoints.

On the day of but after brachytherapy, patients will self-administer two Q-Urol or placebo capsules by mouth with food twice daily. Doses should be taken at about the same time every day (± 4 hours) and recorded on the patient's dosing diary. Doses missed outside of the dosing window should not be made up but rather patients should be instructed to take their next dose at their regularly scheduled time.

7.2 Q-Urol and Identical Placebo

7.2.1 How Supplied, Stored, Packaged, and Labeled

Q-Urol will be provided by Farr Laboratories. Q-Urol will be provided as 375 mg proprietary blend and 37.5 mg calcium capsules for oral administration. They should be stored at room temperature, away from heat, moisture, and direct light.

Placebo capsules, which do not contain the active ingredients of Q-Urol, will be compounded by the Investigational Drug Services Pharmacy at Huntsman Cancer Institute and will be identical in appearance to Q-Urol.

The Investigator, or an approved representative, will ensure that all investigational products are stored in a secured area with controlled access under required storage conditions and in accordance with applicable regulatory requirements.

According to Farr labs, the Q-Urol is manufactured in laboratories with Current Good Manufacturing Practice regulations enforced by the FDA. In addition, Farr Laboratories ensures consistency and purity via the following measures:

- Ensures that the Certificates of Analysis (CofA's) are in compliance with the United States Pharmacopeia (USP) standards on Identification and Purity Controls
- Monitor manufacturing and quality control product documentation
- Conduct laboratory testing on Finished products for Microbio, Heavy Metals, and Residual Solvents

7.2.2 Preparation and Administration

Subjects will be provided enough Q-Urol/placebo for a full six weeks of treatment at the time of brachytherapy. Subjects will be instructed to self-administer the medication at home orally twice daily (every 12 hours ± 4 hours) with food. Subjects should begin dosing the evening after brachytherapy placement. Subjects should not take extra medication for any reason nor should they re-administer in the case of vomiting after administration. If a dose is missed outside of the dosing window, the dose should not be made up.

7.2.3 Accountability and Compliance

Information pertaining to study drug compliance (i.e., date, time, and dose) will be recorded by patients on the drug diary (see Appendix 6) and recorded in the corresponding electronic case report form (eCRF) by the study team. A member of the study team will review patient drug compliance and provide patient re-education as required. Any reason for non-compliance will be documented in the subject's research chart and the corresponding eCRF. At the discretion of the principal investigator, a subject may be discontinued from the trial for non-compliance with study visits or study drug.

Subjects will be required to return any unused medication or empty bottles at the end of study therapy. Excess or unused study drug should be returned to the investigative site for accounting and destroyed in accordance with GCP after drug accountability has been performed. The total number of capsules dispensed, returned, and documented as taken will be reconciled to support drug accountability. Treatment compliance will be calculated and recorded for the study drug. It will be recorded as a percentage defined as the number of doses taken divided by the expected number of doses taken multiplied by 100%.

7.3 Concomitant Medications and Therapies

Medications specifically prohibited in the exclusion criteria are not allowed during the active treatment period. Concomitant treatment considered necessary for the patient's well-being may be given at the discretion of the treating Investigator.

7.3.1 Allowed Therapy

All supportive measures consistent with optimal patient care may be given throughout the study. Patients should receive appropriate supportive care measures as deemed necessary by the treating Investigator.

7.3.2 Prohibited Therapy

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the active treatment period. Patients are prohibited from receiving the following therapies during the treatment phase of this trial:

- Investigational agents, other than those utilized during study therapy.
- Radiation therapy other than the brachytherapy conducted in conjunction with this study.
- Herbal remedies, other than Q-Urol, defined as any substance derived from a botanical source, not prescribed by the physician that a patient is using without professional medical guidance with the intent of treating prostate specific conditions.
- Cyclosporine
- Digoxin
- Warfarin
- CYP2C8 substrates (e.g., repaglinide, paclitaxel, omeprazole, cisapride)

7.3.3 Allowed therapies to be used with caution and the discretion of the treating physician

- **While on study therapy, the use of anticoagulants should be used with caution.**
- Quercetin may have additive hypoglycemic effects when used with antidiabetic medications; use the combination with caution.
- Quercetin may have varying effects on CYP3A4; substrates of CYP3A4 with a narrow therapeutic index should be used with caution (Appendix 12)
- Quercetin may have additional blood pressure lowering effects when used with anti-hypertensive medications; use the combination with caution
- Quercetin may have inhibitory effects on CYP2C9, CYP2D6, OATP1B1, and P-gp; substrates of these with narrow therapeutic indexes should be used with caution (Appendix 12).

7.4 Duration of Therapy

Each patient will be on study therapy for six weeks starting with the day of brachytherapy.

7.4.1 Criteria for discontinuation of treatment ("off-treatment")

Patients may withdraw from treatment or the study overall at any time at their own request, or they may be withdrawn at the discretion of the Investigator or Sponsor for safety, behavioral reasons, or the inability of the patient to comply with the protocol-required schedule of study visits or procedures. In addition to the drug-specific discontinuation criteria listed in Dose Modification Section, the following will result in treatment discontinuation:

- Unacceptable Toxicity
- Subject requests to discontinue the study treatment and/or study procedures.
- Non-compliance as defined as missing ≥ 30% of the required Q-Urol/placebo doses. At the discretion of the principal investigator, the subject may be permitted to continue on treatment after the first noted occurrence of non-compliance if the subject is re-educated on treatment administration and compliance can be achieved within a reasonable timeframe.
- Significant protocol violation
- Study terminated by investigator sponsor
- Lost to follow-up

7.4.2 Criteria for discontinuation of study ("off study")

Subjects will be taken off study for the following:

- Completed study end of treatment visit.
- Screen failure.
- The subject is lost to follow-up.
- If, in the investigator's opinion, the continuation of the trial would be harmful to the subject's well-being.
- Development of intercurrent illness or situation which would, in the judgment of the investigator, significantly affect assessments of clinical status and trial endpoints.
- Participant requests to be withdrawn from the study
- Death

8 TOXICITIES AND DOSE MODIFICATION

Every effort should be made to administer Q-Urol/Placebo at the planned dose and schedule. In the event of study treatment toxicity, dosing may be interrupted, delayed, and/or discontinued. In the event of multiple toxicities, treatment/dose modifications should be based on the worst toxicity observed (CTCAE v5.0) and/or the most conservative recommendation for any given toxicity. Patients are to be instructed to notify Investigators at the first occurrence of any adverse symptom.

All dose holds must be clearly documented in the patient's medical chart and in the CRF. Appropriate follow-up assessments should be done until adequate recovery occurs as assessed by the Investigator.

8.1 Dose Modifications

While dose reductions are not permitted on trial, dose interruptions for study treatment-related AEs are allowed as deemed necessary by the treating physician. Doses of Q-Urol/Placebo that were not administered due to toxicity will not be replaced. If a toxicity-

related dose delay extends over 12 days, treatment will be discontinued permanently and the patient should be removed from the study.

Study therapy may be held for any treatment-related adverse events, grade ≥ 2 as deemed necessary by the treating investigator. Upon resolution of the treatment-related adverse event, study therapy may be resumed at the prior dose level and frequency.

If a subject on study therapy experiences a grade ≥ 3 SAE attributed to study drug, study therapy will be discontinued.

8.2 Supportive Care

All supportive measures consistent with optimal patient care may be given throughout the study.

8.3 Contraception

Subjects will be instructed to abstain from sexual intercourse for the first two weeks after brachytherapy implantation. After the first two weeks, subjects may engage in sexual intercourse but should use a condom for the duration of study participation and for 5 days after the last dose of study therapy. In addition, female partners of childbearing potential should also use a highly effective contraceptive method during the same period.

