ALLIANCE FOR CLINICAL TRIALS IN ONCOLOGY

ALLIANCE A222001

A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED PHASE II STUDY OF OXYBUTYNIN VERSUS PLACEBO FOR THE TREATMENT OF HOT FLASHES IN MEN RECEIVING ANDROGEN DEPRIVATION THERAPY

A limited access study

Supplied agent: oxybutynin (Alliance IND: 152980, NSC 759108)

ClinicalTrials.gov Identifier: NCT04600336

Study Chair

[redacted]

Community Oncology Co-chair

[redacted]

Study Co-chair

[redacted]

Study Co-chair

[redacted]

Symptom Intervention Committee and Study Co-chair

[redacted]

Health Disparities Co-chairs

[redacted]

Primary Statistician

[redacted]

Secondary Statistician

[redacted]

Data Manager

[redacted]

Protocol Coordinator

[redacted]

Limited Access Institutions: See page 2-3

Participating Organizations:
Alliance/Alliance for Clinical Trials in Oncology (lead), ECOG-ACRIN/ECOG-ACRIN Cancer Research Group, NRG/NRG Oncology, SWOG/SWOG

Limited access institutions

Abbott-Northwestern Hospital, MN008

Altru Cancer Center, ND028

Arizona Breast Cancer Specialists, AZ118

Arizona Breast Cancer Specialists-Gilbert, AZ147

Arizona Breast Cancer Specialists-Phoenix, AZ125

Arizona Breast Cancer Specialists-Scottsdale, AZ146

Arizona Cancer Care-Surprise, AZ149

Arizona Center for Cancer Care-Peoria, AZ127

Ascension All Saints Hospital, WI061

Ascension Calumet Hospital, WI204

Ascension Colombia Saint Mary's Hosp-Milwaukee, WI161

Ascension Colombia Saint Mary's Hosp-Ozaukee, WI140

Ascension Med Group SE Wisc.-Mayfair Road, WI169

Springfield Clinic, IL194

Ascension Mercy Hospital, WI038

Ascension Saint Elizabeth Hospital, WI039

Ascension Saint Francis-Reiman Cancer Center, WI137

Ascension Saint Joseph Hospital, MI364

Ascension Saint Mary's Hospital, MI142

Ascension SE Wisc. Hospital-Elmbrook Campus, WI145

Ascension SE Wisc. Hospital-St Joseph Campus, WI043

Aspirus Cancer Care-Wisconsin Rapids, WI093

Aspirus Langlade Hospital, WI146

Aspirus Regional Cancer Center, WI028

AtlantiCare Cancer Care Institute, NJ237

AtlantiCare Health Park-Cape May Court House, NJ287

Baptist MD Anderson Cancer Center, FL003

Cancer Care Specialists of IL-Decatur, IL185

Cancer Center at Saint Joseph's, AZ151

Carle Cancer Center, IL168

Carle on Vermillion, IL405

Carle Physician Group-Effingham, IL406

Carle Physician Group-Mattoon/Charleston, IL393

Crossroads Cancer Center, IL208

Decatur Memorial Hospital, IL094

Delbert Day Cancer Institute at PCRMC, MO052

Fairview Clinics and Surgery Center-Maple Grove, MN113

Fairview Lakes Medical Center, MN132

Fairview Ridges Hospital, MN070

Fairview Southdale Hospital, MN031

Fremont-Rideout Cancer Center, CA564

Gene Upshaw Memorial Tahoe Forest Therapy Ctr, CA690

Genesee Cancer and Blood Disease Treatment Ctr, MI347

Genesee Hematology Oncology, MI348

Genesys Hurley Cancer Center, MI149

Grand Valley Oncology, CO138

Hawaii Cancer Care Inc, HI022

Hawaii Cancer Care-Westridge, HI049

Heartland Oncology and Hematology, IA147

Hennepin County Medical Center, MN013

Iowa Methodist Medical Center, IA004

Jennie Edmundson Memorial Hospital, IA055

Lakeview Hospital, MN119

Mary Greeley Medical Center, IA067

Mayo Clinic, MN026

McFarland Clinic-Ames, IA003

McFarland Clinic-Boone, IA106

McFarland Clinic-Jefferson, IA105

McFarland Clinic-Marshalltown, IA104

McFarland Clinic-Trinity Cancer Center, IA107

Medical Oncology Hematology Assoc-Des Moines, IA072

Mercy Hospital, MN019

Mercy Medical Center-Des Moines, IA008

Messino Cancer Centers, NC053

Minnesota Oncology Hematology-Maplewood, MN075

Minnesota Oncology Hematology-Woodbury, MN098

Minnesota Oncology-Burnsville, MN145

Montefiore Medical Center-Moses Campus, NY045

Montefiore Medical Center-Einstein Campus, NY313

Montefiore Medical Center-Weiler Hosp, NY043

Monticello Cancer Center, MN141

Nebraska Cancer Specialists-MECC, NE074

Nebraska Methodist Hospital, NE007

New Ulm Medical Center, MN121

North Memorial Medical Health Center, MN054

NYP/Weill Cornell Medical Center, NY018

Ohio State University Comprehensive Cancer Center, OH007

Oncology Hematology Assoc of Saginaw, MI364

Park Nicollet Clinic-St Louis Park, MN014

ProHealth D N Greenwald Center, WI143

ProHealth Oconomowoc Memorial Hospital, WI087

Regions Hospital, MN001

Rice Memorial Hospital, MN028

Ridgeview Medical Center, MN059

Saint Francis Regional Medical Center, MN064

Saint John's Hospital-Healtheast, MN041

Sanford Broadway Medical Center, ND003

Sanford Cancer Center Oncology Clinic, SD004

Sanford Roger Maris Cancer Center, ND005

Sanford USD Medical Center, SD003

Southeastern Medical Oncology Center-Clinton, NC254

Southeastern Medical Oncology Center-Goldsboro, NC065

Southeastern Medical Oncology Center-Jacksonville, NC231

Southern Illinois School of Medicine, IL096

Sovah Health Martinsville, VA043

Sparta Community Hospital, IL413

Springfield Memorial Hospital, IL097

United Hospital, MN002

Unity Hospital, MN018

University of Arizona Cancer Center-North Campus, AZ110

University of Mississippi Medical Center, MS005

University of Missouri-Ellis Fischel, MO036

UW Cancer Center at ProHealth Care, WI207

Westfields Hosp/Cancer Center of Western WI, WI196

Zablocki Veterans Administration Medical Cetner, WI004

Study Resources:

Expedited Adverse Event Reporting

[redacted]

Medidata Rave® iMedidata portal

[redacted]

OPEN (Oncology Patient Enrollment Network)

[redacted]

Biospecimen Management System

[redacted]

Protocol Contacts:

A222001 Nursing Contacts

[redacted]

A222001 Pharmacy Contact

[redacted]

Drug Distribution Contact

[redacted]

Protocol-related questions may be directed as follows:	
Questions	**Contact (via email)**
Questions regarding patient eligibility, treatment, and dose modification:	Study Chair, Nursing Contact, Protocol Coordinator, and (where applicable) Data Manager
Questions related to data submission, RAVE or patient follow-up:	Data Manager
Questions regarding the protocol document and model informed consent:	Protocol Coordinator
Questions related to IRB review	Alliance Regulatory Inbox [redacted]
Questions regarding CTEP-AERS reporting:	Alliance Pharmacovigilance Inbox [redacted]
Questions regarding drug supply	McKesson Clinical Research Services
Questions regarding drug administration	Pharmacy Contact

CANCER TRIALS SUPPORT UNIT (CTSU) ADDRESS AND CONTACT INFORMATION

CONTACT INFORMATION		
For regulatory requirements:	**For patient enrollments:**	**For data submission:**
Regulatory documentation must be submitted to the Cancer Trials Support Unit (CTSU) via the Regulatory Submission Portal. (Sign in at [redacted] and select the Regulatory > Regulatory Submission.) Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately by phone or email: [redacted] to receive further instruction and support. Contact the CTSU Regulatory Help Desk at l[redacted] for regulatory assistance.	Refer to the patient enrollment section of the protocol for instructions on using the Oncology Patient Enrollment Network (OPEN). OPEN is accessed at [redacted] Contact the CTSU Help Desk with any OPEN related questions by phone or email : [redacted]	Data collection for this study will be done exclusively through Medidata Rave. Refer to the data submission section of the protocol for further instructions.

The most current version of the **study protocol and all supporting documents** must be downloaded from the protocol-specific page located on the CTSU members' website [redacted] Access to the CTSU members' website is managed through the Cancer Therapy and Evaluation Program - Identity and Access Management (CTEP-IAM) registration system and requires log in with a CTEP-IAM username and password.

Permission to view and download this protocol and its supporting documents is restricted and is based on person and site roster assignment housed in the CTSU Regulatory Support System (RSS).

Supplies can be ordered by downloading and completing the CTSU Supply Request Form (available on the protocol-specific page on the CTSU website) and submitting it as instructed on the form.

For clinical questions (i.e. patient eligibility or treatment-related) *see the Protocol Contacts, Page 4.*

For non-clinical questions (i.e. unrelated to patient eligibility, treatment, or clinical data submission) Contact the CTSU Help Desk by phone or email:
CTSU General Information Line – [redacted] All calls and correspondence will be triaged to the appropriate CTSU representative.

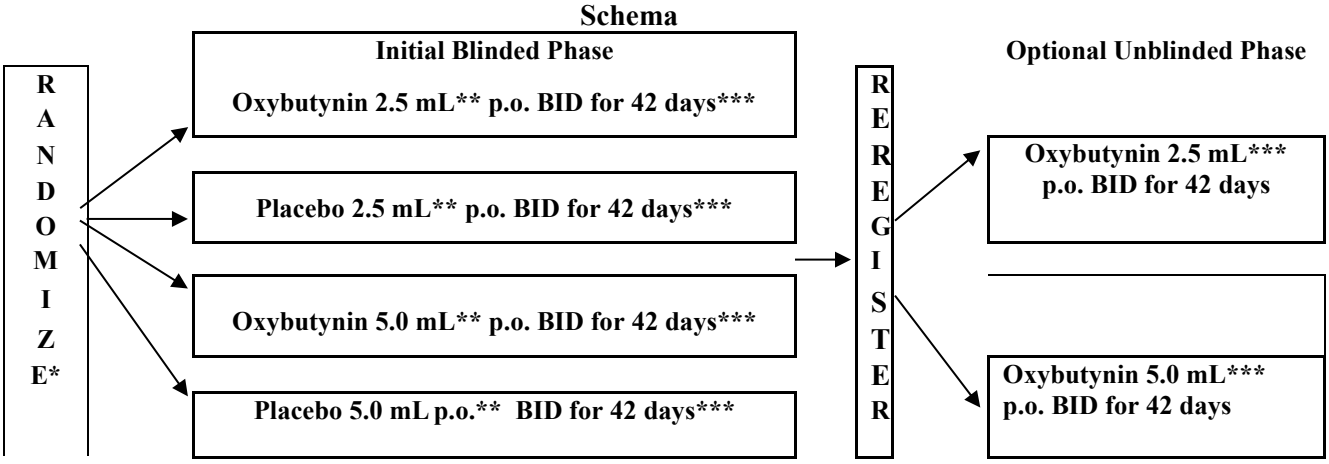
A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED PHASE II STUDY OF OXYBUTYNIN VERSUS PLACEBO FOR THE TREATMENT OF HOT FLASHES IN MEN RECEIVING ANDROGEN DEPRIVATION THERAPY

Eligibility Criteria (see Section 3.0)

- Men who are currently receiving androgen deprivation therapy (ADT) for the treatment of prostate cancer. (See §3.2.1)
- Patients must be on a stable dose of all hormone-directed therapies for at least 28 days prior to registration. Patients receiving radiation therapy are eligible. (See §3.2.2)
- Eligible patient must have bothersome hot flashes for ≥ 14 days prior to registration. (See §3.2.3)
- No current or future planned use of any of the agents listed in Section 3.2.4 during the study period. (See §3.2.4)
- No current or prior use of oxybutynin as a treatment for hot flashes. (See §3.2.5)
- Patients with a history of any of the contraindications to oxybutynin listed in Section 3.2.6 are not eligible. (See §3.2.6)
- IPSS score < 20 (See §3.2.8)
- Life expectancy of greater than 6 months. (See §3.2.9)
- Age ≥ 18 years. (See §3.2.10)
- ECOG Performance Status 0, 1 or 2. (See §3.2.11)
- Participants must be able to speak and read English. (See §3.2.12)

Required Initial Laboratory Values
None

Schema



* **Days 1-7** of study will involve collection of BSD (Baseline Symptom Documentation). Study treatment is to be administered from Days **8-49**.

** The concentration of oxybutynin is 1 mg per 1 mL, so that placebos and active treatments will maintain blinding.

*** Following 6 weeks of study treatment, the patient will be given the option of being unblinded (Section 8.3.2), and if he was on placebo, will be allowed to cross-over, be re-registered (See Section 4.7), receive either 2.5 or 5.0 mL of oxybutynin, equivalent to the amount of the placebo the patient had received prior to unblinding, for 6 weeks..

Please refer to the full protocol text for a complete description of the eligibility criteria and treatment plan.

If the Group credited for enrollment is a non-Alliance Group, then other requirements from the credited Group may apply.

Table of Contents

1.0 BACKGROUND AND RATIONALE

Therapies to decrease testosterone and other androgens are frequently utilized in men diagnosed with prostate cancer, and also in certain salivary gland tumors.[1, 2] Additionally, medications to block estrogen signaling are also commonly employed in men with estrogen and/or progesterone receptor positive breast cancer.[3] Although these therapies can have significant clinical efficacy, a rapid change in the circulating hormone levels can commonly cause patients to experience symptomatic hot flashes. Approximately 60-80% of prostate cancer patients being treated with either surgical (i.e. orchiectomy) or medical androgen deprivation therapy (ADT) will experience hot flashes.[4, 5] Hot flashes have been associated with negative impacts on patients' reported quality of life, fatigue, and sleep disturbance.[6-11] Additionally, patients with bothersome hot flashes may be less likely to complete the recommended course of ADT, which can negatively influence cancer prognosis. Given the prevalence of this symptom and the significance of associated toxicity, further study of potentially effective interventions is warranted.

1.1 Treatment of Hot Flashes in Men

A variety of different therapies have been investigated for reducing hot flashes in men. Two progesterone analogs, megestrol and medoxyprogesterone, have randomized trial evidence demonstrating a significant reduction in hot flashes, with acceptable toxicity profiles.[12, 13] Both of these trials demonstrated that greater than 70% of patients receiving the study agents reported significant reductions in hot flashes. However, some oncologists are hesitant to prescribe these agents due to overexpression of progesterone receptors in a subset of patients with prostate cancer, and the uncertain clinical effects of these medication on oncologic outcomes.[14-16] Megestrol has also been associated with a decrease in prostate-specific antigen (PSA) after withdrawal suggesting some potential therapeutic effect by the drug.[17] Gabapentin, a gamma-aminobutyric acid analog, has also been shown to be effective at reducing hot flash frequency compared to placebo in men receiving ADT.[18] In that study, a dose-dependent response to gabapentin was noted, with only patients receiving the highest dose (900 mg/day) demonstrating a statistically significant moderate improvement in hot flash scores and frequencies, compared to placebo. However, there was only a 20% reduction and that only appeared after 3 weeks. A randomized trial assessing the efficacy of both venlafaxine, a serotonin-norepinephrine reuptake inhibitor (SNRI), and soy protein revealed that neither agent was effective at reducing hot flashes in men with prostate cancer.[19] This result is notable because venlafaxine has been shown, in multiple randomized studies, to improve hot flashes in women [20, 21], thus demonstrating the importance of investigating gender-specific responses to interventions for managing hot flashes. While there are evidence-based options for treating male hot flashes, further study is warranted to identify additional interventions that provide both providers and patients with more effective means of hot flash management, with tolerable side effects.

