Brief Report

Saw Palmetto for Symptom Management During Radiation Therapy for Prostate Cancer

Gwen K. Wyatt, PhD, RN, FAAN, Alla Sikorskii, PhD, Abolfazl Safikhani, PhD, Kevin T. McVary, MD, FACS, and James Herman, MD

College of Nursing (G.K.W.) and Department of Statistics and Probability (A.Si.), Michigan State University, East Lansing, Michigan; Department of Statistics (A.Sa.), Columbia University, New York, New York; School of Medicine (K.T.M.), Southern Illinois University, Springfield, Illinois; and Sparrow Radiation Oncology (J.H.), Sparrow Health System, Lansing, Michigan, USA

Abstract

Context. Lower urinary tract symptoms (LUTSs) affect 75%–80% of men undergoing radiation therapy (RT) for prostate cancer.

Objectives. To determine the safety, maximum tolerated dose (MTD), and preliminary efficacy of *Serenoa repens* commonly known as saw palmetto (SP) for management of LUTS during RT for prostate cancer.

Methods. The dose finding phase used the time-to-event continual reassessment method to evaluate safety of three doses (320, 640, and 960 mg) of SP. Dose-limiting toxicities were assessed for 22 weeks using the Common Terminology Criteria for Adverse Events for nausea, gastritis, and anorexia. The exploratory randomized controlled trial phase assessed preliminary efficacy of the MTD against placebo. The primary outcome of LUTS was measured over 22 weeks using the International Prostate Symptom Score. Additional longitudinal assessments included quality of life measured with the Functional Assessment of Cancer Therapy–Prostate.

Results. The dose finding phase was completed by 27 men who reported no dose-limiting toxicities and with 20 participants at the MTD of 960 mg daily. The exploratory randomized controlled trial phase included 21 men, and no statistically significant differences in the International Prostate Symptom Score were observed. The prostate-specific concerns score of the Functional Assessment of Cancer Therapy–Prostate improved in the SP group ($P = 0.03$). Of 11 men in the placebo group, two received physician-prescribed medications to manage LUTS compared with none of the 10 men in the SP group.

Conclusion. SP at 960 mg may be a safe herbal supplement, but its efficacy in managing LUTS during RT needs further investigation. J Pain Symptom Manage 2016;51:1046–1054. © *2016 American Academy of Hospice and Palliative Medicine. Published by Elsevier Inc. All rights reserved.*

Key Words

Herbal supplement, saw palmetto, prostate cancer, lower urinary tract symptoms

Introduction

Prostate cancer is the most frequently occurring cancer among men.[1] More than 100,000 men undergo radiation therapy (RT) for prostate cancer annually in the U.S.[2,3] Approximately 40% of these patients require medication for relief of acute lower urinary tract symptoms (LUTSs) during RT.[4] One-quarter to one-third have used complementary therapies, including the herb *Serenoa repens*, commonly known as saw palmetto (SP), before or after diagnosis.[5–15] SP has been studied extensively as an intervention for men with benign prostatic hyperplasia (BPH).[16–31] It demonstrated no adverse interactions

Address correspondence to: Gwen K. Wyatt, PhD, RN, FAAN, College of Nursing, Michigan State University, 1355 Bogue Street, East Lansing, MI 48824, USA. E-mail: gwen.wyatt@hc.msu.edu

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with commonly used medications[32,33] nor any effects on the two most common enzymes involved in the metabolic pathway of more than 50% of all marketed prescriptions and over-the-counter medications.[34–36] In addition, SP was found to significantly lower the risk of ejaculatory disorders compared to an alpha-adrenergic blocker (0.6%, 4.2%, respectively) among BPH patients.[16] In other BPH studies, SP did not affect prostate-specific antigen (PSA) levels in vivo or in vitro when taken as a purified extract,[23,37,38] compared to no treatment,[38] or to placebo.[23] McVary et al.[39] reviewed BPH studies from 1999 to 2008 and could not recommend for or against the use of SP for treatment of LUTS. A large scale placebo-controlled trial of SP in BPH found no adverse events and showed that increasing doses of SP (up to 960 mg) did not reduce LUTS more than placebo at the 72-week end point.[40]