Acceptable highly effective contraceptive methods include:

- Bilateral tubal occlusion
- Intra-uterine devise (IUD) or hormone-releasing system (IUS)
- Any hormonal (estrogen combined with progesterone or progesterone alone) contraception associated with inhibition of ovulation: implanted, oral, intravaginal, transdermal, or injectable
- Spermicide in combination with a compatible barrier method (i.e. diaphragm, sponge, or male or female condoms)
- Abstinence from heterosexual intercourse.

9 SCHEDULE OF EVENTS

The Schedule of Events table provides an overview of the protocol visits and procedures. Refer to the Study Procedures section of the protocol for detailed information on each assessment required for compliance with the protocol. The Investigator may schedule visits (unplanned visits) in addition to those listed in the Schedule of Events table in order to conduct evaluations or assessments required to protect the wellbeing of the patient. This Schedule of Events will be followed for the entire study.

Table 1: Schedule of Events

Protocol Activities	Screening	On Treatment Period						Post-Treatment Period	
		Day 1	Day 8	Day 15	Day 22	Day 29	Day 36	EOT (Day 43)	30 days post EOT
Visit Window	(-90 days)		(± 2 days)	(± 2 days)	(± 3 days)	(± 3 days)	(± 3 days)	(+7 days)	(± 7 days)
Informed Consent	X								
Demographics	X								
Medical History	X								
Baseline Characteristics[1]	X								
Eligibility Criteria	X								
Randomization	X								
Clinical Assessments									
Vital Signs[2]	X	X						X	
Physical Exam	X	X						X	
ECOG Score[3]	X	X							
NCCN Risk Stratification[4]	X								
Charlson Comorbidity Index[5]	X								
Phone Call[6]			X	X	X	X	X		X
Adverse events		X							
Concomitant Medications		X							

Protocol Activities	Screening	On Treatment Period						Post-Treatment Period	
		Day 1	Day 8	Day 15	Day 22	Day 29	Day 36	EOT (Day 43)	30 days post EOT
Visit Window	(-90 days)		(± 2 days)	(± 2 days)	(± 3 days)	(± 3 days)	(± 3 days)	(+7 days)	(± 7 days)
Laboratory Studies									
Hematology[7]	X								
Chemistry[8]	X								
Testosterone	X							X	
Inflammatory marker[9]	X							X	
Subject Materials									
Patient questionnaires[10]	X							X	
Q-Urol/Placebo dosing diary[11]		X						X	
Pain management diary[12]		X						X	
Study Therapy									
Q-Urol/Placebo[13]		X							
Brachytherapy		X							

[1] Appendix 9.

[2] Vital signs to include weight and height (height will be measured at screening only), blood pressure, pulse rate and temperature.

[3] Appendix 11.

[4] Appendix 8. NCCN Risk Stratification may be taken from the initial consultation note where brachytherapy was recommended.

[5] Appendix 10.

[6] An appropriately trained and delegated study team member will contact subjects on treatment weekly to assess adverse event and concomitant medication information, to answer subject questions, and to ensure compliance with study medication and procedures. 30 days after the last dose of study drug, a study team member will contact subjects to assess adverse event information.

[7] CBC with differential and platelets.

[8] Complete Metabolic Panel including: Sodium, Potassium, Chloride, Carbon Dioxide, Alkaline Phosphatase, Aspartate Aminotransferase, Alanine Aminotransferase, Urea Nitrogen, Glucose, Creatinine, Calcium, Protein, Albumin, Bilirubin, Anion Gap.

[9] Inflammatory markers include: erythrocyte sedimentation rate, C-reactive protein, prostate-specific antigen (PSA)

[10] Questionnaires include: National Institutes of Health-Chronic Prostatitis Symptom Index (NIH-CPSI), The Expanded Prostate Cancer Index Composite (EPIC), The International Prostate Symptom Score (I-PSS), Rectal Function Assessment Score (R-FAS), The Sexual Health Inventory for Men (SHIM) Questionnaire.

[11] A Q-Urol/Placebo dosing diary will be dispensed on the day of brachytherapy and returned completed at the EOT visit (Appendix 6).

[12] Patients will be asked to maintain a diary of the daily use of medications taken for prostate pain for 28 days post-brachytherapy (Appendix 7).

[13] Q-Urol/Placebo will begin after brachytherapy placement.

10 STUDY PROCEDURES

10.1 Screening

For screening procedures see the Schedule of Events and the Assessments Section. Screening activities may only begin after a subject has signed consent. All screening activities must take place within 90 days prior to brachytherapy unless otherwise noted.

10.2 Treatment Period

Once a subject has completed screening, has been found to be eligible, and has been registered, treatment procedures may begin. On the same day, but after brachytherapy, patients will begin Q-Urol or placebo. Patients on treatment will be contacted weekly by a trained and delegated study member to assess adverse events, concomitant medications, and to answer questions to ensure protocol adherence. See the Schedule of Events and the Assessments Section for treatment period procedures.

10.3 End of Treatment

An End of Treatment visit will occur six weeks after brachytherapy. At this visit, the patient will discontinue Q-Urol, return any remaining medication, the pain medication diary, and the dosing diary for medication reconciliation. For End of Treatment procedures the Schedule of Events and the Assessments Section.

11 STUDY ASSESSMENTS

Every effort should be made to ensure that the protocol-required tests and procedures are completed as described. However, it is anticipated that from time to time there may be circumstances, outside of the control of the Investigator that may make it unfeasible to perform the test. In these cases, the Investigator will take all steps necessary to ensure the safety and well-being of the patient. When a protocol-required test cannot be performed, the Investigator will document the reason for this and any corrective and preventive actions that he or she has taken to ensure that normal processes are adhered to as soon as possible.

11.1 Physical Examinations and Vital Signs

Patients will have physical examinations to include major body systems, vital signs, assessment of ECOG performance status (see Appendix 1), weight and height (height will be measured at screening only) at the time points described in the Schedule of Events. If necessary to facilitate scheduling, the physical exam may occur one day prior to study treatment.

Vital signs, including blood pressure, pulse rate, and temperature will be also recorded at the time points described in the Schedule of Events.

11.2 Baseline Characteristics

The following baseline characteristics will be collected from patients at screening (see also Appendix 9):

- Does the patient have a history of Coronary Artery Disease?
- Has the patient had bacterial prostatitis that went away with antibiotics?
- Does the patient have any family history of prostatitis?
- Alcohol history (never used alcohol, current alcohol user, former alcohol user)
- Smoking history (never smoked, current smoker, former smoker)
- Pack years (average number of packs per day and number of years smoked)
- Current employment status (employed, retired, student, unknown, other)
- Insurance status (private insurance, Medicare, Medicaid, VA, military, not insured, self-pay, unknown, other)
- Prostate volume
- Post-void residual urine volume if available
- Prior use of alpha-blockers for symptoms
- The extent of prostate cancer, including location of the cancer relative to the prostate gland capsule

11.3 Adverse Events

Adverse events experienced during trial participation will be collected per the Schedule of Events and Adverse Events Section. Each study participant will be questioned about the occurrence of adverse events in a non-leading manner. Should the treating investigator feel that the adverse event is attributed to study therapy, then dose modification guidelines in the Dose Modification Section will be followed.

11.4 Laboratory Assessments

Samples for all laboratory assessments will be drawn at the time points indicated in the Study Calendar and when clinically indicated. All safety laboratory analyses will be performed by the local laboratory. All safety laboratory assessments must be reviewed by the treating investigator prior to study drug administration.