1.2 Oxybutynin for Hot Flashes

Oxybutynin is an anti-cholinergic agent which is available in both oral and transdermal formulations. Currently, oxybutynin is approved by the Food and Drug Administration (FDA) for use in managing overactive bladder symptoms. Additionally there are randomized trial data supporting off label use for the management of hyperhidrosis, with studies showing that this effect is equal across both genders.[22-24] Oxybutynin has a very good safety profile, with the most common reported adverse effects being xerostomia, drowsiness, dizziness, mild cognitive effects, and urinary retention, which are typically mild in severity and resolve with discontinuation, if not tolerable.[25]

In 2007, a manuscript reported retrospective data that supported the efficacy of oxybutynin for managing refractory hot flash symptoms in 52 cancer patients, including four men with ADT-

induced hot flashes.[26] The promising results of this study, which suggested a 70% response rate to oxybutynin with acceptable toxicity, led to the development of Phase III, double-blind, randomized trials comparing oxybutynin to placebo in women with hot flashes.[27, 28] One such trial demonstrated that moderate doses of oxybutynin substantially decreased hot flashes with mild to moderate toxicity. [27] More recently, our group completed another study which compared oxybutynin at doses of 2.5 and 5.0 mg BID to placebo in women with symptomatic hot flashes. These results were presented as an oral abstract at the 2018 San Antonio Breast Cancer Symposium, and showed that hot flash scores were significantly reduced from baseline in both the 2.5 mg (-10.6, SD 7.7) and 5.0 mg (-16.9, SD 15.6) treatment arms compared to placebo (-5.7, SD 10.2). Additionally, hot flash frequency was significantly improved for patients receiving both dose levels of oxybutynin (2.5 mg=60% reduction, 5.0 mg=77% reduction) over those treated with placebo (27% reduction). Reported treatment-related adverse effects for participants were typically mild and there was no difference in the discontinuation of the study drug between the oxybutynin and placebo arms. [28]

Additionally, a recent letter to the editor in the *New England Journal of Medicine* highlighted a case study of a man with hot flashes related to ADT which were refractory to high doses of gabapentin and venlafaxine, who then experienced a dramatic improvement after starting oxybutynin 2.5 mg twice daily.[29] Furthermore, members of our study team have anecdotally noted positive effects on hot flash symptoms when prescribing oxybutynin to manage urinary symptoms in men with prostate cancer. These observations, coupled with the positive effect of oxybutynin on hot flashes in women, support the conduct of a double-blind, placebo-controlled trial of oxybutynin for the management of hot flashes in men receiving ADT with a primary endpoint assessing the change in hot flash scores from baseline.

1.3 Study Design

1.3.1 Baseline period:

We will utilize a one week period to obtain data regarding baseline hot flashes.

1.3.2 Hot flash measurement

Patient reported outcome (PRO) measurements will be used as per the methodology that we described 18 years ago,[30] and that has also been used in trials conducted by other investigators. The primary endpoint of this study will assess the effects of the study interventions on patient reported hot flash scores. The calculation of this metric is defined in Section 2.1.1. Definitions of hot flash severity in men will be provided, based on data we collected from male patients who participated in a previous hot flash trial, and published 25 years ago.[31] Previous studies for hot flashes in men have utilized the same outcome measures to assess the study drug's efficacy and the hot flash score represents an ideal tool for quantitating multiple aspects of hot flash symptomatology.[12, 18, 30-32] We plan to use the Hot Flash Related Daily Interference Scale (HFRDIS), a tool developed by Dr. Janet Carpenter.[33] We recently assessed face validity by asking 10 men with androgen deprivation hot flashes to review this tool. All of the HFRDIS items were assessed as clear, appropriate, and easy to interpret. The items related to work and sexuality were identified as potentially difficult to answer if the individual was retired or not sexually active, however all of the men were able to provide a numeric score for these items. We also discussed the above with Dr. Janet Carpenter, who developed the HFRDIS tool and have identified other studies that have used the HFRDIS in men receiving androgen deprivation therapy.[34-36] These studies provide additional data supporting the reliability and validity of the 10-item instrument in this population. For example, Gonzalez, et al., (2015) provided evidence of construct validity in this population by demonstrating significant differences in scores between men receiving androgen deprivation therapy and men who only undergo

prostatectomy. [34] Beer, et al. (2010) demonstrated decreasing scores on both the HFD and HFRDIS following acupuncture in men undergoing androgen deprivation therapy, supporting concurrent validity of the HFRDIS [34].

1.3.4 Cognitive effects

One potential concern when using anti-cholinergic agents, such as oxybutynin, for extended periods is the potential negative impact on cognition via interaction with muscarinic receptors within the central nervous system. Prospective studies, conducted primarily in elderly patients with overactive bladder symptoms, have demonstrated conflicting findings with regard to the effects of oxybutynin on neuro-cognition relative to placebo.[37-40] Questions relating to patient-reported cognition will be asked via the Symptom Experience Questionnaire (Appendix V) at baseline and weekly during the 6-week treatment period to help ascertain the effects of oxybutynin relative to placebo. These data will ultimately provide insight regarding the potential for cognitive toxicity with oxybutynin, which can be useful when considering the therapeutic index of this medication for treating hot flashes.

2.0 OBJECTIVES

2.1 Primary objective

2.1.1 To assess the effects of two doses of oxybutynin on hot flash scores (determined by multiplying the frequency of each defined hot flash grade by the severity [grade 0: none, 1: mild, 2: moderate, 3: severe, and 4: very severe] and summing the values over a 24-hour period) relative to placebo.

2.2 Secondary objectives

2.2.1 To assess study accrual rates and compliance with the therapy.

2.2.2 To characterize the safety and adverse event profile of two doses of oxybutynin in the study population.

2.2.3 To evaluate the consistency of the results across the various methods used to evaluate the efficacy of oxybutynin (i.e., hot flash scores versus hot flash frequencies, mean differences versus 50% or greater reduction since baseline, single day versus full week to define patients' baseline hot flash scores).

2.2.4 To compare patient-reported quality of life and hot flash interference, as measured by the HFRDIS, across arms.

2.2.5 To compare other changes in patient symptoms, as measured by the Symptom Experience Questionnaire, across arms.

3.0 PATIENT SELECTION

For questions regarding eligibility criteria, see the Study Resources page. Please note that the Study Chair cannot grant waivers to eligibility requirements.

3.1 On-Study Guidelines

This clinical trial can fulfill its objectives only if patients appropriate for this trial are enrolled. All relevant medical and other considerations should be taken into account when deciding whether this protocol is appropriate for a particular patient. Physicians should consider the risks and benefits of any therapy, and therefore only enroll patients for whom this treatment is appropriate.

Physicians should consider whether any of the following may render the patient inappropriate for this protocol:

- Psychiatric illness which would prevent the patient from giving informed consent.
- Medical condition such as uncontrolled infection (including HIV), uncontrolled diabetes mellitus or cardiac disease which, in the opinion of the treating physician, would make this protocol unreasonably hazardous for the patient.

3.2 Eligibility Criteria

Use the spaces provided to confirm a patient's eligibility by indicating Yes or No as appropriate. It is not required to complete or submit the following page(s).

When calculating days of tests and measurements, the day a test or measurement is done is considered Day 0. Therefore, if a test were done on a Monday, the Monday one week later would be considered Day 7.

___ **3.2.1 Men who are currently receiving androgen deprivation therapy (ADT) for the treatment of prostate cancer.** ADT is defined by a history of orchiectomy, or ongoing usage of gonadotropin-releasing hormone agonists or antagonists. Men receiving abiraterone, but not enzalutamide, apalutamide, and darolutamide are eligible, as the latter three are metabolized by CYP3A4 and may affect oxybutynin serum concentrations.

___ **3.2.2 Patients must be on a stable dose of all hormone-directed therapies for at least 28 days prior to registration and must not be planning to discontinue this therapy for at least 42 days following registration.**

Patients receiving radiation therapy during the study period are eligible.

___ **3.2.3 Eligible patient must have bothersome hot flashes for ≥ 14 days prior to registration, defined by an occurrence of ≥ 28 times per week and of sufficient severity to cause the patient to seek therapeutic intervention.**

___ **3.2.4 No current use or future planned use of any of the following agents during the study period: drugs that are not FDA approved for use in humans, drugs with category X interactions with oxybutynin [e.g. other anti-cholinergic agents, eluoxadloline, and potassium chloride], androgens, estrogens, progesterone analogs, gabapentin, cholinergic agonists, cholinesterase inhibitors, or complementary/alternative medicine taken for the purpose of managing hot flashes. No current or future planned use of strong CYP3A4 inhibitors (e.g. antipsychotic agents or macrolide antibiotics) during the study.**

Prior use of these agents is permitted as long as they are discontinued before registration.

____ **3.2.5 No current or prior use of oxybutynin for the treatment of hot flashes. Prior use of oxybutynin for other purposes (e.g. bladder symptoms) is allowed, as long as the patient has not taken any oxybutynin for 30 days prior to registration.**

___ **3.2.6 Comorbid conditions**

Patients with a history of any of the following contraindications to oxybutynin are not eligible: gastroparesis or gastrointestinal obstructive disorders; severe constipation defined as 2 or fewer bowel movements per week; significant gastric reflux symptoms not controlled by medication; ulcerative colitis; narrow-angle glaucoma; hypersensitivity to oxybutynin or any other components of the product; current uncontrolled hyperthyroidism; uncontrolled coronary artery disease or a history of myocardial infarction within the prior 12 months; NYHA Class II-IV congestive heart failure; symptomatic cardiac arrhythmias; current uncontrolled hypertension (average systolic >140 mm Hg and diastolic >90 mm Hg); myasthenia gravis; Parkinson's disease; or dementia.

___ **3.2.7 Patients with urinary retention requiring indwelling or intermittent self-catheterization within the prior 6 months are not eligible.**

___ **3.2.8 IPSS (Appendix III) score < 20, unless they have a post void residual confirmation of less than 300 cc residual in the bladder (that is that the patient is eligible with a higher IPSS score if a subsequent PVR test looks good).**

____ **3.2.9 Life Expectancy of greater than 6 months.**

___ **3.2.10 Age ≥ 18 years**

___ **3.2.11 ECOG Performance Status- 0, 1, or 2**

___ **3.2.12 Language:** In order to complete the mandatory patient-completed measures, participants must be able to speak and/or read English.

___ **3.2.13 Required Initial Laboratory Values:** ***None***

4.0 PATIENT REGISTRATION

4.1 Investigator and Research Associate Registration with CTEP

Food and Drug Administration (FDA) regulations and National Cancer Institute (NCI) policy require all individuals contributing to NCI-sponsored trials to register and renew their registration annually. To register, all individuals must obtain a Cancer Therapy Evaluation Program (CTEP) Identity and Access Management (IAM) account at [redacted] In addition, persons with a registration type of Investigator (IVR), Non-Physician Investigator (NPIVR), or Associate Plus (AP) must complete their annual registration using CTEP's web-based Registration and Credential Repository (RCR) at [redacted]

RCR utilizes five person registration types.

- IVR — MD, DO, or international equivalent;
- NPIVR — advanced practice providers (e.g., NP or PA) or graduate level researchers (e.g., PhD);
- AP — clinical site staff (e.g., RN or CRA) with data entry access to CTSU applications such as the Roster Update Management System [RUMS], OPEN, Rave, acting as a primary site contact, or with consenting privileges;
- Associate (A) — other clinical site staff involved in the conduct of NCI-sponsored trials; and
- Associate Basic (AB) — individuals (e.g., pharmaceutical company employees) with limited access to NCI-supported systems.

RCR requires the following registration documents:

Documentation Required	IVR	NPIVR	AP	A	AB
FDA Form 1572	✓	✓			
Financial Disclosure Form	✓	✓	✓		
NCI Biosketch (education, training, employment, license, and certification)	✓	✓	✓		
GCP training	✓	✓	✓		
Agent Shipment Form (if applicable)	✓				
CV (optional)	✓	✓	✓		

An active CTEP-IAM user account and appropriate RCR registration is required to access all CTEP and Cancer Trials Support Unit (CTSU) websites and applications. In addition, IVRs and NPIVRs must list all clinical practice sites and Institutional Review Boards (IRBs) covering their practice sites on the FDA Form 1572 in RCR to allow the following:

- Addition to a site roster;
- Assign the treating, credit, consenting, or drug shipment (IVR only) tasks in OPEN;
- Act as the site-protocol Principal Investigator (PI) on the IRB approval; and
- Assign the Clinical Investigator (CI) role on the Delegation of Tasks Log (DTL).

In addition, all investigators acting as the Site-Protocol PI (investigator listed on the IRB approval), consenting/treating/drug shipment investigator in OPEN, or as the CI on the DTL must be rostered at the enrolling site with a participating organization.

Additional information is located on the CTEP website at [redacted] For questions, please contact the **RCR Help Desk** by email at [redacted]

4.2 CTSU Site Registration Procedures

Permission to view and download this protocol and its supporting documents is restricted and is based on person and site roster assignment housed in the CTSU Regulatory Support System (RSS).

This study is supported by the NCI Cancer Trials Support Unit (CTSU).

IRB Approval

For CTEP and Division of Cancer Prevention (DCP) studies open to the National Clinical Trials Network (NCTN) and NCI Community Oncology Research Program (NCORP) Research Bases after March 1, 2019, all U.S.-based sites must be members of the NCI Central Institutional Review Board (NCI CIRB). In addition, U.S.-based sites must accept the NCI CIRB review to activate new studies at the site after March 1, 2019. Local IRB review will continue to be accepted for studies that are not reviewed by the CIRB, or if the study was previously open at the site under the local IRB. International sites should continue to submit Research Ethics Board (REB) approval to the CTSU Regulatory Office following country-specific regulations.