In contrast to the abundance of research on SP use with BPH, no studies have evaluated the safety and efficacy of SP in LUTS management among men with prostate cancer undergoing RT. RT for prostate cancer causes inflammation,[4,41–47] leading to LUTS, which typically appear during the third week of RT.[41] Although alpha-adrenergic blockers such as tamsulosin are effective in controlling RT-induced LUTS,[48,49] these medications are associated with significant toxicity.[50,51] Side effects of alpha-adrenergic antagonists include dizziness, headache, rhinitis, asthenia, abnormal ejaculation, somnolence, insomnia, nausea, sinusitis, diarrhea, cough, and amblyopia.[51] Approximately 77% of patients receiving RT in a tamsulosin dose-escalation trial demonstrated frequency and nocturia over twice their pre-RT levels.[49] In a meta-analysis of tamsulosin for BPH, the prevalence of side effects increased with dose escalation, reaching 75% at 0.8 mg dose of tamsulosin; the medication discontinuation rate at 0.8 mg was 16%. By comparison, the only noted adverse effects of SP are gastrointestinal, and they generally do not become remarkable when SP is taken with meals at 320 mg per dose.[52–54] It also has been proposed that SP may impact LUTS by relaxing the smooth muscle in the prostate gland,[37,55,56] a mechanism similar to that of alpha-adrenergic drugs.[48,49,57–64] Additionally, SP may have a general anti-inflammatory effect.[38]

To evaluate the use of SP for RT-induced LUTS, the present study was conducted in two phases: 1) a dose finding phase to evaluate the safety of three dose levels, and 2) an exploratory randomized controlled trial (RCT) phase to assess preliminary efficacy of the maximum tolerated dose (MTD) with respect to the management of LUTS and improvement in health-related quality of life (HRQOL) during and after RT.

Methods

Setting

Men with prostate cancer were recruited at five community-based clinics in the Midwest U.S. All sites and the investigators' university provided human subjects approval. Furthermore, the Food and Drug Administration (FDA) provided Investigational New Drug approval for up to 960 mg of SP per day.

Sample

Men referred for RT with early-stage prostate cancer were screened by a nurse recruiter for eligibility, including 21 years of age or older, Karnofsky Performance Status score ≥70%, Gleason Score ≤8, and serum PSA ≤40 ng/mL. Exclusion criteria were T4 or M1 staging; use of other herbs; prior pelvic RT; abnormal liver or kidney function as evidenced by greater than twice normal values of blood urea nitrogen, serum creatinine, serum transaminases, and alkaline phosphatase at baseline; persistent psychological or medical illness such as uncontrolled hypertension with a baseline blood pressure of >150 mm Hg systolic; or major cardiovascular events within the previous 12 months.

Study Procedures

The RT for prostate cancer received by men in this study comprised an eight-week (five days/week) course of 75–80 Gy.[41] Patients were recruited between 2011 and 2014 and followed up for 22 weeks. To use a preventive approach to symptoms, SP was started two weeks before RT began. Also, because LUTSs were expected to last after completion of RT, men were instructed to continue SP for two weeks after ending RT, with no restrictions on independent continuation after this period. All men participating in the study received usual care, which may have included prescription medication for controlling LUTS.

Data Collection. Consent was obtained in the clinic two to three weeks before commencing RT; men completed the demographic and HRQOL assessment at baseline (week 0) using a paper and pencil as they waited for their appointment (Fig. 1). Weekly LUTS and Common Terminology Criteria for Adverse Events (CTCAE) data were collected using a paper form by the study nurse as men came for RT. After completion of RT (Fig. 1), all data were collected via telephone by the study interviewer. Because it is standard practice to monitor blood chemistry and PSA as a marker of tumor control,[65] blood chemistry levels at Study Week 6 (Week 4 of RT) and PSA levels pre- and post-SP were abstracted from patient charts.