Table 2: Laboratory Assessments

Laboratory Assessments	
CBC with Platelet Count and Differential	• White Blood Cell Count • Hemoglobin • Platelets • Absolute Neutrophil Count • Absolute Lymphocytes
Complete Metabolic Panel (Chemistry)	• Sodium • Potassium • Chloride • Carbon Dioxide • Alkaline Phosphatase

	• Aspartate Aminotransferase • Alanine Aminotransferase • Urea Nitrogen • Glucose • Creatinine • Calcium • Protein • Albumin • Bilirubin
Endocrine	• Testosterone
Inflammatory Markers	• Erythrocyte sedimentation rate • C-reactive protein • Prostate-specific antigen (PSA)

11.5 Questionnaire administration

All questionnaires will be completed in the clinic by the patient prior to starting study therapy and after completing six weeks of daily Q-Urol/Placebo therapy.

11.6 Dosing and Pain Diary

Patients will be required to keep a diary of the Q-Urol/Placebo doses taken during the study. If a dose is missed or omitted, comments should be added to indicate why the dose was not taken.

Patients will also be required to keep a diary of any medications used for pain management for 28 days after brachytherapy placement. On the diary, subjects will be asked to indicate yes/no if they took any medications for the management of prostate-related pain during the day. They will be asked to record this information daily for 28 days post-brachytherapy.

12 CRITERIA FOR EVALUATION AND ENDPOINT

12.1 Safety

Routine safety and tolerability will be evaluated from the results of reported signs and symptoms, scheduled physical examinations, vital sign measurements, and clinical laboratory test results. More frequent safety evaluations may be performed if clinically indicated or at the discretion of the investigator.

12.2 Efficacy

The primary outcome variable is the peak score of the National Institutes of Health-Chronic Prostatitis Symptom Index (NIH-CPSI) total score measured from baseline to six weeks post brachytherapy. Efficacy will be determined by the mean difference in outcome variable between the treatment and control groups.

12.3 Population for analyses

12.3.1 Evaluable for toxicity

Subjects who have received one dose of Q-Urol will be evaluable for toxicity.

12.3.2 Evaluable for response

A modified intent-to-treat data set will be used to assess efficacy. Subjects who have successfully undergone brachytherapy and received one dose of Q-Urol will be evaluable for response. Subjects who fail to undergo brachytherapy or begin Q-Urol therapy will be replaced. Those who do not complete the end of treatment patient questionnaires will be considered treatment failures.

12.4 Safety stopping rules

A 5% rate of grade ≥ 3 SAEs attributed as definitely or probably related to study drug is considered acceptable, and a 15% rate of grade ≥ 3 SAEs attributed as definitely or probably related to study drug is excessive. Excessive toxicity will be evaluated at 10, 21, 30, 40, 50, 60, and 70 patients. Toxicity will be declared excessive if the number of patients with an SAE *exceeds* 2/10, 3/21, 3/30, 4/40, 5/50, 6/60, or 6/70. The stopping boundary was calculated using the "toxbdry" function in the R package "clinfun".

Table 3: Operating Characteristics

Operating Characteristics of Strategy			
True Probability of SAE	Probability the Boundary Will Be Crossed at Any Time	Probability the Trial Will Stop Before the End	Average Sample Size
5%	10.9%	9.1%	66.4
7%	29.4%	24.0%	60.9
9%	52.0%	43.3%	53.5
11%	71.8%	62.2%	45.6
13%	85.5%	77.3%	38.5
15%	93.4%	87.6%	32.6

13 STATISTICAL CONSIDERATIONS

13.1 Statistical hypothesis

The primary outcome variable is the peak score of the National Institutes of Health-Chronic Prostatitis Symptom Index (NIH-CPSI) total score measured from baseline to six weeks post brachytherapy. The primary hypothesis is that the mean of the primary outcome variable will be ½ standard deviation lower in patients taking Q-Urol compared to placebo.

13.2 Statistical Analyses

13.2.1 Sample size determination

The outcome for sample size determination is the primary endpoint variable, the peak of the National Institutes of Health-Chronic Prostatitis Symptom Index (NIH-CPSI) total score measured from baseline to six weeks post brachytherapy. The primary hypothesis is that the mean of the primary outcome variable will be ½ standard deviation lower in patients taking Q-Urol compared to placebo. A single interim analysis is planned after N1= 21 subjects per group have outcome data. The interim and final analysis will compare the treatment and control means using nominal *t* statistics (control minus treatment). If the *t* statistic has a value less than -1.16 at the interim analysis the trial will be terminated for futility. If the *t* statistic has a value greater than 2.85 at the interim analysis the trial will be terminated for efficacy.

If the study is not terminated for efficacy or futility at the interim analysis an additional N2 = 49 patients per group will be accrued for a total of N = 70 patients per group. If the interim analysis is done at the planned sample size (21 patients per group) the treatment will be deemed efficacious at the final analysis if the *t* statistic has a nominal value greater than 1.67.

The above design was evaluated using 100,000 simulated data sets for both the null and alternative hypotheses. There is 90% power at overall one-sided Type I error equal to 0.05 (one-sided) to detect a 0.5 standard deviation lower mean of the primary endpoint in the treatment group compared to the control group. The probability of early termination for futility under the null hypothesis is 12%. The probability of early termination for futility under the alternative hypothesis is 0.3%. The probability of early termination for efficacy under the alternative hypothesis is 12%.

If the interim analysis or final analysis is performed at a sample size that is different than the planned sample size the final analysis will be adjusted to maintain an overall Type I error of no more than 0.05 (one-sided).

13.2.2 Primary endpoint

There are two planned analyses of the primary endpoint variable: an interim analysis at N1 = 21 patients per group and a final analysis at N = 70 patients per group. Two sample *t*- statistics will be calculated and evaluated as described in 13.2.1.

Multiple imputation will be used to replace missing end of treatment values of the National Institutes of Health-Chronic Prostatitis Symptom Index (NIH-CPSI) total score. A sensitivity analysis will replace missing values by the largest (i.e. worst) observed value.

In addition to formal testing for a difference between groups, the mean change between groups and the mean change within each group together will be reported together with 95% confidence intervals.

13.2.3 Secondary endpoint

1. Patient questionnaires administered pre- and post-study therapy: The Expanded Prostate Cancer Index Composite (EPIC), The International Prostate Symptom Score (I-PSS), The Rectal Function Assessment Score (R-FAS), and the Sexual Health Inventory for Men (SHIM). The change in questionnaire scores will be compared between groups using two-sample *t*-tests. If normality assumptions are violated, non-parametric Wilcoxon tests may be used. Confidence intervals for the mean change between and within groups will also be reported.
2. Inflammation markers pre and post brachytherapy: erythrocyte sedimentation rate, C-reactive protein, and prostate-specific antigen (PSA). The change in inflammatory markers will be compared between groups using two-sample t-tests. If normality assumptions are violated, non-parametric Wilcoxon tests may be used. Confidence intervals for the mean change between and within groups will also be reported. For laboratory markers that are known to be positivity skewed, such as CRP, the analyses will be based on the log-transformed values.
3. The frequency of adverse events (AEs) will be collected and characterized by type, severity (as defined by CTCAE, version 5.0), seriousness, duration, and relationship to study treatment. Counts and proportions of patients with adverse events will be tabulated and exact 95% binomial confidence intervals will be reported.
4. The number of days during the 28 days post-brachytherapy that any medication is taken for the treatment of prostate-related pain will be summarized using the mean, median and interquartile range. A Wilcoxon test will be used to compare the arms.

13.2.4 Exploratory Analyses

For the analyses involving score changes, the investigators will use ANCOVA in place of 2-sample t-tests, which has been found to be robust to violation of modeling assumptions.

14 REGISTRATION GUIDELINES

Study-related screening procedures can only begin once the patient has signed a consent form.

Patients must meet all of the eligibility requirements listed in Section 5 prior to registration.