Sites participating with the NCI CIRB must submit the Study Specific Worksheet for Local Context (SSW) to the CIRB using IRBManager to indicate their intent to open the study locally. The NCI CIRB's approval of the SSW is automatically communicated to the CTSU Regulatory Office, but sites are required to contact the CTSU Regulatory Office at [redacted] to establish site preferences for applying NCI CIRB approvals across their Signatory Network. Site preferences can be set at the network or protocol level. Questions about establishing site preferences can be addressed to the CTSU Regulatory Office by email or calling [redacted]

In addition, the Site-Protocol Principal Investigator (PI) (i.e. the investigator on the IRB/REB approval) must meet the following criteria in order for the processing of the IRB/REB approval record to be completed:

- Holds an active CTEP status;
- Active status at the site(s) on the IRB/REB approval (*applies to US and Canadian sites only*) on at least one participating organization's roster;
- If using NCI CIRB, active on the NCI CIRB roster under the applicable CIRB Signatory Institution(s) record;
- Includes the IRB number of the IRB providing approval in the Form FDA 1572 in the RCR profile;
- Lists all sites on the IRB/REB approval as Practice Sites in the Form FDA 1572 in the RCR profile; and
- Holds the appropriate CTEP registration type for the protocol.

4.2.1 Additional Requirements

Additional site requirements to obtain an approved site registration status include:

- An active Federal Wide Assurance (FWA) number;
- An active roster affiliation with the Lead Protocol Organization (LPO) or a Participating Organization (PO);
- An active roster affiliation with the NCI CIRB roster under at least one CIRB Signatory Institution (US sites only); and
- Compliance with all protocol-specific requirements (PSRs).

4.2.2 Protocol specific requirements for A222001 site registration

Limited access information

This is a limited access study. Institutions that are interested in participating in this study must first contact [redacted] to review study requirements and procedures. See Section 14.1 for instructions regarding how to be added to this trial.

4.2.3 Downloading Site Registration Documents

Download the site registration forms from the protocol-specific page located on the CTSU members' website. Permission to view and download this protocol and its supporting documents is restricted to institutions and its associated investigators and staff on a participating roster. To view/download site registration forms:

- Log in to the CTSU members' website [redacted] using your CTEP-IAM username and password;
- Click on *Protocols* in the upper left of the screen:
    - Enter the protocol number in the search field at the top of the protocol tree; or
    - Click on the By Lead Organization folder to expand, then select *[Alliance]*, and protocol number *[A222001]*.

Click on *Documents, Protocol Related Documents, and* use the *Document Type* filter and select *Site Registration to* download and complete the forms provided. (Note: For sites under the CIRB, IRB data will load automatically to the CTSU.)

4.2.4 Submitting Regulatory Documents

Submit required forms and documents to the CTSU Regulatory Office using the Regulatory Submission Portal on the CTSU members' website.

To access the Regulatory Submission Portal log in to the CTSU members' website, go to the *Regulatory* section and select *Regulatory Submission*.

Institutions with patients waiting that are unable to use the Regulatory Submission Portal should alert the CTSU Regulatory Office immediately by phone or email: [redacted] in order to receive further instruction and support.

4.2.5 Checking your site's registration status

Site registration status may be verified on the CTSU members' website.

- Click on *Regulatory* at the top of the screen;

- Click on *Site Registration; and*
- Enter the sites 5-character CTEP Institution Code and click on Go.
    - Additional filters are available to sort by Protocol, Registration Status, Protocol Status, and/or IRB Type.

Note: The status shown only reflects institutional compliance with site registration requirements as outlined within the protocol. It does not reflect compliance with protocol requirements for individuals participating on the protocol or the enrolling investigator's status with NCI or their affiliated networks.

4.3 Patient Registration Requirements

4.3.1 Informed consent

The patient must be aware of the neoplastic nature of his/her disease and willingly consent after being informed of the procedure to be followed, the experimental nature of the therapy, alternatives, potential benefits, side-effects, risks, and discomforts. Current human protection committee approval of this protocol and a consent form is required prior to patient consent and registration.

This study includes the use of the mandatory patient completed measures. The patient reported measures are available in English. Participation in Alliance A222001 is restricted to patients who are able to speak, understand and read English.

Patient questionnaire booklets

Patient questionnaire booklets are to be ordered prior to the registration of any patients. Patient completed booklets can be ordered by downloading and completing the CTSU supply request form (located under the site registration documents section of the A222001 CTSU web site) and submitting it through the CTSU regulatory portal. Samples of the booklets are found in Appendices I-VII, which are to be used for reference and IRB submission only. They are not to be used for patient completion.

4.4 Patient Enrollment (registration/randomization procedures (Step 1))

The Oncology Patient Enrollment Network (OPEN) is a web-based registration system available on a 24/7 basis. OPEN is integrated with CTSU regulatory and roster data and with the LPOs registration/randomization systems or the Theradex Interactive Web Response System (IWRS) for retrieval of patient registration/randomization assignment. OPEN will populate the patient enrollment data in NCI's clinical data management system, Medidata Rave.

Requirements for OPEN access:

- A valid CTEP-IAM account;
- To perform enrollments or request slot reservations: Must be on an LPO roster, ETCTN corresponding roster, or participating organization roster with the role of

Registrar. Registrars must hold a minimum of an Associate Plus (AP) registration type;

- If a Delegation of Tasks Log (DTL) is required for the study, the registrars must hold the OPEN Registrar task on the DTL for the site; and
- Have an approved site registration for the protocol prior to patient enrollment.

To assign an Investigator (IVR) or Non-Physician Investigator (NPIVR) as the treating, crediting, consenting, drug shipment (IVR only), or receiving investigator for a patient transfer in OPEN, the IVR or NPIVR must list the IRB number used on the site's IRB approval on their Form FDA 1572 in RCR. If a DTL is required for the study, the IVR or NPIVR must be assigned the appropriate OPEN-related tasks on the DTL.

Prior to accessing OPEN, site staff should verify the following:

- Patient has met all eligibility criteria within the protocol stated timeframes; and
- All patients have signed an appropriate consent form and Health Insurance Portability and Accountability Act (HIPAA) authorization form (if applicable).

Note: The OPEN system will provide the site with a printable confirmation of registration and treatment information. You may print this confirmation for your records.

Access OPEN at [redacted] or from the OPEN link on the CTSU members' website. Further instructional information is in the OPEN section of the CTSU website at [redacted] For any additional questions, contact the CTSU Help Desk at [redacted]

4.5 Stratification Factors and Treatment Assignments

The randomization routine is found in Section 13 (Statistical Considerations).

4.5.1 Stratification Factors

Stratification factors include:

4.5.1.1 Daily hot flash frequency at baseline: 4 to 9 hot flashes per day versus 10 or more hot flashes per day

4.5.1.2 Hot flash duration at baseline: less than 9 months versus 9 or more months, and

4.5.1.3 Number of prior hot flash therapies (0 versus 1 or more).

4.5.2 Treatment Assignments

The factors defined in Section 4.5.1 will be used as stratification factors.

After the patient has been registered into the study, the values of the stratification factors will be recorded, and the patient will be assigned to one of the following treatment groups using the Pocock and Simon dynamic allocation procedure [41] which balances the marginal distributions of the stratification factors between the treatment groups.

- Oxybutynin: 2.5 mL oral BID Days 8 through 49 (total of 42 days)
- Oxybutynin: 5 mL oral BID Days 8 through 49 (total of 42 days)
- Placebo: 2.5 mL oral BID Days 8 through 49 (total of 42 days)
- Placebo: 5 mL oral BID Days 8 through 49 (total of 42 days)

Note: Oxybutynin concentration = 1mg/mL.

4.6 Procedures for Double-Blinding the Treatment Assignment

After the treatment assignment has been ascertained by randomization, the Registration Specialist will notify the designated unblinded data manager/nurse/pharmacist at the patient's institution. The name of this designated unblinded contact person is to be indicated in the OPEN registration system at the time of registration. **This contact person may not be involved in assessing adverse events or any other outcome measure** and should not be the same person listed on page one of the OPEN registration form as the person completing the form. The OPEN registration form should provide the source of communication, either fax or e-mail, and the appropriate contact information. The Registration Specialist will then communicate the treatment assignment "Oxybutynin 2.5 mL, Placebo 2.5 mL, Oxybutynin 5 mL or Placebo 5 mL" to designated contact at the patient's institution.

Once the treatment assignment has been communicated, the designated contact should prepare the dose of drug or placebo for delivery to the patient.

The dose will be prepared and labeled as "oxybutynin/placebo" so that the contents are not discernible to the person administering the treatment.

The pharmacist or designated contact person will maintain records that indicate the identity of the patient and their corresponding treatment assignment. The pharmacist or designated contact person at the treating site will maintain records that indicate the identity of the patient and their corresponding study medication code number.

4.7 Cross-Over Re-registration (step 2) Procedures

Patients who complete 6 weeks of study treatment and submit their questionnaires will be unblinded per the unblinding procedures in Section 8.3.2. In order to unblind the patient, site staff must call the Alliance Registration Office (507-284-4130) during regular business hours to find out if the patient was receiving oxybutynin or placebo. Site staff must ensure that the questionnaires associated with the initial cycle of treatment have been completed and sent to the study staff by the patient before proceeding with unblinding, as these are related to the assessment of the primary endpoint of the study.

If the patient was receiving placebo, he will be allowed to cross over and receive oxybutynin at the discretion of the treating physician.

Patients who choose to enter the cross-over phase will be re-registered as follows:

1. Site staff will log into the OPEN registration system and select the appropriate patient.
2. Then select the next registration step. (Step 2)
3. Complete the OPEN Enrollment Form for the patient to be re-registered for the continuation phase. The patient will be re-registered to oxybutynin 2.5 or 5.0 mL, equivalent to whichever dose of placebo the patient was receiving prior to unblinding.
4. Verify the patient turned in their questionnaires for the initial cycle of treatment, yes/no.
5. Once the re-registration to the crossover phase is successfully completed, a confirmation email will be sent to the CRP.

If assistance is needed with this process, contact the Alliance Registration Office at [redacted]

Following re-registration, the designated contact will be notified by the CRP so that s/he can prepare drug for delivery to the patient. Patient should be told that he may need to come back to the clinic to pick up open label supplies.

5.0 STUDY CALENDAR

Pre-study Testing Intervals:

The pre-study testing intervals are guidelines only. Laboratory and clinical parameters during treatment are to be followed using individual institutional guidelines and the best clinical judgment of the responsible physician. It is expected that patients on this study will be cared for by physicians experienced in the treatment and supportive care of patients on this trial.

When calculating days of tests and measurements, the day a test or measurement is done is considered Day 0. Therefore, if a test were done on a Monday, the Monday one week later would be considered Day 7.

To be completed ≤ 60 DAYS before registration: History and physical.

	Prior to Registration	**Baseline booklets (Days 1-7)**	**Daily during treatment (Days 8-49)**	**End of each week of treatment**
Tests & Observations				
History and physical, including Vital signs	X			
Height, Weight, ECOG PS	X			
Baseline Symptom Documentation (Appendix II)		X (1)		
International Prostate Symptom Score- (Appendix III)	X			X
Hot Flash Diary (Appendix IV)			X	
Symptom Experience Questionnaire (Appendix V)		A (1)		X
Hot Flash Related Daily Interference Scale (HFRDIS) (Appendix VI)		A (1)		B(2)
Telephone Contact and AE assessment (Appendix VII)				X (2)

1 Nurse/research coordinator should call the patient, to remind him to send in the baseline questionnaire booklets to the site, which are required to be completed prior to start of study treatment.

2 All patients will receive weekly phone calls from study staff (nurse or research coordinator), to document compliance with study drug, encourage completion of patient questionnaires, assess adverse events, and address any patient concerns or problems. They will also remind the patient to return the completed questionnaire booklets. For patients who choose to cross over, nurse phone calls will occur weekly to assess adverse events during the unblinded cross over phase. (See Section 7.3)

A To be completed on Day 7.

B To be completed at the end of Weeks 2, 4 and 6 only (Weeks 3, 5 and 7 when measured from registration).

6.0 DATA SUBMISSION

6.1 Data Collection and Submission

6.1.1 Data submission schedule

A Data Submission Schedule (DSS) is available on the Alliance study webpage, within the Case Report Forms section. The Data Submission Schedule is also available on the CTSU site within the study-specific Case Report Forms folder.

6.1.2 Medidata Rave

Medidata Rave is a clinical data management system being used for data collection for this trial/study. Access to the trial in Rave is controlled through the CTEP-IAM system and role assignments.

Requirements to access Rave via iMedidata:

- A valid CTEP-IAM account; and
- Assigned a Rave role on the LPO or PO roster at the enrolling site of: Rave CRA, Rave Read Only, Rave CRA (LabAdmin), Rave SLA, or Rave Investigator.

Rave role requirements:

- Rave CRA or Rave CRA (Lab Admin) role must have a minimum of an Associate Plus (AP) registration type;
- Rave Investigator role must be registered as an Non-Physician Investigator (NPIVR) or Investigator (IVR); and
- Rave Read Only role must have at a minimum an Associates (A) registration type.

Refer to [redacted] for registration types and documentation required.

This study has a Delegation of Tasks Log (DTL). Therefore, those requiring write access to Rave must also be assigned the appropriate Rave tasks on the DTL.

Upon initial site registration approval for the study in Regulatory Support System (RSS), all persons with Rave roles assigned on the appropriate roster will be sent a study invitation email from iMedidata. To accept the invitation, site staff must either click on the link in the email or log in to iMedidata via the CTSU members' website under *Data Management > Rave Home* and click to *accept* the invitation in the *Tasks* pane located in the upper right corner of the iMedidata screen. Site staff will not be able to access the study in Rave until all required Medidata and study specific trainings are completed. Trainings will be in the form of electronic learnings (eLearnings) and can be accessed by clicking on the eLearning link in the *Tasks* pane located in the upper right corner of the iMedidata screen. If an eLearning is required for a study and has not yet been taken, the link to the eLearning will appear under the study name in the *Studies* pane located in the center of the iMedidata screen; once the successful completion of the eLearning has been recorded, access to the study in Rave will be granted, and a *Rave EDC* link will replace the eLearning link under the study name.

Site staff that have not previously activated their iMedidata/Rave account at the time of initial site registration approval for the study in RSS will receive a separate invitation from iMedidata to activate their account. Account activation instructions are located on

the CTSU website in the Data Management section under the Rave resource materials (Medidata Account Activation and Study Invitation Acceptance). Additional information on iMedidata/Rave is available on the CTSU members' website in the Data Management > Rave section at [redacted] or by contacting the CTSU Help Desk at [redacted] or by email at [redacted]

6.1.3 Data Quality Portal

The Data Quality Portal (DQP) provides a central location for site staff to manage unanswered queries and form delinquencies, monitor data quality and timeliness, generate reports, and review metrics.

The DQP is located on the CTSU members' website under Data Management. The Rave Home section displays a table providing summary counts of Total Delinquencies and Total Queries. DQP Queries, DQP Delinquent Forms, DQP Form Status and the DQP Reports modules are available to access details and reports of unanswered queries, delinquent forms, forms with current status and timeliness reports. Review the DQP modules on a regular basis to manage specified queries and delinquent forms.

The DQP is accessible by site staff that are rostered to a site and have access to the CTSU website. Staff that have Rave study access can access the Rave study data using a direct link on the DQP.

To learn more about DQP use and access, click on the Help icon displayed on the Rave Home, DQP Queries, DQP Delinquent Forms, DQP Form Status, and DQP Reports modules.