	Baseline	Week													
		1	2	3	4	5	6	7	8	9	10	11	12	14	22
Consent	X														
Liver & Kidney Labs	X						X								
Serum PSA	X														X
Saw Palmetto		X	X	X	X	X	X	X	X	X	X	X	X		
Radiation Therapy				X	X	X	X	X	X	X	X				
CTCAE	X		X	X	X	X	X	X	X	X	X	X	X	X	X
Efficacy Data															
• IPSS	X			X	X	X	X	X	X	X	X	X	X	X	X
• QOL	X												X	X	X
Covariate Data															
• LUTS Medication Tracking	X			X	X	X	X	X	X	X	X	X			
• Demographic Data	X														

Fig. 1. Data collection schedule. PSA = prostate-specific antigen; CTCAE = Common Terminology Criteria for Adverse Events; IPSS = International Prostate Symptom Score; QOL = quality of life; LUTS = lower urinary tract symptom.

Dose Finding Phase. Each consented man was assigned a dose of SP using the time-to-event continual reassessment method (TITE-CRM). The TITE-CRM incorporated a decision rule for the allocation of the next patient to a dose of SP based on the current estimate of the prevalence of toxicity. Using each patient's data, the algorithm updated the distribution of toxicity defined as CTCAE Grade 2 or higher for gastrointestinal symptoms (nausea, gastritis, anorexia). These three symptoms were selected as adverse events for the TITE-CRM algorithm because they were the only known potential side effects of SP.[20,53,54]

The allowable combined prevalence of these adverse events was set to 10%. If the estimate of toxicity for the current dose exceeded 10%, then the next patient was allocated to a lower dose, otherwise the dose was escalated. The first three men were allocated to the lowest dose (320 mg); if no adverse events were reported during 12 weeks of SP, the dose would be increased to 640 mg for the next four men, and then to 960 mg in the absence of adverse events. MTD was defined as the highest dose (among 320, 640, or 960 mg) at which prevalence of adverse events was <10%. The dose was not escalated beyond 960 mg based on the FDA study approval. Men stayed on the assigned dose for the entire protocol unless adverse events required a dose reduction or discontinuation.

Men knew they were taking the SP. Men assigned to 320 mg were given one bottle; 640 mg two bottles, and 960 mg three bottles. The daily dose was one to three soft gels because all SPs were packaged as 320 mg soft gels. Men were told to take no more than one soft gel at a time, with food, to avoid gastrointestinal side effects.

Exploratory RCT Phase. Once the MTD was determined, an exploratory RCT was conducted. The goal was to generate hypotheses of preliminary efficacy of SP on LUTS and HRQOL; therefore, no statistical determination of the sample size was made. Based on ethical considerations of the unknown efficacy of SP, it was planned to randomize 10 men into each group, SP or placebo.

The study statistician implemented the computer program for randomization via minimization of differences on the recruitment location to control for variations in standard care.[66–69] Men and clinic nurses who collected data were blinded to the group assignment. After Study Week 22, men were debriefed, and those assigned to the placebo group were given a bottle of SP as a thank you for taking part in the study.

Measures

The CTCAE form was completed weekly during weeks 2–12 and during Weeks 14 and 22. It includes anorexia, nausea, gastritis, hematuria, hemorrhoids, diarrhea, proctitis, pruritis/itching, and fatigue. Each event, if experienced by patients within the past seven days, was graded 0–4. Any of the three gastrointestinal events (anorexia, nausea, and gastritis) of grade 2 or higher were considered as adverse events for the TITE CRM algorithm per FDA-approved protocol. Other possible side effects were monitored using this form and reported to clinic staff as appropriate.

The International Prostate Symptom Score (IPSS)[70] was used to evaluate LUTS at Study Weeks 2–10, 12, 14, and 22. The instrument has six items reflecting -urinary tract symptoms (incomplete emptying, frequency, urgency, intermittency, urgency, and weak stream) rated on a six-point scale from 0 "not at all" to 5 "almost always." Additional

questions assess nocturia and quality of life as a result of urinary symptoms. Evidence of reliability and validity has been reported.[70]

The Functional Assessment of Cancer Therapy—Prostate[71] has six subscales reflecting emotional, functional, physical, and social well-being; and prostate-specific and additional concerns.[72] Items are rated on a five-point scale from 0 "not at all" to 4 "very much." The additional concerns subscale has 12 items; other subscales consist of six to seven items. Higher scores reflect better HRQOL.