Patients must be registered before receiving any study treatment and must begin treatment as soon as logistically possible after registration.

To register eligible patients on study, complete a Clinical Trials Office Patient Registration Form and submit to CTORegistrations@hci.utah.edu.

15 DATA SUBMISSION SCHEDULE

The Case Report Forms (CRFs) are a set of (electronic or paper) forms for each patient that provides a record of the data generated according to the protocol. CRF's should be created prior to the study being initiated and updated (if applicable) when amendments to the protocol are IRB approved. These forms will be completed on an on-going basis during the study. The medical records will be a source of verification of the data. During the study, the CRFs will be monitored for completeness, accuracy, legibility and attention to detail by a member of the Research Compliance Office. The CRFs will be completed by the Investigator or a member of the study team as listed on the Delegation of Duties Log. The data will be reviewed no less than annually by the Data and Safety Monitoring Committee. The Investigator will allow the Data and Safety Monitoring Committee or Research Compliance Office personnel access to the patient source documents, clinical supplies dispensing and storage area, and study documentation for the above-mentioned purpose. The Investigator further agrees to assist the site visitors in their activities.

Data capture should be restricted to endpoints and relevant patient information required for planned manuscripts.

16 ETHICAL AND REGULATORY CONSIDERATIONS

16.1 Human Subject Protections

The study will be conducted in accordance with the appropriate FDA, IRB, ICH GCP, and other federal and local regulatory requirements, as applicable. Informed consent will be obtained from all research participants prior to performing any study procedures using the most recent IRB-approved version. All patients must be at least 18 years of age to participate.

16.2 Institutional Review

Before study initiation, the investigator must have written and dated approval/favorable opinion from the IRB/IEC for the protocol, consent form, subject recruitment materials (e.g., advertisements), and any other applicable patient-facing documents. The investigator should also provide the IRB/IEC with a copy of the Investigator Brochure or product labeling information.

The investigator or designee should provide the IRB/IEC with reports, updates, and other information (e.g., expedited safety reports, amendments, and administrative letters) according to regulatory requirements or institution procedures.

16.3 Data and Safety Monitoring Plan

A Data and Safety Monitoring Committee (DSMC) is established at Huntsman Cancer Institute (HCI) to ensure the well-being of patients enrolled on Investigator Initiated Trials that do not have an outside monitoring review. The roles and responsibilities of the DSMC are set forth in the NCI-approved Data and Safety Monitoring (DSM) plan. The activities of the committee include reviewing adverse events (including SAEs), deviations, important medical events, significant revisions or amendments to the protocol, and approving cohort/dose escalations. If the DSMC and/or the PI have concerns about unexpected safety issues or rising AE trends, the study will be stopped and an unplanned safety data analysis

may take place. Enrollment will not resume until the issues are resolved. The DSMC also reviews and approves audit reports generated by the Research Compliance Office.

This is a Phase II study holding an IND and is classified as high risk per the NCI-approved DSM plan.

Each high-risk study will be assigned a physician member of the DSMC as a medical monitor, or in rare cases, an external medical monitor. The medical monitor will be notified of all serious adverse events (SAEs). All serious adverse events (SAEs) occurring in patients treated at HCI or its affiliates will also be reviewed by the full DSMC monthly.

Each high-risk study will also be assigned a dedicated research compliance officer who will monitor the trial. High-risk studies will be monitored by RCO personnel after the first patient is enrolled and every three months thereafter during active enrollment. The RCO monitor will review the study status and summarize enrollment, toxicities, SAEs, dose-escalation, statistical endpoints (e.g., stopping rules), deviations, etc. for the full DSMC membership at the regularly scheduled meetings. Amendments that increase risk, change dosing, or impact study objectives will be reviewed by the DSMC and approved by the PRMC and IRB. High-risk trials will be formally reviewed by the DSMC after the first patient is enrolled and then quarterly thereafter.

An initial audit of high-risk studies will be conducted by the RCO approximately one year after enrollment begins and annually thereafter. Audits of high-risk studies may be conducted more frequently as requested by the DSMC, IRB, PRMC, RCO management, or the PI.

16.4 Adverse Events and Serious Adverse Events

This study will utilize the CTCAE (NCI Common Terminology Criteria for Adverse Events) Version 5.0 for AE and SAE reporting.

16.4.1 Adverse Events (AEs)

An adverse event is the appearance or worsening of any undesirable sign, symptom, or medical condition occurring after starting the study drug even if the event is not considered to be related to the study drug. For the purposes of this study, the terms toxicity and adverse event are used interchangeably. Medical conditions/diseases present before starting study drug are only considered adverse events if they worsen after starting the study drug. Abnormal laboratory values or test results constitute adverse events only if they induce clinical signs or symptoms, are considered clinically significant, or require therapy.

The collection of adverse events will begin after the study drug has been started and end 30 days after the last dose study drug (or until new cancer treatment is initiated).

Information about all adverse events, whether volunteered by the subject, discovered by investigator questioning, or detected through physical examination, laboratory test, or other means, will be collected, recorded, and followed as appropriate.

The adverse event should be evaluated to determine:

1. The severity grade based on CTCAE v5.0 (grade 1-5)

2. Its relationship to the study drug, brachytherapy, and ADT (definite, probable, possible, unlikely, not related)
3. Its duration (start and end dates or if continuing at the final exam)
4. Action taken (no action taken; study drug dosage adjusted/temporarily interrupted; study drug permanently discontinued due to this adverse event; concomitant medication taken; non-drug therapy given; hospitalization/prolonged hospitalization)
5. Whether it constitutes an SAE

All adverse events will be treated appropriately. Such treatment may include changes in study drug treatment as listed in the dose modification section of this protocol (see section 8 for guidance). Once an adverse event is detected, it should be followed until its resolution, and assessment should be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the study drug, the interventions required to treat it, and the outcome.

Information about common side effects already known about Q-Urol is described in the Drug Information (Section 3). This information will be included in the patient informed consent and will be discussed with the patient during the study as needed.

All adverse events will be immediately recorded in the patient research chart.

16.4.2 Abnormal Test Findings

Abnormal test finding, such as incidental image findings, should only be listed as an adverse event if it meets the following criteria:

- Is associated with accompanying symptoms; and/or
- Requires additional testing or intervention; and/or
- Leads to changes in study therapy dosing; and/or
- Leads to the addition or change of a concomitant medication or therapy; and/or
- Is considered an adverse event by the treating investigator.

An abnormal test considered to be an error should not be listed as an adverse event. Repeating a test due to an abnormal result in the absence of any of the criteria above does not require listing as an adverse event.

16.4.3 Serious Adverse Event (SAE)

Information about all serious adverse events will be collected and recorded. A serious adverse event is an undesirable sign, symptom, or medical condition which:

- Is fatal or life-threatening
- Results in persistent or significant disability/incapacity
- Is medically significant, i.e., defined as an event that jeopardizes the patient or may require medical or surgical intervention to prevent one of the outcomes listed above

- Causes congenital anomaly or birth defect
- Requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
    - Routine treatment or monitoring of the studied indication, not associated with any deterioration in condition (procedures such as central line placements, paracentesis, pain control)
    - Elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since the start of the study drug
    - Treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of an SAE given above and not resulting in hospital admission
    - Social reasons and respite care in the absence of any deterioration in the patient's general condition

Collection of serious adverse events will begin with the initiation of Q-Urol and end 30 days after the last dose study drug or upon initiation of new cancer treatment, whichever happens the soonest.

Any death occurring after the SAE following-up period that is felt to be related to study therapy will be reported according to SAE reporting guidelines.