6.2 Submission of Patient Completed Measures

Patient-completed questionnaire booklets for this study are to be ordered prior to the registration of any patients (see Section 4.3). Samples of questionnaire booklets are available in Appendices I-VII for reference and IRB submission only. They are not to be used for patient completion. Booklets must be given to patients to complete and patients should be instructed to return the booklets to site staff either in person or by mail and site staff will enter patient responses into Medidata Rave. At visits in which booklets are to be completed, the booklet should be given to the patient before any discussion of the patient's health status or test results. The PRO submission schedule is provided in the Study Calendar.

Weekly Booklets: Six booklets to be completed weekly must be given to patients to complete at home and patients should be instructed to return the booklets by mail weekly or to return the booklets at their regularly scheduled clinic visit. Institutions must provide patients with sufficient self-addressed stamped envelopes for this purpose. Site staff will enter patient responses into Rave upon receipt of the completed booklets.

Verbal administration of the measures for visually impaired patients is permitted if the verbal administration of the measure is conducted in a language understandable to the patients.

6.2.1 Patient Language Considerations

The patient reported measures are available in English. Participation in Alliance A222001 is restricted to patients who are able to speak, understand and read English. Ad-hoc translation of patient-completed measures is not permitted.

7.0 TREATMENT PLAN/INTERVENTION

Protocol treatment is to begin ≤ 8 days of registration.

For questions regarding treatment, please see the study contacts page.

This is a randomized, double-blind trial. The pharmacist or designated contact (see Section 4.6) at the institution will be informed of the patient's randomization, so that they may prepare oxybutynin or placebo for delivery to the patient (see Section 10.0).

The placebo arms will be half the size as the oxybutynin arms, as they will be combined to have a placebo group with the same number of patients as the two different dose groups. This allows all patients to be blinded as to whether they are receiving active drug or a placebo.

Patients will be assigned to one of the following treatment groups, and continue to receive treatment for 6 weeks (i.e., 42 days):

	Days 1-7	Days 8-49
Oxybutynin 2.5 mL	Patients on all arms will be asked to complete questionnaires as baseline symptom documentation on Days 1-7, before starting study treatment on Day 8.	**Oxybutynin 2.5 mL* PO twice a day**
Placebo 2.5 mL		**Placebo 2.5 mL* PO twice a day**
Oxybutynin 5 mL		**Oxybutynin 5.0 mL* PO twice a day**
Placebo 5.0 mL		**Placebo 5.0 mL* PO twice a day**

* *Note that the concentration of oxybutynin is 1 mg per 1 ml, so that placebos and active treatments will maintain blinding.*

Upon completion of the 6-week study period, patients will be contacted to ensure they have completed all required questionnaires.

7.1 Baseline Symptom Documentation

The patient will be instructed not to take any study medication for the first seven days of the study, but to complete their daily questionnaires (Baseline Symptom Documentation – Appendix II) during this baseline period. At the end of the week, patients will complete Symptom Experience Questionnaire (Appendix V) and Hot Flash Related Daily Interference Scale (Appendix VI).

7.2 Oxybutynin/Placebo

Beginning on Day 8 of the study, and for the subsequent six weeks, patients will be instructed to take their study medication as illustrated below.

- Oxybutynin: 2.5 mL oral BID Days 8 through 49 (total of 42 days)
- Placebo: 2.5 mL oral BID Days 8 through 49 (total of 42 days)
- Oxybutynin: 5.0 mL oral BID Days 8 through 49 (total of 42 days)
- Placebo: 5.0 mL oral BID Days 8 through 49 (total of 42 days)

7.3 Patient Unblinding and optional crossover

Patients will be contacted on their last scheduled day of the study treatment. It should be assured that the patient has completed his questionnaires. Then the patient may be unblinded per the procedures described in Section 8.3.

If the patient was receiving placebo, he may choose to crossover to oxybutynin 2.5 or 5.0 mL, equivalent to whichever dose of placebo the patient was receiving prior to unblinding. This crossover will require a second registration (see Section 4.7 for re-registration instructions). The duration of treatment for patients who crossover will be 6 weeks.

8.0 DOSE AND TREATMENT MODIFICATIONS, UNBLINDING

8.1 Ancillary Therapy, Concomitant Medications, and Supportive Care

8.1.1 Patients should not receive any other treatment or participate in trials which would be considered treatment for hot flashes or impact the primary endpoint. Simultaneous enrollment on other treatment studies is not allowed during the 7 week study period.

8.1.2 Patients should receive full supportive care while on this study. This includes blood product support, antibiotic treatment, and treatment of other newly diagnosed or concurrent medical conditions. All blood products and concomitant medications such as antidiarrheals, analgesics, and/or antiemetics received from the first day of study treatment administration until 30 days after the final dose will be recorded in the medical records.

8.1.3 Treatment of the patient's cancer should not be influenced by this study. If the patient stops ADT while participating in the study, it should be recorded on the study forms.

8.2 Dose Modifications

Dose modifications to the patient's cancer treatment are up to the discretion of the treating physician. During participation in the study, if the patient develops any symptoms attributed to the drug that are considered to be of unacceptable severity by the patient and/or physician, oxybutynin/placebo doses will be adjusted as follows:

Dose modifications for adverse events	
Low Dose (2.5 mL BID)	Maintain prescribed dose, but decrease frequency from BID to once daily. If symptoms are still unacceptable by the patient and/or physician, drug will be discontinued and patient will be taken off study.
High Dose (5.0 mL BID)	If toxicity occurs, decrease dose from 5 mL BID to 2.5 mL BID. If symptoms persist, decrease dose from 2.5 mL BID to 2.5 mL once daily. If symptoms are still unacceptable by the patient and/or physician, the drug will be discontinued and patient will be asked to complete questionnaires to date and then be taken off study.

Urinary retention: For patients on both doses, if at any time during treatment, the patient develops severe urinary symptoms, he should immediately discontinue study treatment and get a post void residual ultrasound assessment as clinically indicated.

8.3 Unblinding Procedures

Unblinding can be done only in cases of an emergency or at the end of study treatment. Follow the directions below to unblind patient treatment. Please note that if a treatment assignment is unblinded, the patient must discontinue protocol therapy.

8.3.1 Emergency Unblinding Procedures

Examples of emergencies include 1) a life-threatening unexpected adverse event that is at least possibly related to the investigational agent and for which unblinding would influence treatment decisions; or 2) medication error, such as accidental overdose. Expected adverse events are listed in the "Toxicities" section below.

Contact the Alliance Executive Officer on call by calling [redacted]

The institution must provide the following information to the Alliance Executive Officer:

- Alliance study ID (i.e., "A222001")
- Alliance patient ID number (e.g., "999999")
- Patient initials (e.g., "L,F,M")
- Institution name
- Name and telephone number of treating physician
- Name and contact information of person requesting the unblinding procedure
- Name and contact information of person to inform of treatment assignment
- Reason for emergency unblinding

Please remember that emergency unblinding request may be authorized only by an Alliance Executive Officer, and emergency unblinding applies only if unblinding would influence management of the medical situation. After the Executive Officer deems unblinding is warranted, the treatment assignment will be provided to the contact person at the treating site.

8.3.2 Protocol-specified unblinding—Crossover Unblinding at end of treatment

The steps for unblinding a patient upon completion of study treatment are as follows:

1. Patient has completed 6 weeks of study treatment.
2. Site completes the form documenting end of treatment in Rave.
3. Site calls the registration office to unblind the patient; registration office confirms receipt of the end of treatment form with statistics and data center in order to communicate patient treatment assignment to site.

Contact the Alliance Registration Office at [redacted] during regular business hours. Upon confirmation by the Primary Statistician (or designee) that the criteria for unblinding have been met, the treatment assignment may be unblinded. No Alliance Executive Officer (or designee) approval is required.

9.0 ADVERSE EVENTS

The prompt reporting of adverse events is the responsibility of each investigator engaged in clinical research, as required by Federal Regulations. Adverse events must be described and graded using the terminology and grading categories defined in the NCI's Common Terminology Criteria for Adverse Events (CTCAE), Version 5.0. The CTCAE is available at [redacted] Attribution to protocol treatment for each adverse event must be determined by the investigator and reported on the required forms. Please refer the NCI Guidelines: Adverse Event Reporting Requirements for further details on AE reporting procedures.

9.1 Routine Adverse Event Reporting

Adverse event data collection and reporting, which are required as part of every clinical trial are done to ensure the safety of patients enrolled in the studies as well as those who will enroll in future studies using similar agents. Adverse events are reported in a routine manner at scheduled times according to the study calendar in Section 5.0.

9.1.1 Solicited adverse events

There are no additional solicited adverse events for this trial.

9.2 CTCAE Routine Reporting Requirements

The following table outlines the combinations of time points, grades and attributions of AEs that require routine reporting to the Alliance Statistics and Data Center. Questions about routine reporting should be directed to the Data Manager.

Combinations of CTCAE Grade & Attribution Required for Routine AE Data Submission on Case Report Forms (CRFs)

Attribution	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Unrelated			a	a	a
Unlikely			a	a	a
Possible		a	a, b	a, b	a, b
Probable		a	a, b	a, b	a, b
Definite		a	a, b	a, b	a, b

a) **Adverse Events: Other CRF** - Applies to AEs occurring between registration and within 30 days of the patient's last treatment date, or as part of the Clinical Follow-Up Phase.

b) **Adverse Events: Late CRF** - Applies to AEs occurring greater than 30 days after the patient's last treatment date.

9.3 Expedited Adverse Event Reporting (CTEP-AERS)

Investigators are required by Federal Regulations to report serious adverse events as defined in the table below. The descriptions and grading scales found in the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for AE reporting. The CTCAE is identified and located on the CTEP website at: [redacted] All appropriate treatment areas should have access to a copy of the CTCAE. All reactions determined to be "reportable" in an expedited manner must be reported using the Cancer Therapy Evaluation Program Adverse Event Reporting System (CTEP-AERS).

For further information on the NCI requirements for SAE reporting, please refer to the 'NCI Guidelines for Investigators: Adverse Event Reporting Requirements' document published by the NCI.

Note: All deaths on study require both routine and expedited reporting regardless of causality. Attribution to treatment or other cause should be provided.

9.3.1 Late Phase 2 and Phase 3 Studies: Expedited Reporting Requirements for Adverse Events that Occur on Studies under an IND/IDE within 30 Days of the Last Administration of the Investigational Agent/Intervention[1, 2]

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)
NOTE: Investigators **MUST** immediately report to the sponsor (NCI) **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)
An adverse event is considered serious if it results in **ANY** of the following outcomes:

1) Death
2) A life-threatening adverse event
3) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5) A congenital anomaly/birth defect.
6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

ALL SERIOUS adverse events that meet the above criteria **MUST** be immediately reported to the NCI via electronic submission within the timeframes detailed in the table below.

Hospitalization	Grade 1 Timeframes	Grade 2 Timeframes	Grade 3 Timeframes	Grade 4 & 5 Timeframes
Resulting in Hospitalization ≥ 24 hrs	10 Calendar Days			24-Hour 5 Calendar Days
Not resulting in Hospitalization ≥ 24 hrs	Not required		10 Calendar Days	

NOTE: Protocol specific exceptions to expedited reporting of serious adverse events are found in the Specific Protocol Exceptions to Expedited Reporting (SPEER) portion of the CAEPR

Expedited AE reporting timelines are defined as:

- "24-Hour; 5 Calendar Days" - The AE must initially be submitted electronically within 24 hours of learning of the AE, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.
- "10 Calendar Days" - A complete expedited report on the AE must be submitted electronically within 10 calendar days of learning of the AE.

[1]Serious adverse events that occur more than 30 days after the last administration of investigational

agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:
Expedited 24-hour notification followed by complete report within 5 calendar days for:
- All Grade 4, and Grade 5 AEs

Expedited 10 calendar day reports for:
- Grade 2 adverse events resulting in hospitalization or prolongation of hospitalization
- Grade 3 adverse events

[2]For studies using PET or SPECT IND agents, the AE reporting period is limited to 10 radioactive half-lives, rounded UP to the nearest whole day, after the agent/intervention was last administered. Footnote "1" above applies after this reporting period.

Effective Date: May 5, 2011

9.3.2 Expedited AE reporting timelines defined

- "24 hours; 5 calendar days" – The investigator must initially report the AE via CTEP-AERS ≤ 24 hours of learning of the event followed by a complete CTEP-AERS report ≤ 5 calendar days of the initial 24-hour report.
- "10 calendar days" - A complete CTEP-AERS report on the AE must be submitted ≤ 10 calendar days of the investigator learning of the event.

Any medical event equivalent to CTCAE grade 3, 4, or 5 that precipitates hospitalization (or prolongation of existing hospitalization) must be reported regardless of attribution and designation as expected or unexpected with the exception of any events identified as protocol-specific expedited adverse event reporting exclusions (see below).

Any event that results in persistent or significant disabilities/incapacities, congenital anomalies, or birth defects must be reported via CTEP-AERS if the event occurs following treatment with an agent under an IND.

Use the NCI protocol number and the protocol-specific patient ID provided during trial registration on all reports.

9.3.3 Additional Instructions or Exclusions to CTEP-AERS Expedited Reporting Requirements

All adverse events reported via CTEP-AERS (i.e., serious adverse events) should also be forwarded to your local IRB.

Alliance A222001 uses a drug under an Alliance IND. The reporting requirements for investigational agents under a CTEP IND should be followed for all agents (any arm) in this trial.

Treatment expected adverse events include those listed in Section 10.0 and in the package insert.

CTEP-AERS reports should be submitted electronically.

Death

Death due to progressive disease should be reported as Grade 5 "Disease progression" in the system organ class (SOC) "General disorders and administration site conditions." Evidence that the death was a manifestation of underlying disease (e.g., radiological changes suggesting tumor growth or progression: clinical deterioration associated with a disease process) should be submitted.

Any death occurring within 30 days of the last dose, regardless of attribution to the investigational agent/intervention requires expedited reporting within 24 hours.

Any death occurring greater than 30 days after the last dose of the investigational agent/intervention requires expedited reporting within 24 hours only if it is possibly, probably, or definitely related to the investigational agent/intervention.

New Malignancies

All new malignancies must be reported via CTEP-AERS whether or not they are thought to be related to either previous or current treatment. All new malignancies should be reported, i.e. solid tumors (including non-melanoma skin malignancies), hematologic malignancies, myelodysplastic syndrome/acute myelogenous leukemia, and in situ tumors.

Whenever possible, the CTEP-AERS reports for new malignancies should include tumor pathology, history or prior tumors, prior treatment/current treatment including duration, any associated risk factors or evidence regarding how long the new malignancy may have been present, when and how the new malignancy was detected, molecular characterization or cytogenetics of the original tumor (if available) and of any new tumor, and new malignancy treatment and outcome, if available.

Secondary Malignancy

A secondary malignancy is a cancer caused by treatment for a previous malignancy (e.g., treatment with investigational agent/intervention, radiation or chemotherapy). A secondary malignancy is not considered a metastasis of the initial neoplasm.

CTEP requires all secondary malignancies that occur following treatment with an agent under an NCI IND/IDE be reported via CTEP-AERS. Three options are available to describe the event:

- Leukemia secondary to oncology chemotherapy (e.g., acute myelocytic leukemia [AML])
- Myelodysplastic syndrome (MDS)
- Treatment-related secondary malignancy

Any malignancy possibly related to cancer treatment (including AML/MDS) should also be reported via Rave.