Statistical Analysis

Because patient blinding in the randomized phase or lack thereof in the dose escalation phase was not expected to affect blood chemistry or PSA level, those who received 960 mg were compared to those who received placebo in the analysis of safety. The least square means were obtained from the general linear model that included baseline value and study group as explanatory variables. Differences between the least square means for the SP vs. placebo groups were tested.

The preliminary efficacy analysis was of the intent-to-treat type. To check the success of randomization, baseline group comparisons were performed using t- or Fisher exact tests. Linear mixed effects (LME) models were used to compare the randomized SP group to the placebo group on LUTS and HRQOL. The LME modeling generalizes classical analysis of repeated measures and allows for data missing at random, so that all available longitudinal data were used from men who completed all or some of the assessments. All available repeated measures of LUTS and HRQOL were related to baseline value and study group (SP vs. placebo) as explanatory variables. The adjusted means were output from the LME model and reflected average difference between groups over time (main group effect).

Table 1
Baseline Characteristics of the Study Sample

	Dose Finding Phase	Exploratory RCT Phase		
Characteristic	Those Who Received MTD[a] of 960 mg Saw Palmetto $n = 20$	960 mg of Saw Palmetto $n = 10$	Placebo $n = 11$	*P*-Value[a]
Age, mean (SD)	61.95 (5.40)	66.70 (11.30)	67.82 (7.22)	0.10
Race, *n* (%)				
White	16 (80)	9 (90)	10 (91)	0.99
African American	3 (15)	1 (10)	0 (0)	
Unknown	1 (5)	0 (0)	1 (9)	
Ethnicity, *n* (%)				
Hispanic or Latino	1 (5)	0 (0)	0 (0)	0.99
Not Hispanic or Latino	14 (70)	8 (80)	8 (73)	
Unknown	5 (25)	2 (20)	3 (27)	
Education, *n* (%)				
High school or less	7 (35)	8 (80)	7 (64)	0.99
At least some college	11 (55)	2 (20)	2 (18)	
Unknown or other	2 (10)	0 (0)	2 (18)	
Marital status, *n* (%)				
Married	15 (75)	8 (80)	7 (64)	0.99
Not married	5 (25)	2 (20)	3 (27)	
Unknown	0 (0)	0 (0)	1 (9)	
Employment status, *n* (%)				
Employed outside	7 (35)	3 (30)	3 (27)	0.99
Retired or disabled	13 (65)	7 (70)	7 (64)	
Unknown	0 (0)	0 (0)	1 (9)	
Annual household income, *n* (%)				
8000–25,000	3 (15)	2 (20)	1 (9)	0.99
25,000–50,000	5 (25)	3 (30)	4 (36)	
>50,000 or unknown	12 (60)	5 (50)	6 (55)	
Combined Gleason Score, *n* (%)				
6	5 (25)	1 (10)	1 (9)	0.99
7	14 (70)	6 (60)	7 (64)	
8	1 (5)	2 (20)	1 (9)	
Unknown	0 (0)	1 (10)	2 (18)	
T stage, *n* (%)				
T2, NOS	1 (5)	0 (0)	0 (0)	—
T2a	1 (5)	0 (0)	0 (0)	
T2b	1 (5)	0 (0)	0 (0)	
Unknown	17 (85)	10 (100)	11 (100)	

MTD = maximum tolerated dose; RCT = randomized controlled trial; NOS = not otherwise specified.
[a]For categorical variables, the *P*-value is for the comparison of most prevalent category by study group.