Toxicities that fall within the definitions listed above must be reported as an SAE regardless if they are felt to be treatment-related or not. Toxicities unrelated to treatment that do NOT fall within the definitions above must simply be documented as AEs in the patient research chart.

16.5 SAE Reporting Requirements

All serious adverse events should be reported as soon as possible but no later than one business day after the Investigator becomes aware. All SAEs must be reported via the HCI CTMS (OnCore) and submitted to HCI-RCO@utah.edu and Farr Laboratories. The HCI Clinical Site Monitor will in turn, submit the report to the Medical Monitor. The RCO will summarize and present all reported SAEs according to the Data and Safety Monitoring Plan at the monthly DSMC meeting.

At a minimum, initial SAE reports must include a description of the event, assessment of event causality, event grade, and the expectedness of the event. Although the Investigator may not know all the information at the time of the event, the available information should be reported. An SAE follow-up may be submitted at a later date once more information is known. It is required that follow-up reports be submitted until the SAE is resolved.

Follow-Up Information

It is recommended that follow-up reports be submitted as new information becomes available, however, a follow-up report should be submitted within 3 days of knowledge of event resolution. Follow-up information will be added to the SAE in OnCore and submitted to the DSMC via RCO.

16.5.1 FDA Notifications

Per 21 CRF 312.32 adverse events and serious adverse events will be reported on a MedWatch 3500A form to the FDA. Reportable events will be reported by the RCO according to the following guidelines:

MedWatch 3500A Reporting Guidelines

In addition to completing appropriate participant demographic (Section A) and suspect medication information (Section C & D), the report should include the following information within the Event Description (Section B.5) of the MedWatch 3500A form:

- Protocol number and title description
- Description of event, severity, treatment, and outcome if known
- Supportive laboratory results and diagnostics (Section B.6)
- Investigator's assessment of the relationship of the adverse event to each investigational product and suspect medication
- Expectedness of the event (i.e., expected or unexpected event).

FDA Reporting Timelines:

- *7 Calendar Day Report:*

Any event that is fatal or life-threatening, unexpected, and definitely, probably or possibly related to study medication will be reported to the FDA by telephone or fax within seven calendar days of first learning of the event.

- *15 Calendar Day Report:*

Any event that is serious, unexpected, and definitely, probably or possibly related to study medication will be reported to the FDA in an IND safety report within 15 calendar days of first learning of the event.

In accordance with 21 CFR 312.32, an Analysis of Similar Events should be included in the IND Safety Report. All safety reports previously filed by the investigator with the IND concerning similar events should be analyzed and the significance of the new report in light of the previous, similar reports commented on.

FDA fax number for IND Safety Reports:
1 (800) FDA 0178

16.5.2 IRB Notification

The University of Utah IRB requires any unanticipated problems that may increase the risk to research participants be promptly reported. All study-therapy related, unexpected adverse events whose nature, severity, or frequency is not consistent with either:

- The unknown or foreseeable risk of adverse events that are described in the protocol related-documents, such as the IRB-approved research protocol, applicable investigator brochure, the current IRB-approved informed consent document, and/or other relevant sources of information, such as product labeling and package inserts; or

- The expected natural progression of any underlying disease or condition of the participant(s) experiencing the adverse event.

Adverse events meeting this criterion must be promptly reported to the IRB within 10 business days of awareness.

16.6 Reporting of Pregnancy

Although pregnancy is not considered an adverse event, it is the responsibility of investigators or their designees to report any pregnancy or lactation in a subject, including the pregnancy of a male subjects' female partner as an SAE. Pregnancies or lactation that occurs during the course of the trial or with 5 days of completing the trial or starting another new anticancer therapy, whichever is earlier, must be reported to the DSMC, IRB, FDA, and the sponsor as applicable. All subjects and female partners who become pregnant must be followed to the completion/termination of the pregnancy. Pregnancy outcomes of spontaneous abortion, missed abortion, fetal death, intrauterine death, miscarriage, and stillbirth must be reported as serious events.

16.7 Protocol Amendments

Any amendments or administrative changes to an IRB approved protocol will not be initiated without submission and approval from the IRB of record.

These requirements for approval will in no way prevent any immediate action from being taken by the investigator in the interests of preserving the safety of all subjects included in the trial.

Any amendments to the protocol that significantly affect the safety of subjects, the scope of the investigation, or the scientific quality of the study are required to submit the amendment for FDA review.

16.8 Protocol Deviations

A protocol deviation (or violation) is any departure from the defined procedures and treatment plans as outlined in the protocol version submitted and previously approved by the IRB. Protocol deviations have the potential to place participants at risk and can also undermine the scientific integrity of the study thus jeopardizing the justification for the research. Protocol deviations are unplanned and unintentional events.

Because some protocol deviations pose no conceivable threat to participant safety or scientific integrity, reporting is left to the discretion of the PI within the context of the guidelines below. The sponsor requires the **prompt reporting** to HCI RCO of protocol deviations which are:

- Exceptions to eligibility criteria.
- Intended to eliminate an apparent immediate hazard to a research participant or
- Harmful (caused harm to participants or others, or place them at increased risk of harm - including physical, psychological, economic, or social harm), or
- Possible serious or continued noncompliance

16.9 FDA Annual Reporting

An annual progress report will be submitted to the FDA within 60 days of the anniversary of the date that the IND went into effect. (21 CFR 312.33).

16.10 Clinical Trials Data Bank

The study will be registered on **http://clinicaltrials.gov** and the NCI CTRP (Clinical Trials Reporting Program) by the Clinical Trials Office.

16.11 Record Keeping

Per 21 CFR 312.57, the Investigator records shall be maintained for a period of 2 years following the date a marketing application is approved; or, if no application is filed or the application is not approved, until 2 years after the investigation is discontinued and the FDA is notified.

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Subject ID:	Subject Initials:
	Date:

Appendix 1: National Institutes of Health-Chronic Prostatitis Symptom Index (NIH-CPSI)

Pain or Discomfort

1. In the last week, have you experienced any pain or discomfort in the following areas?

   Area between rectum and testicles (perineum)

   ☐ Yes

   ☐ No

   Testicles

   ☐ Yes

   ☐ No

   Tip of the penis (not related to urination)

   ☐ Yes

   ☐ No

   Below your waist, in your pubic or bladder area

   ☐ Yes

   ☐ No

2. In the last week, have you experienced:

   Pain or burning during urination?

   ☐ Yes

   ☐ No

   Pain or discomfort during or after sexual climax (ejaculation)?

   ☐ Yes

   ☐ No

3. How often have you had pain or discomfort in any of these areas over the last week?

   0. Never
   1. Rarely
   2. Sometimes
   3. Often
   4. Usually
   5. Always

4. Which number best describes your AVERAGE pain or discomfort on the days that you had it over the last week?

No Pain –	0	1	2	3	4	5	6	7	8	9	10 –	Pain as bad as you can imagine

Subject ID:	Subject Initials:
	Date:

Urination

5. How often have you had a sensation of not emptying your bladder completely after you finished urinating during the last week?
   0. Not at all
   1. Less than 1 time in 5
   2. Less than half the time
   3. About half the time
   4. More than half the time
   5. Almost always
6. How often have you had to urinate again less than 2 hours after you finished urinating, over the last week?
   0. Not at all
   1. Less than 1 time in 5
   2. Less than half the time
   3. About half the time
   4. More than half the time
   5. Almost always

Impact of Symptoms

7. How much have your symptoms kept you from doing the kinds of things you would usually do, over the last week?
   0. None
   1. Only a little
   2. Some
   3. A lot
8. How much did you think about your symptoms during the last week?
   0. None
   1. Only a little
   2. Some
   3. A lot

Quality of Life

9. If you were to spend the rest of your life with your symptoms just the way they have been during the last week, how would you feel about that?
   0. Delighted
   1. Pleased
   2. Mostly satisfied
   3. Mixed (about equally satisfied and dissatisfied)
   4. Mostly dissatisfied
   5. Unhappy
   6. Terrible

Patient Signature _____ Date _____

Subject ID:	Subject Initials:
	Date:

For research team member use:

Scoring	
Pain (total from questions 1, 2, 3 and 4; Yes = 1, No = 0)	
Urinary Symptoms (total of items 5 and 6)	
Quality of life impact (total of items 7, 8, 9)	
Pain and urinary score (total of items 1 through 6)	
Total Score:	

_____ _____

Research Team Member Signature Date

Appendix 2: The Expanded Prostate Cancer Index Composite (EPIC)

EPIC
The Expanded Prostate Cancer Index Composite

This questionnaire is designed to measure Quality of Life issues in patients with Prostate cancer. To help us get the most accurate measurement, it is important that you answer all questions honestly and completely.