Second Malignancy

A second malignancy is one unrelated to the treatment of a prior malignancy (and is NOT a metastasis from the initial malignancy). Second malignancies require ONLY routine reporting unless otherwise specified.

10.0 DRUG INFORMATION

10.1 Oxybutynin Chloride Oral Syrup (Ditropan)

IND: Alliance A222001 uses Oxybutynin under an Alliance IND.

Procurement

Oxybutynin Chloride 5mg/5 mL oral syrup (473 mL) and ORA-Sweet® Solution (473 mL) stock bottles will be provided and shipped by McKesson Clinical Research Services to sites.

After receiving IRB approval for this study, each participating institution will order a starter supply of three bottles of oxybutynin oral syrup and two bottles of ORA-Sweet® solution from McKesson Clinical Research Services by faxing or emailing the Alliance Clinical Drug Order/Return Form to:

[redacted]

The A222001 Oxybutynin/Placebo Order Form can be found on the A222001 study page of the Alliance and CTSU websites.

Each site is responsible for monitoring their inventory and ordering additional bottles as needed. Each site will provide their own 16 oz. amber bottles.

Sites are also expected to provide each patient with an oral syringe to measure and take their medication, along with instructions for rinsing and reusing it for the duration of the study.

Main member institutions will be provided a per patient reimbursement by the Alliance for their rebottling services and supplies.

Within ninety days after the last patient is treated at the institution, any expired or remaining supplies should be destroyed according to institutional procedure.

Preparation

The designated unblinded person at each institution will transfer either oxybutynin chloride 5 mg/5 mL oral syrup or ORA-Sweet® solution into one 16 oz amber bottles based on the patient's treatment assignment. This should be a sufficient supply for the entire 42 days of treatment. The bottles will be labeled "oxybutynin 5 mg/5 mL or placebo solution". A maximum expiration date of 6 months should be assigned to the dispensed bottles. If drug supply will expire less than 6 months from the dispense date, then site must confirm that sufficient in-date supply is available for the duration of intervention.

Below is the label template for the blinded phase:

RX#_____DATE_____

PT NAME _____

INVESTIGATOR _____

Study A222001: Take by mouth twice daily for 42 days as directed by the study team.

Oxybutynin 5mg/5ml or Placebo Oral Syrup

Dispense: 473ml Expiration Date: _____

Store at room temperature, 15– 30 °C (59 to 86°F)

Sponsor: [redacted]

CAUTION: NEW DRUG -LIMITED BY FEDERAL (OR UNITED STATES) LAW TO INVESTIGATIONAL USE ONLY

For patients who are re-registered to the cross over phase, the bottles need to be open label "Oxybutynin 2.5 or 5.0 mL" depending on which dose the patient is assigned to receive.

Below is the label template for the cross over phase:

RX#_____DATE_____

PT NAME _____

INVESTIGATOR _____

Study A222001: Take by mouth twice daily for 42 days as directed by the study team.

Oxybutynin 5mg/5ml Oral Syrup

Dispense: 473ml Expiration Date: _____

Store at room temperature, 15– 30 °C (59 to 86°F)

Sponsor: [redacted]

CAUTION: NEW DRUG -LIMITED BY FEDERAL (OR UNITED STATES) LAW TO INVESTIGATIONAL USE ONLY

Drug Accountability

Drug accountability logs must be kept for the oxybutynin 5 mg/5 mL oral syrup and the ORA-Sweet® oral solution.

Investigator Brochure Availability

The current version of the package insert for the agents will be accessible to site investigators and research staff through the Alliance office.

Availability

Oxybutynin oral syrup is available as 5 mg/5mL concentration with raspberry flavor. The solution contains citric acid, D&C Yellow No 10, FD&C Blue No 1, glycerin, liquid sugar, methylparaben, propylene glycol, sodium citrate, and sorbitol solution.

Storage and Stability

Store at Controlled Room Temperature, 15–30°C (59–86°F).

Administration

Oxybutynin/placebo will be administered at a dosage of either 2.5mg/2.5ml or 5mg/5ml two times daily. Study medication can be taken with or without food.

Drug Interactions

The concomitant use of oxybutynin with other anticholinergic drugs or with other agents which produce dry mouth, constipation, somnolence (drowsiness), and/or other anticholinergic-like effects may increase the frequency and/or severity of such effects.

Anticholinergic agents may potentially alter the absorption of some concomitantly administered drugs due to anticholinergic effects on gastrointestinal motility. Anticholinergic agents may also antagonize the effects of prokinetic agents, such as metoclopramide.

Mean oxybutynin plasma concentrations were approximately 3 to 4 fold higher when oxybutynin chloride tablets were administered with ketoconazole, a potent CYP3A4 inhibitor.

Other CYP3A4 inhibitors, such as antimycotic agents (e.g., itraconazole and miconazole) or macrolide antibiotics (e.g., erythromycin and clarithromycin), may alter oxybutynin mean pharmacokinetic parameters. The clinical relevance of such potential interactions is not known. Caution should be used when such drugs are co-administered.

Pharmacokinetics

Time to peak concentration: Oral: 0.89 $\pm$ 0.34 hours. Oxybutynin contains both the R- and S-isomers, the R-isomer contributes most to the antimuscarinic activity of oxybutynin.

Bioavailability: The absolute bioavailability of oxybutynin is 6%, although there is wide interindividual variation following oral administration. Food slightly delays absorption and increases bioavailability by 25%.

Metabolism: Hepatic, extensive particularly the CYP3A4 isoenzyme

Half-life elimination: Normal renal function: 2-3 hours

Excretion: Renal, less than 0.1% unchanged as parent compound or as the metabolite N-desethyloxybutynin.

Adverse Events

Consult the package insert for the most current and complete information.

Following administration of oxybutynin chloride, the following symptoms may occur:

Cardiovascular: Palpitations, tachycardia, vasodilatation

Dermatologic: Decreased sweating, rash

Gastrointestinal/Genitourinary: Constipation, decreased gastrointestinal motility, dry mouth, nausea, urinary hesitance and retention

Nervous System: Asthenia, dizziness, drowsiness, hallucinations, insomnia, restlessness

Ophthalmic: Amblyopia, cycloplegia, decreased lacrimation, mydriasis

Other: Impotence, suppression of lactation

Nursing Guidelines

1. Use extreme caution when oxybutynin is administered with any other anticholinergic agents as increased side effects can occur (i.e. dry mouth, constipation, somnolence).
2. Instruct patients to report any palpitations or tachycardia to the study team.
3. Patients may experience rash. Inform patients to report skin changes to the study team.
4. Warn patients that they may have decreased sweating abilities. They should use caution if out in the heat and to avoid becoming overheated.
5. Gastrointestinal effects can be seen including constipation, decreased GI motility, nausea, vomiting, and dry mouth. Treat symptomatically and monitor for effectiveness.
6. Warn patients of possible urinary hesitation and retention. If patient has difficulty voiding they should report this to the study team immediately.
7. Patients may experience neurologic side effects including dizziness, hallucinations, drowsiness and/or insomnia. Instruct patients to use caution when operating a vehicle or other activities that require close attention until they know how they respond to agent.

8. Effects on the eye can include amblyopia (lazy eye), cycloplegia (paralysis of ciliary muscle-leading to inability to focus on close objects), decreased tears and mydriasis (abnormal pupil dilation). Instruct patient to report any of these to the study team.
9. Warn men that this agent can cause impotence and suppress lactation in women.

10.2 Placebo Oral Solution

Procurement

Please see ordering instructions in Section 10.1, for both active agent and placebo.

The placebo for this study will be ORA-Sweet® SF and ORA-Sweet®. ORA-Sweet® SF and ORA-Sweet® are a berry citrus flavored inert syrup vehicle. The ORA-Sweet® SF contains purified water, sorbitol, sodium saccharin, xanthan gum, and flavoring. It is buffered with citric acid and sodium phosphate, and preserved with methylparaben, propylparaben, and potassium sorbate. ORA-Sweet® SF contains FD&C Red#40 and is sugar-free and alcohol-free. ORA-Sweet® contains purified water, sucrose, glycerin, sorbitol, and flavoring. It is buffered with citric acid and sodium phosphate, and preserved with methylparaben and potassium sorbate.

Storage and Stability

Store at Controlled Room Temperature, 15–30°C (59–86°F). Store in original container, protected from direct sunlight and moisture.

11.0 MEASURES

Before they start treatment and during the course of study treatment, patients will be asked to assess the severity of their hot flashes (descriptions provided in Appendix I) and complete a baseline symptoms determination (Appendix II) (Week 1 only), daily Hot Flash Diaries (Appendix IV), along with weekly Symptom Experience Questionnaires (Appendix V). The Hot Flash Related Daily Interference Scale (HFRDIS) (Appendix VI) will be completed prior to initiation of and at the conclusion of study treatment. All patients will receive weekly phone calls from study staff (Appendix VII) to document compliance with study drug, encourage completion of requisite study questionnaires, collect adverse events and address any patient concerns or problems.

11.1 Baseline Symptom Determination (Appendix II)

The baseline symptoms determination is completed after registration and randomization but prior to initiation of study treatment. This form has patients record the number of total hot flashes they experience on a daily basis, along with the number of hot flashes according to severity (mild, moderate, severe, or very severe) over the first 7 days of the study period. It is estimated that completing the baseline symptom determination will take 3-5 minutes daily. Questionnaires should be returned to the investigator at the end of the baseline week (week 1) and at the end of treatment (i.e., after the 7th week following study entry). The patient should be supplied with two addressed/stamped envelopes for returning the forms.

11.2 International Prostate Symptom Score (IPSS) (Appendix III)

This tool has been added to this study at screening and to be completed at the end of every week of treatment in response to FDA recommendations to ensure that patients do not have urinary retention issues. This is an 8-item scale, widely used in clinical practice, which measures lower urinary tract symptoms. It includes questions encompassing incomplete bladder emptying, frequent urination, urgency, nocturia, intermittency, weak stream, straining, and quality of life related to urinary symptoms[42].

There are robust data to suggest that prostate cancer patients on active surveillance experience significantly decreased urinary health relative to men without prostate cancer. In a cohort analysis of 6,000 community dwelling older men, we observed that compared to men without prostate cancer, men with prostate cancer on active surveillance (i.e. those who had not undergone treatment) reported a significantly diminished quality of life due to urinary symptoms[43].

11.3 Hot Flash Diary (Appendix IV)

The Hot Flash Diary is completed daily during each of the 6 weeks that patients are taking the study treatment. Like the Baseline Symptom Determination, the form has patients report the number and severity of their daily hot flashes. Additionally, it has them report how many doses of the study drug they took on each day. Completion of the Hot Flash Diary is anticipated to take less than a minute per day.

11.4 Symptom Experience Questionnaire (Appendix V)

The Symptom Experience Questionnaire is collected at the end each of the 7 weeks of the study period. This form collects patient reported toxicity and quality of life data using a 0-10 scale, with one question that allows an unstructured response to report symptoms not captured in the questions provided. Estimated completion time for the Symptom Experience Questionnaire is 10-15 minutes each week.

11.5 Hot Flash Related Daily Interference Scale (HRFDIS) (Appendix VI)

Hot Flash Related Daily Interference Scale (HFRDIS), a tool developed by Dr. Janet Carpenter.[33] We recently asked 10 men with androgen deprivation hot flashes, to review this tool. All of the HFRDIS items were assessed as clear, appropriate, and easy to interpret. The items related to work and sexuality were identified as potentially difficult to answer if the individual was retired or not sexually active, however all of the men were able to provide a numeric score for these items. We also discussed the above with Dr. Janet Carpenter, who developed the HFRDIS tool and have identified other studies that have used the HFRDIS in men receiving androgen deprivation therapy [34-36]. These studies provide additional data supporting the reliability and validity of the 10-item instrument in this population.

The Hot Flash Related Daily Interference Scale is to be completed by all participants at baseline (Week 1) and at the conclusion of the study (Week 7). It will also be completed at the end of Weeks 2 and 4 of study treatment, as it asks questions related to hot flashes over the past two weeks. This 10-item questionnaire uses a 1-10 scale to assess the interference caused by hot flash symptoms with specific aspects of patients' personal lives. Each completion of the HFRDIS is expected to take 5 minutes.

11.6 Nurse Telephone Contact (Appendix VII)

All patients will receive weekly phone calls from study staff, to document compliance with study drug, encourage completion of requisite study questionnaires, and address any patient concerns or problems and assess adverse events. The nurse weekly phone calls will continue during the optional cross over phase, to assess and collect adverse events during this time.

12.0 END OF TREATMENT/INTERVENTION

12.1 Duration of Protocol Treatment

Protocol treatment is to continue for 6 week*s* from the time of start of treatment. Please see the study calendar (Section 5.0) and the treatment section (Section 7.0) for treatment and follow up time periods.

12.2 Criteria for Discontinuation of Protocol Treatment/Intervention

In the absence of treatment delays due to adverse event(s), treatment may continue until one of the following criteria applies:

- Disease progression (if applicable)
- Intercurrent illness that prevents further administration of treatment
- Unacceptable adverse event(s)
- Patient decides to withdraw from the study
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator
- Patient non-compliance
- Termination of the study by sponsor
- The drug manufacturer can no longer provide the study agent (if applicable)

The reason(s) for protocol therapy discontinuation, the reason(s) for study removal, and the corresponding dates must be documented in the Case Report Form (CRF).

12.3 Follow-up

12.3.1 Duration of Follow-up

Protocol treatment is to continue for 6 weeks. Please follow the data submission requirements outlined in the study calendar (Section 5.0). There is no further clinical or survival follow up beyond the 6-week study period. For patients who participate in the optional crossover phase, there will be a 6-week follow up.

12.3.2 Follow-up for Patients who Stop Study Treatment Early

Protocol treatment is to continue for 6 weeks. Patients who do not complete 6 weeks of protocol treatment for any reason will still be expected to follow the data submission requirements outlined in the study calendar (Section 5.0) and will thus be followed up until 6 weeks post-randomization.

Follow up for patients who stop due to toxicity

If the patient decides to discontinue the study medication because of unacceptable side effects, he is to call the study nurse. The patient should be encouraged to complete diaries/questionnaires to date and send them in. The patient can then be taken off study. The off-study date to be used is either (1) the day after the patient took some study medication OR (2) the day after the patient last recorded some research data on the patient questionnaire--whichever occurred last.

12.4 Extraordinary Medical Circumstances

If, at any time the constraints of this protocol are detrimental to the patient's health and/or the patient no longer wishes to continue protocol therapy, protocol therapy shall be discontinued. In this event:

- Document the reason(s) for discontinuation of therapy on data forms.
- Follow the patient for protocol endpoints as required by the Study Calendar.

12.5 Managing ineligible patients and registered patients who never receive protocol intervention

Definition of ineligible patient

A study participant who is registered to the trial but does not meet all of the eligibility criteria is deemed to be ineligible.