Table 2
Baseline Laboratory, IPSS, and FACT-P Data

	Dose Finding Phase	Exploratory RCT Phase		
	Those Who Received MTD of 960 mg Saw Palmetto, $n = 20$	960 mg of Saw Palmetto, $n = 10$	Placebo, $n = 11$	
Variable	Mean (SD)	Mean (SD)	Mean (SD)	*P*-Value
Blood urea nitrogen	19.65 (6.24)	16.30 (6.34)	19.28 (5.85)	0.24
Serum creatinine	1.03 (0.20)	1.01 (0.13)	1.07 (0.37)	0.57
Alkaline phosphatase	70.85 (23.57)	72.12 (17.28)	75.88 (20.24)	0.57
Serum alanine aminotransferase	24.25 (12.31)	21.12 (7.47)	25.22 (10.16)	0.36
Serum aspartate aminotransferase	21.15 (6.17)	23.75 (6.34)	25.66 (17.09)	0.92
White blood cell	6.97 (2.39)	5.96 (1.07)	7.22 (1.73)	0.11
Red blood cell	4.65 (0.38)	4.78 (0.33)	4.63 (0.58)	0.82
Hemoglobin	14.17 (1.92)	14.71 (1.12)	14.26 (2.03)	0.76
Platelet	219.20 (53.00)	205.29 (34.18)	233.55 (60.63)	0.46
Prostate-specific antigen	4.16 (6.33)	6.71 (4.78)	9.66 (12.89)	0.45
International Prostate Symptom Score	8.10 (6.28)	5.56 (5.13)	7.73 (4.41)	0.30
FACT-P total	124.60 (16.86)	127.93 (15.08)	118.68 (17.18)	0.22
FACT-P emotional well-being	18.35 (4.22)	18.96 (2.86)	18.40 (4.17)	0.73
FACT-P functional well-being	22.05 (5.18)	23.60 (4.12)	19.33 (4.59)	0.04
FACT-P physical well-being	25.15 (3.73)	25.80 (2.78)	25.30 (2.26)	0.66
FACT-P social well-being	22.34 (6.38)	21.87 (6.17)	20.85 (7.28)	0.74
FACT-P prostate-specific concerns	36.70 (5.55)	37.70 (4.95)	34.80 (3.68)	0.15

IPSS = International Prostate Symptom Score; FACT-P = Functional Assessment of Cancer Therapy—Prostate; MTD = maximum tolerated dose.

Results

During the entire study (both phases), 56 men were approached, and 48 (84%) consented. The majority of participants were white, not of Hispanic or Latino ancestry, married, and retired or disabled (Table 1). There were no significant differences among the groups at baseline, with the exception of better functional well-being among those randomized to SP (Table 2). The covariance adjustment controlled for this difference in later analyses.