Remember, as with all medical records, information contained within this survey will remain strictly confidential.

Date survey completed): Month _____ Day _____ Year_____

Subject number: _____

Subject initials: _____

Do Not Mark in This Space

URINARY FUNCTION

This section is about your urinary habits. Please consider **ONLY THE LAST 4 WEEKS**.

1. Over the **past 4 weeks**, how often have you leaked urine?

   More than once a day..... 1
   About once a day..... 2
   More than once a week..... 3 (Circle one number) 23/
   About once a week.....4
   Rarely or never..... 5

2. Over the **past 4 weeks**, how often have you urinated blood?

   More than once a day..... 1
   About once a day..... 2
   More than once a week..... 3 (Circle one number) 24/
   About once a week.....4
   Rarely or never..... 5

3. Over the **past 4 weeks**, how often have you had pain or burning with urination?

   More than once a day..... 1
   About once a day..... 2
   More than once a week..... 3 (Circle one number) 25/
   About once a week.....4
   Rarely or never..... 5

4. Which of the following best describes your urinary control **during the last 4 weeks**?

   No urinary control whatsoever.....1
   Frequent dribbling..... 2 (Circle one number) 26/
   Occasional dribbling..... 3
   Total control..... 4

Do Not Mark in This Space

5. How many pads or adult diapers per day did you usually use to control leakage **during the last 4 weeks**?

None	0	
1 pad per day	1	
2 pads per day	2	(Circle one number)
3 or more pads per day	3	

27/

6. How big a problem, if any, has each of the following been for you **during the last 4 weeks**?

(Circle one number on each line)

		No Problem	Very Small Problem	Small Problem	Moderate Problem	Big Problem	
a.	Dripping or leaking urine	0	1	2	3	4	28/
b.	Pain or burning on urination	0	1	2	3	4	29/
c.	Bleeding with urination	0	1	2	3	4	30/
d.	Weak urine stream or incomplete emptying	0	1	2	3	4	31/
e.	Waking up to urinate	0	1	2	3	4	32/
f.	Need to urinate frequently during the day	0	1	2	3	4	33/

7. Overall, how big a problem has your urinary function been for you **during the last 4 weeks**?

No problem	1	
Very small problem	2	
Small problem	3	(Circle one number)
Moderate problem	4	
Big problem	5	

34/

Do Not Mark in This Space

BOWEL HABITS

The next section is about your bowel habits and abdominal pain.
Please consider **ONLY THE LAST 4 WEEKS**.

8. How often have you had rectal urgency (felt like I had to pass stool, but did not) **during the last 4 weeks**?

More than once a day..... 1
About once a day..... 2
More than once a week..... 3 (Circle one number) 42/
About once a week.....4
Rarely or never..... 5

9. How often have you had uncontrolled leakage of stool or feces?

More than once a day..... 1
About once a day..... 2
More than once a week..... 3 (Circle one number) 43/
About once a week.....4
Rarely or never..... 5

10. How often have you had stools (bowel movements) that were loose or liquid (no form, watery, mushy) **during the last 4 weeks**?

Never..... 1
Rarely..... 2
About half the time..... 3 (Circle one number) 44/
Usually..... 4
Always.....5

11. How often have you had bloody stools **during the last 4 weeks**?

Never.....1
Rarely..... 2
About half the time..... 3 (Circle one number) 45/
Usually..... 4
Always.....5

Do Not Mark in This Space

12. How often have your bowel movements been painful **during the last 4 weeks**?

Never..... 1
Rarely..... 2
About half the time..... 3 (Circle one number) 46/
Usually..... 4
Always.....5

13. How many bowel movements have you had on a typical day **during the last 4 weeks**?

Two or less..... 1
Three to four.....2 (Circle one number) 47/
Five or more.....3

14. How often have you had crampy pain in your abdomen, pelvis or rectum **during the last 4 weeks**?

More than once a day..... 1
About once a day..... 2
More than once a week.....3 (Circle one number) 48/
About once a week.....4
Rarely or never..... 5

15. How big a problem, if any, has each of the following been for you? (Circle one number on each line)

	No Problem	Very Small Problem	Small Problem	Moderate Problem	Big Problem	
a. Urgency to have a bowel movement	0	1	2	3	4	49/
b. Increased frequency of bowel movements.....	0	1	2	3	4	50/
c. Watery bowel movements.....	0	1	2	3	4	51/
d. Losing control of your stools.....	0	1	2	3	4	52/
e. Bloody stools	0	1	2	3	4	53/
f. Abdominal/ Pelvic/Rectal pain...	0	1	2	3	4	54/

16. Overall, how big a problem have your bowel habits been for you **during the last 4 weeks**?

No problem..... 1
Very small problem..... 2
Small problem.....3 (Circle one number) 55/
Moderate problem..... 4
Big problem..... 5

Do Not Mark in This Space

SEXUAL FUNCTION

The next section is about your **current** sexual function and sexual satisfaction. Many of the questions are very personal, but they will help us understand the important issues that you face every day. Remember, THIS SURVEY INFORMATION IS COMPLETELY **CONFIDENTIAL**. Please answer honestly about **THE LAST 4 WEEKS ONLY**.

17. How would you rate each of the following during the last 4 weeks? (Circle one number on each line)

	Very Poor to None	Poor	Fair	Good	Very Good	
a. Your level of sexual desire?	1	2	3	4	5	56/
b. Your ability to have an erection?	1	2	3	4	5	57/
c. Your ability to reach orgasm (climax)?	1	2	3	4	5	58/

18. How would you describe the usual QUALITY of your erections **during the last 4 weeks**?

None at all 1
Not firm enough for any sexual activity 2
Firm enough for masturbation and foreplay only ..... 3 (Circle one number) 59/
Firm enough for intercourse 4

19. How would you describe the FREQUENCY of your erections **during the last 4 weeks**?

I NEVER had an erection when I wanted one 1
I had an erection LESS THAN HALF the time I wanted one 2
I had an erection ABOUT HALF the time I wanted one ..... 3 (Circle one number) 60/
I had an erection MORE THAN HALF the time I wanted one 4
I had an erection WHENEVER I wanted one 5

20. How often have you awakened in the morning or night with an erection **during the last 4 weeks**?

Never 1
Less than once a week 2
About once a week ..... 3 (Circle one number) 61/
Several times a week 4
Daily 5

Do Not Mark in This Space

21. **During the last 4 weeks**, how often did you have <u>any</u> sexual activity?

Not at all	1		
Less than once a week	2		
About once a week	3	(Circle one number)	62/
Several times a week	4		
Daily	5		

22. **During the last 4 weeks**, how often did you have sexual intercourse?