Follow-up for ineligible patients who continue with protocol treatment

Patients who are deemed ineligible after registering may continue protocol treatment, provided the treating physician, study chair, and executive officer agree there are no safety concerns if the patient continues protocol treatment. All scans, tests, and data submission are to continue as if the patient were eligible. Notification of the local IRB may be necessary per local IRB policies.

Follow-up for ineligible patients who discontinue protocol treatment

For patients who are deemed ineligible after registering to the trial, who start treatment, but then discontinue study treatment, the same data submission requirements are to be followed as for those patients who are eligible and who discontinue study treatment.

Follow-up for patients who are registered, but who never start study treatment

For all study participants who are registered to the trial but who never receive study intervention (regardless of eligibility), the follow-up requirements are specified below:

Baseline and off-treatment notice data submission required. See the Data Submission Schedule accompanying the All Forms Packet.

13.0 STATISTICAL CONSIDERATIONS

13.1 Overview

This randomized four-arm, double-blind, placebo-controlled phase II trial will assess the efficacy and safety of oxybutynin for reducing hot flash scores in men receiving androgen deprivation therapy. The primary endpoint of this phase II trial is hot flash scores at 6 weeks post-randomization. All analyses will follow an intent-to-treat approach that includes all randomized patients who meet eligibility criteria.

13.2 Study Design

Patients will be randomly assigned to oxybutynin at 2.5 mL twice daily, oxybutynin at 5.0 mL twice daily, placebo at 2.5 mL twice daily, or placebo at 5.0 ml twice daily in a 2:2:1:1 ratio according to the dynamic allocation scheme. Stratification factors will include daily hot flash frequency at baseline (4 to 9 hot flashes per day versus 10 or more hot flashes per day), hot flash duration at baseline (less than 9 months versus 9 or more months), and number of prior hot flash therapies (0 versus 1 or more). The study design includes two placebo arms to match the dose of the two oxybutynin arms; however, patients randomized to the two placebo arms will be combined to form a single placebo arm for analysis. All analyses will follow an intent-to-treat approach that includes all randomized patients who meet eligibility criteria.

13.3 Study Endpoints

Important endpoints for this phase II trial relate to (1) efficacy of oxybutynin as measured by hot flash scores (primary) and hot flash frequency, (2) safety as measured by the presence of CTCAE v5.0-determined grade 3 or higher adverse events, (3) tolerability as measured by relevant patient-reported symptoms on the Symptom Experience Questionnaire (Appendix V), (4) feasibility regarding the conduct of this trial as measured by patient accrual and treatment adherence, and (5) patient-reported quality of life and hot flash interference as measured by the Hot Flash Related Daily Interference Scale (HFRDIS; Appendix VI). Treatment adherence rates will be calculated by dividing the number of patients who completed treatment per protocol by the number of patients who started treatment. Hot flash scores and frequencies will be measured by patients' hot flash diaries (Appendix IV). Daily hot flash scores will be computed by multiplying the frequency of each hot flash grade within a 24-hour period by the severity of the hot flash (grade 0: none, 1: mild, 2: moderate, 3: severe, and 4: very severe) and then summing all the values. Weekly hot flash scores will be computed by averaging these hot flash scores across the 7 days of each week. Weekly hot flash scores will be computed as long as hot flash scores from at least 1 of the 7 days of each week are available. However, the number of missing (daily) hot flash scores each week will be tabulated.

13.4 Analysis Plan

To assess efficacy, a mixed model will be estimated that includes baseline and weekly hot flash scores across the 6-week treatment period. The mixed model will include a fixed intercept; fixed effect for time, arm, and arm by time interaction; and residual covariance matrix based on the observed covariances. Alternative structures will be investigated for the residual covariance matrix, with final selection based on convergence of the mixed model and minimization of the Akaike information criterion. Stratification factors used in the randomization as well as baseline patient characteristics and prognostic factors may be included in the mixed model as covariates if imbalances across arms occur. For this mixed model, time will be treated as nominal (not continuous), such that the mixed model will not be making assumptions about the trajectory of

patients' hot flash scores over time. Estimates from the mixed model will be used to construct 90% confidence intervals for mean differences in hot flash score reduction from baseline to 6 weeks post-randomization between the oxybutynin and placebo arms (i.e., Arm A versus Arms C and D combined; Arm B versus Arms C and D combined). To control the Type I error rate, a fixed sequence procedure will be employed such that the following two tests will be sequenced rather than conducted simultaneously. Hot flash score reduction from baseline to 6 weeks will be compared across patients assigned to oxybutynin at 5.0 mL twice daily (Arm B) and patients assigned to placebo (Arms C and D combined) using a contrast estimated via the mixed model. The contrast will involve a two-sided *t*-test with a nominal significance level of $\alpha = .10$. If and only if this test is significant, hot flash score reduction from baseline to 6 weeks will be formally compared across patients assigned to oxybutynin at 2.5 mL twice daily (Arm A) and patients assigned to placebo (Arms C and D combined) using a second contrast estimated via the mixed model. This contrast will also involve a two-sided *t*-test with a nominal significance level of $\alpha = .10$. The proposed sequencing is based on the assumption that the effect of oxybutynin will increase monotonically with respect to dose. If $p \leq .10$ for both tests, we will conclude that both dosing schedules significantly improved hot flash scores at 6 weeks relative to placebo. If $p \leq .10$ for the first test but $p > .10$ for the second test, we will conclude that the higher dosing schedule significantly improved hot flash scores at 6 weeks relative to placebo but that the lower dosing schedule did not significantly improve hot flash scores at 6 weeks relative to placebo. Finally, if $p > .10$ for the first test, we will conclude that neither dosing schedule significantly improved hot flash scores at 6 weeks relative to placebo. In practice, if $p > .10$ for the first test, we will still conduct the second test, but as an exploratory analysis rather than as a primary analysis. We will also conduct a responder analysis at 6 weeks comparing the proportion of patients who experience a clinically significant improvement in hot flash scores since baseline across the oxybutynin and placebo arms using Fisher's exact test, χ^2 test, or logistic regression. Stratification factors used in the randomization as well as baseline patient characteristics and prognostic factors may be included in the logistic regression model as covariates if imbalances across arms occur. A clinically significant improvement will be defined as a 50% or greater reduction in hot flash scores since baseline based on preliminary evidence suggesting that patients consider a 50% or greater reduction in frequency of moderate to severe hot flashes to be a meaningful improvement.[41, 42] Patients who experience a 50% or greater reduction in hot flash scores since baseline will be deemed responders, while the remaining patients (including those with missing hot flash scores) will be deemed non-responders. As an exploratory analysis, we will investigate whether these efficacy results differ when using a single day rather than a full week to define patients' baseline hot flash scores.

Weekly hot flash frequencies (as opposed to weekly hot flash scores) will be compared across the oxybutynin and placebo arms in a manner similar to above using a mixed model that accounts for the observed distribution of weekly hot flash frequencies. A fixed sequence procedure will be employed. For the responder analysis, patients who experience a 50% or greater reduction in hot flash frequency since baseline will be deemed responders, while the remaining patients (including those with missing hot flash frequencies) will be deemed non-responders. Finally, consistency of the results will be assessed across the various methods used to evaluate the efficacy of oxybutynin in this trial (i.e., hot flash scores versus hot flash frequencies, mean differences versus 50% or greater reduction since baseline, single day versus full week to define patients' baseline hot flash scores).

To assess safety, the proportion of patients experiencing a grade 3 or higher adverse event will be summarized by arm. We expect this proportion to be extremely low for all arms.

To assess tolerability, mixed models similar to the one described above will be estimated that include baseline and weekly patient-reported symptoms as measured by the Symptom

Experience Questionnaire (Appendix V) across the 6-week treatment period. A single mixed model will be developed for each patient-reported symptom. Estimates from the mixed models will be used to construct 90% confidence intervals for mean differences in patient-reported symptoms between the oxybutynin and placebo arms (i.e., Arm A versus Arms C and D combined; Arm B versus Arms C and D combined) at 6 weeks post-randomization. Contrasts estimated via the mixed models will involve a two-sided *t*-test with a nominal significance level of $\alpha = .10$.

To assess feasibility, the time required to accrue 87 patients will be reported. To move forward with a phase III trial, an average accrual rate of 4 patients per month (starting 4 months after enrollment begins, to account for the time required for multiple institutions to activate the trial) would be desired. The treatment adherence rate (i.e., the number of patients who completed treatment per protocol divided by the number of patients who started treatment) will be summarized by arm.

To assess patient-reported quality of life and hot flash interference, mixed models similar to the one described above will be estimated that include patients' scores on the HFRDIS (Appendix VI) across the 6-week treatment period. A single mixed model will be developed for each HFRDIS item. Estimates from the mixed models will be used to construct 90% confidence intervals for mean differences in patient-reported quality of life and hot flash interference between the oxybutynin and placebo arms (i.e., Arm A versus Arms C and D combined; Arm B versus Arms C and D combined) at 6 weeks post-randomization. Contrasts estimated via the mixed models will involve a two-sided *t*-test with a nominal significance level of $\alpha = .10$.

Attempts to minimize **missing data** will be made through site training and data monitoring (e.g., form delinquency notifications, queries; see Section 6.1.3). The proportion of, and reported reasons for, missing data will be presented by time point and arm. Correlation analysis and logistic regression analysis will be used to examine whether baseline patient characteristics and prognostic factors predict missingness. The primary analysis will provide unbiased parameter estimates under a missing completely at random or missing at random mechanism. However, a sensitivity analysis will be conducted to assess the robustness of the results across various assumptions about the missing data.

13.5 Sample Size and Power

As this is a pilot trial, the sample size was determined based on feasibility and logistical considerations rather than on power for hypothesis testing. We aim to enroll 26 evaluable patients per oxybutynin arm and 13 evaluable patients per placebo arm (i.e., 78 evaluable patients total). For the primary aim, 26 evaluable patients per oxybutynin arm and 13 evaluable patients per placebo arm with 6 weekly hot flash scores provide 76% power to detect a mean difference in hot flash score reduction from baseline when comparing each oxybutynin arm (5.0 mL twice daily or 2.5 mL twice daily to the placebo arm (both placebo arms combined) based on a two-sided *t*-test estimated via a mixed model, nominal significance level of $\alpha = .10$, intraclass correlation of .50, and population standardized mean difference of 0.50 (i.e., Cohen's convention for a moderate effect size)[44]. In a similar study in women, Cohen's *d* equaled 0.85 when comparing the higher dose oxybutynin arm (2.5 mL twice daily escalated to 5.0 mL twice daily) to the placebo arm, and Cohen's *d* equaled 0.54 when comparing the lower dose oxybutynin arm (2.5 mL twice daily) to the placebo arm [45]. An additional 9 patients will be accrued to account for a 10% loss in sample size due to ineligibility, major treatment violation, or cancellation. Maximum projected accrual is, therefore, 87 patients.

13.6 Accrual Time and Study Duration

The anticipated accrual rate is approximately 7 patients per month, based on our most-recent previous male hot flash trial (conducted 15 years ago to evaluate gabapentin) and recent survey information. Therefore, the accrual period for this phase II trial is expected to be 13 months. The final analysis is predicted to begin approximately 15 months after the trial begins (i.e., as soon as the last patient has been observed for 6 weeks).

13.7 Data and Safety Monitoring

The study chair(s) and the study statistician will review the study at regular intervals to identify accrual and adverse events. The Alliance Data Safety Monitoring Board (DSMB) is responsible for reviewing accrual and safety data for this trial at least twice a year, based on reports provided by the Alliance Statistics and Data Management Center (SDMC).

Required submission of patient demographic data for this study will be submitted automatically via OPEN.

Note: Serious adverse events must be submitted via CTEP-AERS per protocol guidelines.

13.7.1 Adverse Event Stopping Rules

The stopping rules specified below are based on the knowledge available at study development. We note that the adverse event stopping rule may be adjusted in the event of either (1) the study re-opening to accrual or (2) at any time during the conduct of the trial and in consideration of newly acquired information regarding the adverse event profile of the treatment(s) under investigation. The study team may choose to suspend accrual because of unexpected adverse event profiles that have not crossed the specified rule below.

Accrual will be temporarily suspended to this study if at any time we observe adverse events considered at least possibly related to study treatment (i.e., an adverse event with attribute specified as “possible”, “probable”, or “definite”) that satisfy either of the following:

- if 2 or more patients in the first 10 treated patients experience a grade 3 or higher adverse event felt to be attributed to the study agent and the event rate is higher in the treatment arms than the placebo arm.
- if after the first 10 patients have been treated, 10% of all patients experience a grade 3 or higher adverse event felt to be attributed to the study agent and the event rate is higher in the treatment arms than the placebo arm.

We note that we will review grade 4 and 5 adverse events deemed “unrelated” or “unlikely to be related,” to verify their attribution and to monitor the emergence of a previously unrecognized treatment-related adverse event.

13.8 Minority Accrual

Enrollment will be open to all eligible patients, regardless of race or ethnicity. There is no information currently available regarding differential effects of oxybutynin by race or ethnicity, and there is no reason to expect such differences to exist. Therefore, although the planned analysis will, as always, look for differences in treatment effect based on race and ethnicity, the sample size is not increased in order to provide additional power for subset analyses. However, it is well known that the incidence of prostate cancer is greater in African American men. Given this, an Alliance Health Disparities Committee member was added as a study co-chair to

facilitate appropriate accrual of minority patients. Efforts will be made to accrue a substantial number of African American men to this trial.

Based on prior Alliance studies involving similar disease sites, expected sizes of racial and ethnic subsets for patients registered to this study are shown in the following table:

13.9 Inclusion of Minorities

PLANNED ENROLLMENT REPORT					
Racial Categories	**Ethnic Categories**				**Total**
	Not Hispanic or Latino		**Hispanic or Latino**		
	Female	**Male**	**Female**	**Male**	
American Indian/ Alaska Native	0	1	0	0	1
Asian	0	1	0	0	1
Native Hawaiian or Other Pacific Islander	0	1	0	0	1
Black or African American	0	9	0	0	9
White	0	70	0	4	74
More Than One Race	0	1	0	0	1
Total	0	83	0	4	87

Ethnic Categories:

- Hispanic or Latino – a person of Cuban, Mexican, Puerto Rican, South or Central American, or other Spanish culture or origin, regardless of race. The term "Spanish origin" can also be used in addition to "Hispanic or Latino."
- Not Hispanic or Latino

Racial Categories:

- American Indian or Alaskan Native – a person having origins in any of the original peoples of North, Central, or South America, and who maintains tribal affiliations or community attachment.
- Asian – a person having origins in any of the original peoples of the Far East, Southeast Asia, or the Indian subcontinent including, for example, Cambodia, China, India, Japan, Korea, Malaysia, Pakistan, the Philippine Islands, Thailand, and Vietnam. (Note: Individuals from the Philippine Islands have been recorded as Pacific Islanders in previous data collection strategies.)
- Black or African American – a person having origins in any of the black racial groups of Africa.
- Native Hawaiian or other Pacific Islander – a person having origins in any of the original peoples of Hawaii, Guam, Samoa, or other Pacific Islands.
- White – a person having origins in any of the original peoples of Europe, the Middle East, or North Africa.