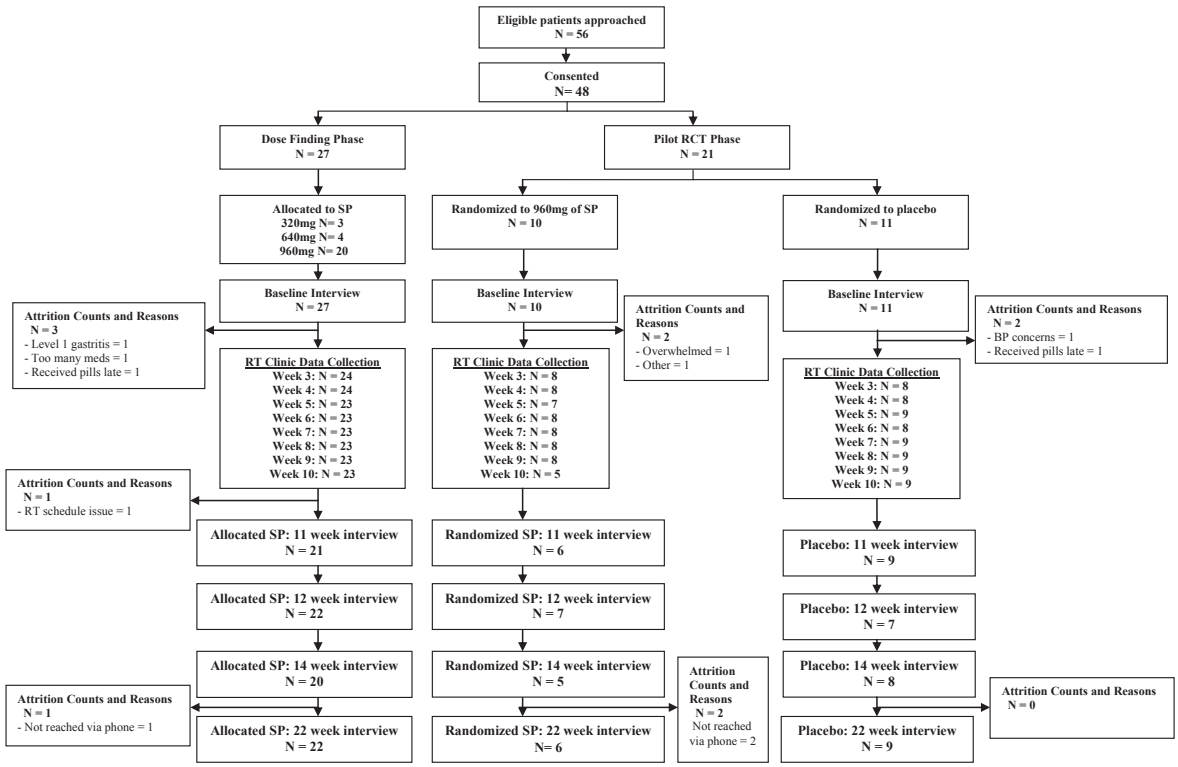

Fig. 2. Consolidated Standards of Reporting Trials (CONSORT) chart saw palmetto study. RCT = randomized controlled trial; SP = saw palmetto; RT = radiation therapy.

Table 3
LS Means of Blood Chemistry and Their SEs at Study Week 6 and PSA at End of Study (Week 22) Adjusted for the Respective Values at Baseline

Variable	MTD of 960 mg of SP: LS Mean (SE) (Allocated and Randomized Combined)	Placebo: LS Mean (SE)	*P*-Value
Blood urea nitrogen	18.14 (1.30)	22.90 (1.99)	0.06
Serum creatinine	1.01 (0.05)	1.11 (0.07)	0.23
Alkaline phosphatase	70.93 (2.29)	66.72 (3.42)	0.32
Serum alanine aminotransferase	26.49 (1.63)	24.38 (2.42)	0.47
Serum aspartate aminotransferase	23.02 (0.88)	22.06 (1.31)	0.55
White blood cell	5.03 (0.28)	5.19 (0.42)	0.76
Red blood cell	4.60 (0.06)	4.47 (0.08)	0.23
Hemoglobin	13.95 (0.18)	13.50 (0.27)	0.17
Platelet	195.64 (6.07)	190.69 (9.06)	0.65
Prostate-specific antigen	0.54 (0.14)	0.06 (0.26)	0.12

LS = least square; PSA = prostate-specific antigen; MTD = maximum tolerated dose.

Dose Finding Phase

As no adverse events were observed for three men on 320 mg and four men on 640 mg of SP over 12 weeks, the dose was escalated to 960 mg, again with no dose-limiting toxicities. Of 20 men who received 960 mg of SP, 17 completed the 12-week data collection point during the dose finding phase (Fig. 2). Of these 17 men, five (29%) received alpha-adrenergic drugs during the study period. The medications prescribed for men in the sample were tamsulosin, doxazosin, terazosin, and prazosin hydrochloride, and the prescription dates corresponded to Weeks 3–7 of the study (first five weeks of RT). One man who received 320 mg of SP was on an alpha-adrenergic drug at intake and throughout the study.

Exploratory RCT Phase

Of the 10 men randomized to 960 mg of SP, none were prescribed alpha-adrenergic drugs. Of the 11 patients randomized to placebo, two (18%) were prescribed alpha-adrenergic drugs during Week 3 of the study (start of RT). No significant differences in blood chemistry or PSA levels were found at Study Weeks 6 or 22 between those who received 960 mg of SP vs. those who received placebo (Table 3).