Not at all	1		
Less than once a week	2		
About once a week	3	(Circle one number)	63/
Several times a week	4		
Daily	5		

23. Overall, how would you rate your ability to function sexually **during the last 4 weeks**?

Very poor	1		
Poor	2		
Fair	3	(Circle one number)	64/
Good	4		
Very good	5		

24. How big a problem **during the last 4 weeks**, if any, has each of the following been for you?
(Circle one number on each line)

	No Problem	Very Small Problem	Small Problem	Moderate Problem	Big Problem	
a. Your level of sexual desire	0	1	2	3	4	65/
b. Your ability to have an erection.	0	1	2	3	4	66/
c. Your ability to reach an orgasm.	0	1	2	3	4	67/

25. Overall, how big a problem has your sexual function or lack of sexual function been for you **during the last 4 weeks**?

No problem	1		
Very small problem	2		
Small problem	3	(Circle one number)	68/
Moderate problem	4		
Big problem	5		

Do Not Mark in This Space

HORMONAL FUNCTION

The next section is about your hormonal function. Please consider **ONLY THE LAST 4 WEEKS**.

26. **Over the last 4 weeks,** how often have you experienced hot flashes?

More than once a day..... 1
About once a day..... 2
More than once a week..... 3 (Circle one number) 69/
About once a week..... 4
Rarely or never..... 5

27. How often have you had breast tenderness **during the last 4 weeks**?

More than once a day..... 1
About once a day..... 2
More than once a week..... 3 (Circle one number) 70/
About once a week..... 4
Rarely or never..... 5

28. **During the last 4 weeks,** how often have you felt depressed?

More than once a day..... 1
About once a day..... 2
More than once a week..... 3 (Circle one number) 71/
About once a week..... 4
Rarely or never..... 5

29. **During the last 4 weeks,** how often have you felt a lack of energy?

More than once a day..... 1
About once a day..... 2
More than once a week..... 3 (Circle one number) 72/
About once a week..... 4
Rarely or never..... 5

30. How much change in your weight have you experienced **during the last 4 weeks**, if any?

Gained 10 pounds or more.....1
Gained less than 10 pounds 2
No change in weight..... .....3 (Circle one number) 73/
Lost less than 10 pounds 4
Lost 10 pounds or more.....5

Do Not Mark in This Space

31. How big a problem **during the last 4 weeks**, if any, has each of the following been for you?
(Circle one number on each line)

	No Problem	Very Small Problem	Small Problem	Moderate Problem	Big Problem	
a. Hot flashes.....	0	1	2	3	4	74/
b. Breast tenderness/enlargement..	0	1	2	3	4	75/
c. Loss of Body Hair.....	0	1	2	3	4	76/
d. Feeling depressed.....	0	1	2	3	4	77/
e. Lack of energy.....	0	1	2	3	4	78/
f. Change in body weight	0	1	2	3	4	79/

Overall Satisfaction

32. Overall, how satisfied are you with the treatment you received for your prostate cancer?

Extremely dissatisfied..... 1
Dissatisfied..... 2
Uncertain..... 3 (Circle one number) 80/
Satisfied..... 4
Extremely satisfied..... 5

THANK YOU VERY MUCH!!

Patient Signature Date

Subject ID:	Subject Initials:
	Date:

Appendix 3: The International Prostate Symptom Score (I-PSS)

	Not at all	Less than 1 time in 5	Less than half the time	About half the time	More than half the time	Almost always	Your Score
1. Incomplete emptying – It does not feel like I empty my bladder all the way	0	1	2	3	4	5	
2. Frequency – I have to go again less than two hours after I finish urinating.	0	1	2	3	4	5	
3. Intermittency – I stop and start again several times when I urinate.	0	1	2	3	4	5	
4. Urgency – It is hard to wait when I have to urinate.	0	1	2	3	4	5	
5. Weak stream – I have a weak urinary stream.	0	1	2	3	4	5	
6. Straining – I have to push or strain to begin urination	0	1	2	3	4	5	
	None	1 time	2 times	3 times	4 times	5 times or more	
7. Nocturia – I get up to urinate after I go to bed until the time I get up in the morning.							

Which of the above do you regard as the most troublesome (1-7)? ____

Total Score ____
(to be completed by the research team)

Quality of life due to urinary symptoms
If you were to spend the rest of your life with your urinary condition just the way it is now, how would you feel about that? (Pick one)

0. Delighted
1. Pleased
2. Mostly Satisfied
3. Mixed – satisfied and dissatisfied
4. Mostly dissatisfied
5. Unhappy
6. Terrible

_____ _____
Patient Signature Date

Subject ID:	Subject Initials:
	Date:

American Urological Association Symptom (AUA) Score
Mild = 0-7 Moderate = 8-19 Severe = 20-35

Research Team Member Signature Date

Subject ID:	Subject Initials:
	Date:

Appendix 4: Rectal Function Assessment Score (R-FAS)

1. Frequency of stools per day:
   - ☐ 0-1 stool per day
   - ☐ 2 stools per day
   - ☐ 3 stools per day
   - ☐ 4 or more stools per day
2. Consistency of stools:
   - ☐ All stools formed
   - ☐ Stools Formed and loose
   - ☐ Stools loose
   - ☐ Watery stools
3. Urgency of stools:
   - ☐ No urgency
   - ☐ Somewhat urgent
   - ☐ Urgent
   - ☐ Very urgent
4. Abdominal discomfort:
   - ☐ No discomfort
   - ☐ Mild to moderate discomfort
   - ☐ Somewhat severe discomfort
   - ☐ Very severe discomfort
5. Hemorrhoid discomfort:
   - ☐ No discomfort
   - ☐ Required mild treatments (i.e. tucks, sitz baths)
   - ☐ Requires topical medication (i.e.Prep H, etc.)
   - ☐ Requires oral analgesics or narcotics for relief
6. Rectal bleeding
   - ☐ No rectal bleeding
   - ☐ Blood on toilet paper: 1 time per week
   - ☐ 2-3 times per week
   - ☐ ≥ 4 times per week
7. Continence:
   - ☐ Normal continence; able to control stool movement at all times
   - ☐ Gas incontinence only; able to control stool movements but not gas
   - ☐ Minor spotting or leakage of stool (up to coin size) about once per week
   - ☐ Minor spotting or leakage of stool (up to coin sixe) more than once per week

Subject ID:	Subject Initials:
	Date:

- ☐ Significant leakage of stool (larger than coin size about once per week)
- ☐ Significant leakage of stool (larger than coin size more than once per week

8. Nighttime bowel movements (total number of nights in last week that you had to get up from bed to have a bowel movement):
   - ☐ 0
   - ☐ 1
   - ☐ 2
   - ☐ 3
   - ☐ 4
   - ☐ More than
9. Completeness of evacuation:
   - ☐ Complete evacuation (requires one movement to completely empty bowel or feel you're "all done")
   - ☐ Occasional multiple evacuations (about once a week feel like you're not "all done" or it takes more than one movement to finish)
   - ☐ Frequent multiple evacuations (more than once a week feel like you're not "all done" or it takes more than one movement to finish)
   - ☐ Requires enema to obtain complete emptying.
10. My Bowel Movements after radiation or implant are:
   - ☐ Better
   - ☐ Worse
   - ☐ Same
   - ☐ Not Applicable

_____ _____

Patient Signature Date

Subject ID:	Subject Initials:
	Date:

Appendix 5: The Sexual Health Inventory for Men (SHIM) Questionnaire

1. How do you rate your confidence that you could get and keep an erection?
    1. Very low
    2. Low
    3. Moderate
    4. High
    5. Very high
2. When you had erections with sexual stimulation, how often were your erections hard enough for penetration (entering your partner)?
    0. No sexual activity
    1. Almost never or never
    2. A few times (much less than half the time)
    3. Sometimes (about half the time)
    4. Most times (much more than half the time)
    5. Almost always or always
3. During sexual intercourse, how often were you able to maintain your erection after you had penetrated (entered) your partner?
    0. Did not attempt intercourse
    1. Almost never or never
    2. A few times (much less than half the time)
    3. Sometimes (about half the time)
    4. Most times (much more than half the time)
    5. Almost always or always
4. During sexual intercourse, how difficult was it to maintain your erection to completion of intercourse?
    0. Did not attempt intercourse
    1. Extremely difficult
    2. Very difficult
    3. Difficult
    4. Slightly difficult
    5. Not difficult
5. When you attempted sexual intercourse, how often was it satisfactory for you?
    0. Did not attempt intercourse
    1. Almost never or never
    2. A few times (much less than half the time)
    3. Sometimes (about half the time)
    4. Most times (much more than half the time)
    5. Almost always or always

_____ _____

Patient Signature Date

Total: _____

SHIM Scores	**You may have . . .**
1-7	Severe ED
8-11	Moderate ED
12-16	Mild to Moderate ED
17-21	Mild ED
22-25	No signs of ED

_____ _____

Research Team Member Signature Date

Appendix 6: Patient Dosing Diary

Subject ID: _____ Subject Initials:_____

Week #: _____ Week Start Date: _____

Take two Q-Urol capsules with food twice daily at about the same time every day (± 4 hours). If a dose is missed or forgotten outside of the 4-hour window, it should not be made up but rather, the next dose should be taken at the regularly scheduled time.

Date	Time	Number of capsules taken	Comments
	:		
	:		
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	:		

_____ _____

Patient Signature Date

Appendix 7: Pain Management Diary

Subject ID: ___________________________ Subject Initials:_______________________

Week #: ___________________________ Week Start Date: _____________________

Please record any use of medications intended for the management of prostate pain.

Date	**Medication Taken**
	Have you taken any medication today for prostate pain? ☐ Yes ☐ No
	Have you taken any medication today for prostate pain? ☐ Yes ☐ No
	Have you taken any medication today for prostate pain? ☐ Yes ☐ No
	Have you taken any medication today for prostate pain? ☐ Yes ☐ No
	Have you taken any medication today for prostate pain? ☐ Yes ☐ No
	Have you taken any medication today for prostate pain? ☐ Yes ☐ No
	Have you taken any medication today for prostate pain? ☐ Yes ☐ No
	Have you taken any medication today for prostate pain? ☐ Yes ☐ No
	Have you taken any medication today for prostate pain? ☐ Yes ☐ No
	Have you taken any medication today for prostate pain? ☐ Yes ☐ No

____ ___________________

Patient Signature Date

Appendix 8: NCCN Risk Stratification

Risk Group	**Clinical Pathologic Features**
Very Low	● T1c AND ● Gleason Score ≤ 6/ grade group 1 AND ● PSA < 10 ng/mL AND ● Fewer than 3 prostate biopsy fragments/cores, positive, ≤ 50% cancer in each fragment/core[b] AND ● PSA density < 0.15 ng/mL/g
Low	● T1-T2a AND ● Gleason score ≤ 6/grade group 1 AND ● PSA < 10 ng/mL
Favorable Intermediate	● T2b – T2c OR ● Gleason score 3 + 4 =7/grade group 2 OR ● PSA 10-20 ng/mL AND ● Percentage of positive biopsy cores < 50%
Unfavorable Intermediate	● T2b – T2c OR ● Gleason score 3 + 4 = 7/grade group 2 or Gleason score 4 + 3 = 7/grade group 3 OR ● PSA 10-20 ng/mL
High	● T3a OR ● Gleason score 8/grade group 4 or Gleason score 4 + 5 = 9/grade group 5 OR ● PSA > 20 ng/mL
Very High	● T3b – T4 OR ● Primary Gleason pattern 5 OR ● > 4 core with Gleason score 8-10/ grade group 4 or 5
Regional	Any T, N1, M0
Metastatic	Any T, Any N, M1

Subject ID:	Subject Initials:
	Date:

Appendix 9 Baseline Characteristics

1. Does the patient have a history of Coronary Artery Disease? Yes□ No□
2. Has the patient had bacterial prostatitis that went away with antibiotics? Yes□ No□
3. Does the patient have any family history of prostatitis? Yes□ No□
4. Alcohol history:
    - ☐ Never used alcohol
    - ☐ Current alcohol user
    - ☐ Former alcohol user
5. Smoking history:
    - ☐ Never smoked
    - ☐ Current smoker
        - Average number of packs per day _____
        - Number of years smoked _____
    - ☐ Former smoker
        - Average number of packs per day_____
        - Number of years smoked ____
6. Employment status
    - ☐ Employed
    - ☐ Retired
    - ☐ Student
    - ☐ Unknown
    - ☐ Other
7. Insurance status
    - ☐ Private insurance
    - ☐ Medicare
    - ☐ Medicaid
    - ☐ VA
    - ☐ Military
    - ☐ Not insured
    - ☐ Self pay
    - ☐ Unknown

    Other

Appendix 10: Charlson Comorbidity Index

Date of Assessment: _____ Study Patient ID: _____

Study Patient Initials:_____

Instructions: Select one option per line.

	None	Uncomplicated	End-organ Damage
Diabetes mellitus			

	None	Mild	Moderate/Severe
Liver disease			

	None	Leukemia, Lymphoma, or Localized Solid Tumor	Metastatic Solid Tumor
Malignancy – exclude basal cell carcinoma			

	Yes	No
HIV or AIDS		
Moderate to severe chronic kidney disease		
Congestive heart failure		
Myocardial infarction		
Chronic obstructive pulmonary disease (COPD)		
Peripheral vascular disease		
Cerebrovascular accident (CVA) or transient ischemic attack (TIA)		
Dementia		
Hemiplegia		
Connective tissue disease		
Peptic ulcer disease		

Investigator Signature _____

Appendix 11: Eastern Cooperative Oncology Group Performance Status Criteria (ECOG) & Karnofsky Performance Scale Index (KPS) equivalency

ECOG Performance Status Scale[1]		**Karnofsky Performance Scale[2]**	
Grade	Descriptions	Percent	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or to do active work.
2	In bed < 50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead.	0	Dead.

1. Oken M, Creech R, Tormey D, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol.*1982;**5**:649-655.

2. Karnofsky D, Burchenal J, The clinical evaluation of chemotherapeutic agents in cancer. In: MacLeod C, ed. Evaluation of Chemotherapeutic Agents. New York, NY: Columbia University Press; 1949:191–205

Appendix 12: Cautionary Medications

CYP3A4 substrates with a narrow therapeutic index

Abiraterone	Carbamazepine	Fosphenytoin	Tacrolimus
Acenocoumarol	Cisapride	Isavuconazole	Terfenadine
Aminophylline	Clozapine	Phenprocoumon	Theophylline
Amiodarone	Cyclosporine	Pimozide	Tianeptine
Argatroban	Digitoxin	Quinidine	
Cabergoline	Dofetilide	Ruxolitinib	
Cabozantinib	Dronedarone	Sirolimus	

CYP2D6 substrates with a narrow therapeutic index

Amiodarone	Flecainide	Procainamide	Theophylline
Dosulepin	Pimozide	Sotalol	

CYP2C8 substrates with a narrow therapeutic index

Amiodarone	Fosphenytoin	Phenprocoumon	Phenytoin

OATP1B1 substrates with a narrow therapeutic index

Cyclosporine	Digoxin	Levothyroxine	Methotrexate

P-glycoprotein substrates with a narrow therapeutic index

Cyclosporine	Digoxin	Phenytoin	Sirolimus
Digitoxin	Phenobarbital	Quinidine	Tacrolimus