14.0 GENERAL REGULATORY CONSIDERATIONS AND CREDENTIALING

14.1 Limited Access Requirements

Institutions that are interested in participating in this study must be able to rebottle liquid formulation of drug and placebo into patient specific supplies. In order for the Alliance to monitor starter supply distribution, institutions are asked to document their commitment to the requirements of the study as follows:

- In order for a site to be considered for the study, a "Site Participation Form" must be completed. The form can be requested from and once completed returned to [redacted]
- Upon approval, the site will be added to the list of limited access institutions with the next update to this protocol.

  Sites will receive extra per patient reimbursement for the effort involved with rebottling liquid formulations of the drug.

15.0 MONITORING PLAN

Use standard Alliance monitoring procedures, including regular review by the Alliance Data Safety Monitoring Board (DSMB) as outlined in Section 13.7.

16.0 REFERENCES

1. Nguyen, P.L., et al., *Adverse effects of androgen deprivation therapy and strategies to mitigate them.* Eur Urol, 2015. **67**(5): p. 825-36.
2. Boon, E., et al., *Androgen deprivation therapy for androgen receptor-positive advanced salivary duct carcinoma: A nationwide case series of 35 patients in The Netherlands.* Head Neck, 2018. **40**(3): p. 605-613.
3. Khan, M.H., R. Allerton, and L. Pettit, *Hormone Therapy for Breast Cancer in Men.* Clin Breast Cancer, 2015. **15**(4): p. 245-50.
4. Thompson, C.A., T.D. Shanafelt, and C.L. Loprinzi, *Andropause: symptom management for prostate cancer patients treated with hormonal ablation.* Oncologist, 2003. **8**(5): p. 474-87.
5. Jones, J.M., M. Kohli, and C.L. Loprinzi, *Androgen deprivation therapy-associated vasomotor symptoms.* Asian J Androl, 2012. **14**(2): p. 193-7.
6. Clark, J.A., et al., *Dimensions of quality of life expressed by men treated for metastatic prostate cancer.* Soc Sci Med, 1997. **45**(8): p. 1299-309.
7. Challapalli, A., et al., *Evaluating the prevalence and predictive factors of vasomotor and psychological symptoms in prostate cancer patients receiving hormonal therapy: Results from a single institution experience.* Clin Transl Radiat Oncol, 2018. **10**: p. 29-35.
8. Gonzalez, B.D., et al., *Sleep disturbance in men receiving androgen deprivation therapy for prostate cancer: The role of hot flashes and nocturia.* Cancer, 2018. **124**(3): p. 499-506.
9. Hunter, M.S. and E. Stefanopoulou, *Vasomotor symptoms in prostate cancer survivors undergoing androgen deprivation therapy.* Climacteric, 2016. **19**(1): p. 91-7.
10. Savard, J., S. Hervouet, and H. Ivers, *Prostate cancer treatments and their side effects are associated with increased insomnia.* Psychooncology, 2013. **22**(6): p. 1381-8.
11. Sharpley, C.F., V. Birsika, and J.W. Denham, *Factors associated with feelings of loss of masculinity in men with prostate cancer in the RADAR trial.* Psychooncology, 2014. **23**(5): p. 524-30.
12. Loprinzi, C.L., et al., *Megestrol acetate for the prevention of hot flashes.* N Engl J Med, 1994. **331**(6): p. 347-52.
13. Irani, J., et al., *Efficacy of venlafaxine, medroxyprogesterone acetate, and cyproterone acetate for the treatment of vasomotor hot flushes in men taking gonadotropin-releasing hormone analogues for prostate cancer: a double-blind, randomised trial.* Lancet Oncol, 2010. **11**(2): p. 147-54.
14. Bonkhoff, H., et al., *Progesterone receptor expression in human prostate cancer: correlation with tumor progression.* Prostate, 2001. **48**(4): p. 285-91.
15. Sartor, O. and J.A. Eastham, *Progressive prostate cancer associated with use of megestrol acetate administered for control of hot flashes.* South Med J, 1999. **92**(4): p. 415-6.
16. Geller, J., J. Albert, and S.S. Yen, *Treatment of advanced cancer of prostate with megestrol acetate.* Urology, 1978. **12**(5): p. 537-41.
17. Burch, P.A. and C.L. Loprinzi, *Prostate-specific antigen decline after withdrawal of low-dose megestrol acetate.* Journal of clinical oncology, 1999. **17**(3): p. 1086a-1086a.
18. Loprinzi, C.L., et al., *A phase III randomized, double-blind, placebo-controlled trial of gabapentin in the management of hot flashes in men (N00CB).* Ann Oncol, 2009. **20**(3): p. 542-9.
19. Vitolins, M.Z., et al., *Randomized trial to assess the impact of venlafaxine and soy protein on hot flashes and quality of life in men with prostate cancer.* J Clin Oncol, 2013. **31**(32): p. 4092-8.
20. Joffe, H., et al., *Low-dose estradiol and the serotonin-norepinephrine reuptake inhibitor venlafaxine for vasomotor symptoms: a randomized clinical trial.* JAMA Intern Med, 2014. **174**(7): p. 1058-66.
21. Evans, M.L., et al., *Management of postmenopausal hot flushes with venlafaxine hydrochloride: a randomized, controlled trial.* Obstet Gynecol, 2005. **105**(1): p. 161-6.

22. Artzi, O., et al., *Topical Oxybutynin 10% Gel for the Treatment of Primary Focal Hyperhidrosis: A Randomized Double-blind Placebo-controlled Split Area Study.* Acta Derm Venereol, 2017. **97**(9): p. 1120-1124.
23. Wolosker, N., et al., *Oxybutynin treatment for hyperhidrosis: a comparative analysis between genders.* Einstein (Sao Paulo), 2012. **10**(4): p. 405-8.
24. Campanati, A., et al., *Oxybutynin for the Treatment of Primary Hyperhidrosis: Current State of the Art.* Skin Appendage Disord, 2015. **1**(1): p. 6-13.
25. Medicine, U.S.N.L.o. *MedlinePlus-Oxybutynin Drug Information*. 01/04/2019]; Available from: https://medlineplus.gov/druginfo/meds/a682141.html.
26. Sexton, T., et al., *Oxybutynin for refractory hot flashes in cancer patients.* Menopause, 2007. **14**(3 Pt 1): p. 505-9.
27. Simon, J.A., et al., *Extended-release oxybutynin therapy for vasomotor symptoms in women: a randomized clinical trial.* Menopause, 2016. **23**(11): p. 1214-1221.
28. Leon-Ferre, R.A., et al., *A randomized, doubleblind, placebo-controlled trial of oxybutynin (Oxy) for hot flashes (HF): ACCRU study SC-1603.* Cancer Research, 2019. **79**(4).
29. Smith, T.J., C.L. Loprinzi, and C. Deville, *Oxybutynin for Hot Flashes Due to Androgen Deprivation in Men.* N Engl J Med, 2018. **378**(18): p. 1745-1746.
30. Sloan, J.A., et al., *Methodologic lessons learned from hot flash studies.* J Clin Oncol, 2001. **19**(23): p. 4280-90.
31. Quella, S., C.L. Loprinzi, and A.M. Dose, *A qualitative approach to defining "hot flashes" in men.* Urol Nurs, 1994. **14**(4): p. 155-8.
32. Loprinzi, C.L., et al., *Transdermal clonidine for ameliorating post-orchiectomy hot flashes.* J Urol, 1994. **151**(3): p. 634-6.
33. Carpenter, J.S., *The Hot Flash Related Daily Interference Scale: a tool for assessing the impact of hot flashes on quality of life following breast cancer.* J Pain Symptom Manage, 2001. **22**(6): p. 979-89.
34. Gonzalez, B.D., et al., *Course and Moderators of Hot Flash Interference during Androgen Deprivation Therapy for Prostate Cancer: A Matched Comparison.* J Urol, 2015. **194**(3): p. 690-5.
35. Beer, T.M., et al., *Acupuncture for hot flashes in patients with prostate cancer.* Urology, 2010. **76**(5): p. 1182-8.
36. Rich, T., et al., *Intermittent 96-Hour Auricular Electroacupuncture for Hot Flashes in Patients with Prostate Cancer: A Pilot Study.* Med Acupunct, 2017. **29**(5): p. 313-321.
37. Kay, G., et al., *Differential effects of the antimuscarinic agents darifenacin and oxybutynin ER on memory in older subjects.* Eur Urol, 2006. **50**(2): p. 317-26.
38. Wagg, A., et al., *Randomised, multicentre, placebo-controlled, double-blind crossover study investigating the effect of solifenacin and oxybutynin in elderly people with mild cognitive impairment: the SENIOR study.* Eur Urol, 2013. **64**(1): p. 74-81.
39. Katz, I.R., et al., *Identification of medications that cause cognitive impairment in older people: the case of oxybutynin chloride.* J Am Geriatr Soc, 1998. **46**(1): p. 8-13.
40. Lackner, T.E., et al., *Randomized, placebo-controlled trial of the cognitive effect, safety, and tolerability of oral extended-release oxybutynin in cognitively impaired nursing home residents with urge urinary incontinence.* J Am Geriatr Soc, 2008. **56**(5): p. 862-70.
41. Pocock, S.J. and R. Simon, *Sequential treatment assignment with balancing for prognostic factors in the controlled clinical trial.* Biometrics, 1975: p. 103-115.
42. Barry, M. and F. Fowler Jr, *O'Leary MP et al. The American Urological Association symptom index for benign prostatic hyperplasia. The Measurement Committee of the American Urological Association.* J Urol, 1992. **148**(5): p. 1549-1557.
43. Parsons, J.K., et al., *494 PROSTATE CANCER AND LOWER URINARY TRACT SYMPTOMS IN COMMUNITY DWELLING OLDER MEN.* The Journal of Urology, 2010. **183**(4S): p. e195-e195.

44. Cohen, J., *Statistical Power Analysis for the Behavioral Sciences (2nd edn), 411 Lawrence Erlbaum Associates.* Hillsdale, NJ, 1988. **412**.
45. Leon-Ferre, R.A., et al., *Oxybutynin vs Placebo for Hot Flashes in Women With or Without Breast Cancer: A Randomized, Double-Blind Clinical Trial (ACCRU SC-1603).* JNCI Cancer Spectrum, 2020. **4**(1): p. pkz088.

APPENDIX I HOT FLASH DEFINITIONS FOR THE MALE PATIENT

Patient Information Sheet

Please refer to these examples of hot flashes that have been given by cancer survivors in previous studies when describing their hot flash severity. One or more of these descriptions may help to categorize your hot flash as mild, moderate, severe, or very severe.

MILD

Duration: Lasting less than 3 minutes

Physical symptoms: Very light perspiration, generalized warmth or a flushed sensation

Emotional symptoms: None or rare

Action needed: Usually no action taken

MODERATE

Duration: Lasting up to 5 minutes

Physical symptoms: Light-to-moderate perspiration, moderate warmth and/or perspiration

Emotional symptoms: Mild anxiety, some irritability, loss of concentration

Action needed: Needed to use a fan, needed to loosen clothing, needed to remove clothing, needed to remove bedding

SEVERE

Duration: Lasting up to 10 minutes

Physical symptoms: Described as feeling "hotter" or "very hot," heavy perspiration, dizziness, nausea, shortness of breath, weakness, extreme discomfort

Emotional symptoms: Moderate anxiety, moderate irritability

Action needed: Needed to loosen clothing, needed to change clothing, needed to change bedding

VERY SEVERE

Duration: Lasting up to 30 minutes

Physical symptoms: Described as feeling "very hot," drenching perspiration, dizziness, nausea, shortness of breath, weakness, chest discomfort, extreme discomfort

Emotional symptoms: Severe anxiety, severe irritability, restlessness, totally out of control

Action needed: Needed to change clothing, needed to towel off, needed to change bedding, used wet towels, took a bath or shower, needed a rest

APPENDIX II BASELINE SYMPTOM DOCUMENTATION

Directions:

- The baseline symptom determination is divided into 7 rows, one for each day of the week.
- Enter the day and the date your week started.
- Start in the row for Day 1.
- Write in the number of mild, moderate, severe and very severe hot flashes experienced in the boxes.
- Repeat for each day of the week.
- See page 2 of this booklet for the definitions of each type of hot flashes.

Day week started: _____ Date week started: __ __ / __ __ / __ __ __ __
m m d d y y y y

Day	Number of mild hot flashes	Number of moderate hot flashes	Number of severe hot flashes	Number of very severe hot flashes
Day 1				
Day 2				
Day 3				
Day 4				
Day 5				
Day 6				
Day 7				

*A day should be considered a 24-hour period (i.e. 7 a.m. to 7 a.m. or midnight to midnight).

APPENDIX III INTERNATIONAL PROSTATE SYMPTOM SCORE (IPSS)

(To be completed at screening and at the end of each week of treatment)

INTERNATIONAL-PROSTATE SYMPTOM SCORE

Question	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
1. Over the past week, how often have you had a sensation of not emptying your bladder completely after you finished urinating?	0	1	2	3	4	5
2. Over the past week, how often have you had to urinate again less than two hours after you finished urinating?	0	1	2	3	4	5
3. Over the past week, how often have you found you stopped and started again several times when you urinated?	0	1	2	3	4	5
4. Over the past week, how often have you found it difficult to postpone urination?	0	1	2	3	4	5
5. Over the past week, how often have you had a weak urinary stream?	0	1	2	3	4	5
6. Over the past week, how often have you had to push or strain to begin urination?	0	1	2	3	4	5
	None	1 time	2 times	3 times	4 times	5 or more times
7. Over the past week, how many times did you most typically get up to urinate from the time you went to bed at night until the time you got up in the morning?	0	1	2	3	4	5

I-PSS - United States/English
ID 5070 / I-PSS1a_AU1.0_eng-USori.doc

INTERNATIONAL-PROSTATE SYMPTOM SCORE (cont'd)

QUALITY OF LIFE DUE TO URINARY SYMPTOMS

Question	Delighted	Pleased	Mostly satisfied	Mixed about equally satisfied and dissatisfied	Mostly dissatisfied	Unhappy	Terrible
1. 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?	0	1	2	3	4	5	6

APPENDIX IV HOT FLASH DIARY (SAMPLE INCLUDED ON THE NEXT PAGE)

Directions:

The hot flash diary is divided into 7 rows, one for each day* of the week.
Enter the day and the date your week started.
Start in the row for Day 1.
Write in the number of mild, moderate, severe and very severe hot flashes experienced in the boxes.
Repeat for each day of the week.
See page 2 of this booklet for the definitions of each type of hot flashes.

Day week started: _____ Date week started: __ __ / __ __ / __ __ __ __
m m d d y y y y

Day	Number of mild hot flashes	Number of moderate hot flashes	Number of severe hot flashes	Number of very severe hot flashes	How many doses of study medication did you take? *(circle one)*
Day 1					0 1 2
Day 2					0 1 2
Day 3					0 1 2
Day 4					0 1 2
Day 5					0 1 2
Day 6					0 1 2
Day 7					0 1 2

*A day should be considered a 24-hour period (i.e. 7 a.m. to 7 a.m. or midnight to midnight).