Table 4 summarizes the longitudinal comparisons of the randomized groups on LUTS and HRQOL. No differences between groups were found with the exception of a better score on the prostate-specific concerns subscale of the Functional Assessment of Cancer Therapy–Prostate for the SP group. Based on this finding, a hypothesis regarding possible improvement in this HRQOL dimension as a result of SP can be formulated and formally tested in future studies.

Discussion

This study addresses the problem of men experimenting with SP in the absence of evidence. Because of the putative slower onset of symptom relief with SP compared with prescription medications, the dosing schedule can be started a few weeks before the expected symptom onset. The decrease in adverse events with SP may make it an attractive supplement, if shown to be efficacious.

An interesting contrast occurred between the dose finding and exploratory RCT phases of the study. During the dose finding phase, patients were not blinded to receiving SP, whereas those randomized to SP in the exploratory RCT phase were blinded to whether they were receiving SP or a placebo. The IPSS scores of the randomized men were no different from placebo, whereas the scores of men who knew they were taking SP improved. This finding underscores the importance of conducting placebo-controlled blinded trials, especially when outcomes are patient reported. It is possible that when men knew they were getting some dose of SP in the dose finding phase, they may have been more likely to report symptom control.

Table 4
LS Means and Their SEs for IPSS (Lower Score Is Better) and Subscales and Total of FACT-P (Higher Score Is Better) by Study Group Adjusted for Baseline Values

Variable	Dose Finding Phase: 960 mg, LS Mean (SE)	Pilot RCT Phase: 960 mg, LS Mean (SE)	Pilot RCT Phase: Placebo, LS Mean (SE)	*P*-Value: Randomized Group Comparison
IPSS	7.44 (0.89)	10.54 (1.29)	9.41 (1.21)	0.12
FACT-P total	133.31 (2.79)	124.77 (4.37)	124.48 (4.18)	0.13
FACT-P emotional well-being	21.30 (0.53)	20.77 (0.84)	21.62 (0.79)	0.76
FACT-P functional well-being	23.97 (0.82)	22.24 (1.30)	21.20 (1.25)	0.17
FACT-P physical well-being	25.75 (0.54)	24.00 (0.86)	25.67 (0.81)	0.22
FACT-P social well-being	23.30 (0.68)	23.38 (1.08)	21.02 (1.01)	0.16
FACT-P prostate-specific concerns	39.59 (1.21)	35.13 (1.92)	33.81 (1.82)	0.03

LS = least square; IPSS = International Prostate Symptom Score; FACT-P = Functional Assessment of Cancer Therapy–Prostate; RCT = randomized controlled trial.

When men could not be sure if they were getting SP, they may have been more likely to report symptoms.

An alternative interpretation of this finding is to account for the use of alpha-adrenergic drugs. In the exploratory RCT phase, two of 11 men randomized to placebo were prescribed alpha-adrenergic drugs in contrast to none of the men in the SP arm. The resulting IPSS scores did not differ between arms indicating about equal success of LUTS management. Those randomized in the exploratory RCT phase to SP were not prescribed any alpha-adrenergic drugs; their LUTS were managed using SP with about equal success compared to those in the placebo arm where some men received alpha-adrenergic drugs. During the dose finding phase of the study, 29% of patients received both SP and alpha-adrenergic drugs, which may explain better outcomes in this group of patients.

The limitations of this study include a small sample size in the exploratory RCT phase. It would have been unethical to conduct a larger study in the absence of safety data and preliminary efficacy data for hypothesis generation. Also, ideally, men in the exploratory RCT phase would not be taking any other medications for the control of LUTS so that the effect of SP could be isolated. But again, denial of the standard of care for LUTS management would have been unethical. Finally, a longer period of taking SP and weekly follow-up after completion of RT may be needed in future studies.

Conclusion

This study has demonstrated the safety of the 960 mg dose and has resulted in a hypothesis of efficacy with respect to prostate-specific concerns of HRQOL. This hypothesis should be tested in future studies.

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