Directions:

The hot flash diary is divided into 7 rows, one for each day of your week.
Enter the day and the date your week started.
Start in the row for Day 1.
Write in the number of mild, moderate, severe and very severe hot flashes experienced in the boxes.
Repeat for each day of the week.
See page 2 of this booklet for the definitions of each type of Hot Flashes.

Example:

Day week started: Friday

Date week started: 0 9 / 1 2 / 2 0 1 6
m m d d y y y y

Day	Number of mild hot flashes	Number of moderate hot flashes	Number of severe hot flashes	Number of very severe hot flashes	How many doses did you take today? *(circle one)*
Day 1	3	2	1	0	0 1 (2)
Day 2	7	3	0	0	(0) 1 2
Day 3	6	0	1	2	0 1 (2)
Day 4	2	1	0	0	0 1 (2)
Day 5	3	3	1	1	0 1 (2)
Day 6	2	1	0	0	0 1 (2)
Day 7	5	2	2	0	0 (1) 2

APPENDIX V SYMPTOM EXPERIENCE QUESTIONNAIRE

Completed at baseline and weekly for six weeks

Date completed:_____

INSTRUCTIONS: Please complete at the end of each study week by circling the one number for each item below that best describes you.

1. Over the past week, have you experienced stomach pain or cramps?

0	1	2	3	4	5	6	7	8	9	10
Not at all										As bad as it can be

2. Over the past week, have you experienced diarrhea (loose stools)?

0	1	2	3	4	5	6	7	8	9	10
Not at all										As bad as it can be

3. Over the past week, have you experienced constipation?

0	1	2	3	4	5	6	7	8	9	10
Not at all										As bad as it can be

4. Over the past week, have you experienced nausea?

0	1	2	3	4	5	6	7	8	9	10
Not at all										As bad as it can be

5. Over the past week, have you experienced any vomiting?

0	1	2	3	4	5	6	7	8	9	10
Not at all										As bad as it can be

6. Over the past week, have you experienced dry mouth?

0	1	2	3	4	5	6	7	8	9	10
Not at all										As bad as it can be

7. Over the past week, have you experienced dizziness?

0	1	2	3	4	5	6	7	8	9	10
Not at all										As bad as it can be

8. Over the past week, have you experienced decrease in appetite?

0	1	2	3	4	5	6	7	8	9	10
Not at all										As bad as it can be

9. Over the past week, have you experienced headaches?

0	1	2	3	4	5	6	7	8	9	10
Not at all										As bad as it can be

10. Over the past week, have you experienced fatigue?

0	1	2	3	4	5	6	7	8	9	10
Not at all										As bad as it can be

11. Over the past week, have you experienced excessive somnolence (sleepiness)?

0	1	2	3	4	5	6	7	8	9	10
Not at all										As bad as it can be

12. Over the past week, have you experienced blurry vision?

0	1	2	3	4	5	6	7	8	9	10
Not at all										As bad as it can be

13. Over the past week, have you experienced dry eyes?

0	1	2	3	4	5	6	7	8	9	10
Not at all										As bad as it can be

14. Over the past week, have you experienced episodes of confusion?

0	1	2	3	4	5	6	7	8	9	10
Not at all										As bad as it can be

15. Over the past week, have you had a skin rash?

0	1	2	3	4	5	6	7	8	9	10
Not at all										As bad as it can be

16. Over the past week, did you experience any muscle/joint aches or pains?

0	1	2	3	4	5	6	7	8	9	10
Not at all										As bad as it can be

17. Over the past week, did you experience trouble sleeping?

0	1	2	3	4	5	6	7	8	9	10
Not at all										As bad as it can be

18. Over the past week, have you had trouble concentrating?

0	1	2	3	4	5	6	7	8	9	10
Not at all										As bad as it can be

19. Over the past week, have you experienced any difficulties with your memory?

0	1	2	3	4	5	6	7	8	9	10
Not at all										As bad as it can be

20. Over the past week, have you experienced difficulties urinating (difficulties emptying your bladder)?

0	1	2	3	4	5	6	7	8	9	10
Not at all										As bad as it can be

21. Over the past week, have you experienced any trouble with urine incontinence (leaking)?

0	1	2	3	4	5	6	7	8	9	10
Not at all										As bad as it can be

22. Over the past week, how distressing was your experience with hot flashes?

0	1	2	3	4	5	6	7	8	9	10
Not at all										As bad as it can be

23. Did you experience any other symptoms this past week that were not mentioned above?

No_____Yes_____

If so, please describe

The following question will ONLY be asked at baseline:

23a. How much do you think the study medication will be able to help hot flashes?

0	1	2	3	4	5	6	7	8	9	10
Probably won't work										Will work extremely well

The following question will NOT be asked at baseline:

23b. Over the past week, how satisfied are you with the control of your hot flashes?

0	1	2	3	4	5	6	7	8	9	10
Extremely Satisfied										Extremely Dissatisfied

23c Given your experience with the study medication on this trial would you want to continue it after the trial is over if given the choice?

No_____Yes_____

APPENDIX VI HOT FLASH RELATED DAILY INTERFERENCE SCALE (HFRDIS)

Completed on Day 7, at the end of Weeks 3, 5, and 7 (i.e., Days 21, 35, and 49

Please circle one number to the right of each phrase to describe how much **DURING THE PAST TWO WEEKS** hot flashes **INTERFERED** with each aspect of your life.

	Did not interfere										**Completely interfered**
1. Work (work outside the home and housework)	0	1	2	3	4	5	6	7	8	9	10
2. Social activities (time spent with family, friends, etc)	0	1	2	3	4	5	6	7	8	9	10
3. Leisure activities (time spent relaxing, doing hobbies, etc.)	0	1	2	3	4	5	6	7	8	9	10
4. Sleep	0	1	2	3	4	5	6	7	8	9	10
5. Mood	0	1	2	3	4	5	6	7	8	9	10
6. Concentration	0	1	2	3	4	5	6	7	8	9	10
7. Relations with others	0	1	2	3	4	5	6	7	8	9	10
8. Sexuality	0	1	2	3	4	5	6	7	8	9	10
9. Enjoyment of life	0	1	2	3	4	5	6	7	8	9	10
10. Overall quality of life	0	1	2	3	4	5	6	7	8	9	10

APPENDIX VII NURSE/CRP PHONE CONTACT GUIDE

Patient Phone No._____
Best Dates/Times to call_____

FOLLOW UP:

1. Please make an appointment to call the patient at home the end of each study week. The purpose of this contact is to remind the patient of dose schedule, document compliance, encourage completion of the booklet, and address problems.

    - It is important to reinforce daily completion of diary as well as weekly side effects on symptom experience questionnaire. Regarding potential side effects, please ask about dry mouth, nausea, vomiting, dizziness, blurred vision, dry eyes, urinary retention, and urinary incontinence. If there are any significant toxicities, then refer to protocol Section 8.2 for potential dose modifications. In addition, determine whether there are any reportable adverse events (Section 9.0).

2. Items to document on the Nurse/CRP Evaluation form in the forms packet include, but are not limited to the following:
    - Date of phone call
    - Study week
    - Side effects:
        - Type of side effect, severity and attribution, if applicable
    - Any changes in medications or other treatments (i.e. behavioral, diet, etc.)
    - Has the participant taken the proper amount of study medication each day? (Choose one: Always_____, Usually_____, Rarely____, or Never_)
    - Questions/Comments

3. Reinforce compliance with study medication.

4. Reinforce completion of questionnaires and request return of them at end of weeks 1 and 4.

    Note – If patient decides to stop study before week 7, ask them to fill out the questionnaires up to that point at the end of the booklet and return in the envelope provided.

APPENDIX VIII: PATIENT MEDICATION DIARY – OXYBUTYNIN/PLACEBO

(For patient and site convenience only)

Today's date _____

Patient Name_____ (initials acceptable) **Patient Study ID** _____

	INSTRUCTIONS FOR THE PATIENT: 1. Complete this form while you take oxybutynin/placebo. This form is a 7 day diary. You may need to complete more than one form between clinic visits, for each week of treatment. 2. You will take your dose of oxybutynin/placebo twice daily. You will be given an oral syringe to measure and take your medication, which you will clean and reuse during the course of the study. 3 Take the oxybutynin/placebo at least one hour before a meal or at least two hours afterwards. 4. Record the date, the dose you took, and when you took it. Record doses as soon as you take them; do not batch entries together at a later time. 5. If a dose is missed, do not make up that dose; resume dosing with the next scheduled dose. 6. Use extreme caution when oxybutynin is administered with any other anticholinergic agents as increased side effects can occur (i.e dry mouth, constipation, somnolence). 2. Report any unusual rapid heart rates to your doctor. 3. Report skin changes like rash to your doctor. 4. You may have decreased sweating abilities. Use caution if out in the heat and to avoid becoming overheated. 5. Gastrointestinal effects can be seen including constipation, decreased GI motility, nausea, vomiting, and dry mouth. 6. If you have trouble urinating, report this to your doctor. 7. Use caution when operating a vehicle or other activities that require close attention. 8. Effects on the eye can include amblyopia (lazy eye), cycloplegia (paralysis of ciliary muscle-leading to inability to focus on close objects), decreased tears and mydriasis (abnormal pupil dilation). Report any of these to your doctor. 9. If you have any comments or notice any side effects, please record them in the comments column. If you make a mistake while you write, please cross it out with one line, put your initials next to it, and then write the corrected information next to your initials. 10. Please return this form to your doctor or study staff. You may need to return more than one form per clinic visit.

WEEK: _____

Day	Date	Time of daily dose	Dose#1	Dose#2	Comments
1					
2					
3					
4					
5					
6					
7					
Patient's Signature					**Date**

APPENDIX IX PATIENT INFORMATION SHEETS

PATIENT INFORMATION SHEET
BASELINE

Patient Completed Quality of Life Booklet (Baseline/Week 1)

You have been given a booklet to complete for this study. The booklet contains some questions about your 'quality of life' as a patient receiving treatment for hot flashes. Your answers will help us to better understand how the treatment you are receiving is affecting the way you feel.

Do not take any study medication this week.

1. This booklet is to be completed before you start study treatment.

2. The booklet contains 3 set of questions:
    a. **Baseline Symptom Documentation (Days 1-7).** This should be completed daily. On page 2 of this booklet, you will find examples of the different hot flash intensities: mild, moderate, severe, and very severe hot flash. This is to help you to decide the intensity of your hot flash, but it is not an absolute rule. Your hot flashes may differ in some ways or may fall just between two descriptions. Try to get as close as you can, but do not worry if your hot flashes do not match exactly what is given.
    b. Symptom Experience Questionnaire (Day 7)
    c. Hot Flash Related Daily Interference Scale (HFRDIS) (Day 7)

3. Directions on how to complete this set of questions are written on the top of the page.

4. Please return your booklet, in the envelope provided or in person when you are finished.

Thank you for taking the time to help us.

PATIENT INFORMATION SHEET
TREATMENT
Patient Completed Quality of Life Booklet (Weeks 2-7)

You have been given a booklet to complete for this study. The booklet contains some questions about your 'quality of life' as a patient receiving treatment for hot flashes. Your answers will help us to better understand how the treatment you are receiving is affecting the way you feel.

1. This booklet is to be completed on days 8-49, while you are receiving treatment. It is divided up into 6 weeks.

2. The booklet contains 4 set of questions:
    a. **Hot Flash Diary (every day during treatment)**: This should be completed daily. On page 2 of this booklet, you will find examples of the different hot flash intensities: mild, moderate, severe, and very severe hot flash. This is to help you to decide the intensity of your hot flash, but it is not an absolute rule. Your hot flashes may differ in some ways or may fall just between two descriptions. Try to get as close as you can, but do not worry if your hot flashes do not match exactly what is given.
    b. **Symptom Experience Questionnaire** (at the end of every week)
    c. **International Prostate Symptom Score** tool (at the end of every week)
    d. **Hot Flash Related Daily Interference Scale** (HFRDIS) (at the end of Weeks 2 and 4 of treatment, and at the end of treatment)

3. Directions on how to complete this set of questions are written on the top of the page.

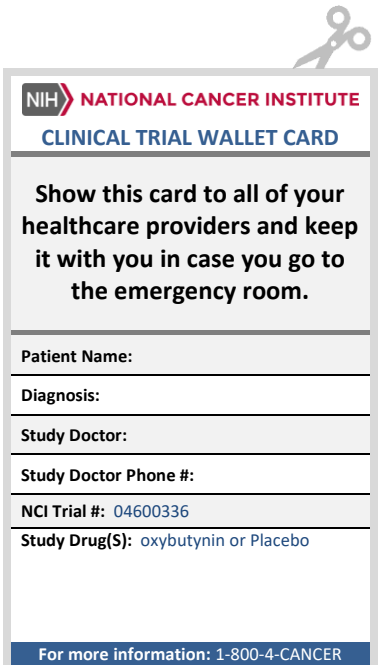
4. You may call a member of the study team to answer any questions you might have. You will be given a name and telephone number. You can call anytime with any concerns or questions. A nurse/research coordinator will also call you at the end of every week and they can answer questions you might have.

5. It is very important that you return the booklet to us, whether you finish the study or not.

6. When the booklet is complete, return it in the provided envelope.

Thank you for taking the time to help us.

APPENDIX X PATIENT CLINICAL TRIAL WALLET CARD



NIH NATIONAL CANCER INSTITUTE

CLINICAL TRIAL WALLET CARD

Show this card to all of your healthcare providers and keep it with you in case you go to the emergency room.

Patient Name:

Diagnosis:

Study Doctor:

Study Doctor Phone #:

NCI Trial #: 04600336

Study Drug(S): oxybutynin or Placebo

For more information: 1-800-4-CANCER

APPENDIX XI PATIENT THANK YOU LETTERS

Guidance for Disseminating
Thank You Letters to Trial Participants

Trial Participant Thank You Letter

We ask that the physician use the template to prepare a letter thanking the participant for enrolling in this Alliance trial. The template is intended as a guide and can be downloaded from the study page on the Alliance website at [redacted] As this is a personal letter, physicians may elect to further tailor the text to their situation.

This small gesture is a part of a broader program being undertaken by Alliance and the NCI to increase awareness of the importance of clinical trials and improve accrual and follow-through.

We appreciate your help in this effort.

Sample Template

[PARTICIPANT NAME] [DATE] [PARTICIPANT ADDRESS]

Dear [PARTICIPANT SALUTATION],

Thank you for agreeing to take part in this important research study. With the help of people like you who participate in clinical trials, we will achieve our goal of effectively treating and ultimately curing cancer.

There are many reasons why individuals choose to participate in a clinical trial. Sometimes it is because they want access to a specific medication or because they want to do whatever they can to help someone else with cancer. Whatever your reason for participating, you are making a contribution towards finding better treatments and ultimately eliminating this disease for future patients.

You will receive high quality care while participating in this clinical trial. My research staff and I will maintain very close contact with you. This will allow me to provide you with the best care while learning as much as possible to help you and other participants.

On behalf of [INSTITUTION] and the Alliance for Clinical Trials in Oncology, we thank you again for your participation in this clinical trial and look forward to partnering with you.

Sincerely, [PHYSICIAN NAME]