Academic and Community Cancer Research United (ACCRU)

A Phase III, Double-Blind, Controlled Trial of Oxybutynin in the Management of Hot Flashes

For any communications regarding this protocol, please contact the protocol resource person on the following page.

Study Chairs

ACCRU: Charles L. Loprinzi, M.D.
Mayo Clinic
507/284-4565
507/284-5280 (FAX)
loprinzi.charles@mayo.edu

Roberto Leon-Ferre, M.D.
Mayo Clinic
507/284-4565
LeonFerre.Roberto@mayo.edu

Stephanie S. Faubion, M.D.
Mayo Clinic
507/284-4565
Faubion.Stephanie@mayo.edu

Statistician: [redacted]
Mayo
Clinic [redacted]

Drug Availability
Commercial Agents: Oxybutynin (IND exempt)

√ Study contributor(s) not responsible for patient care.

Research Coordinating Center
Academic and Community Cancer Research United
200 First Street Southwest
Rochester, MN 55905
FAX# 507-538-0906

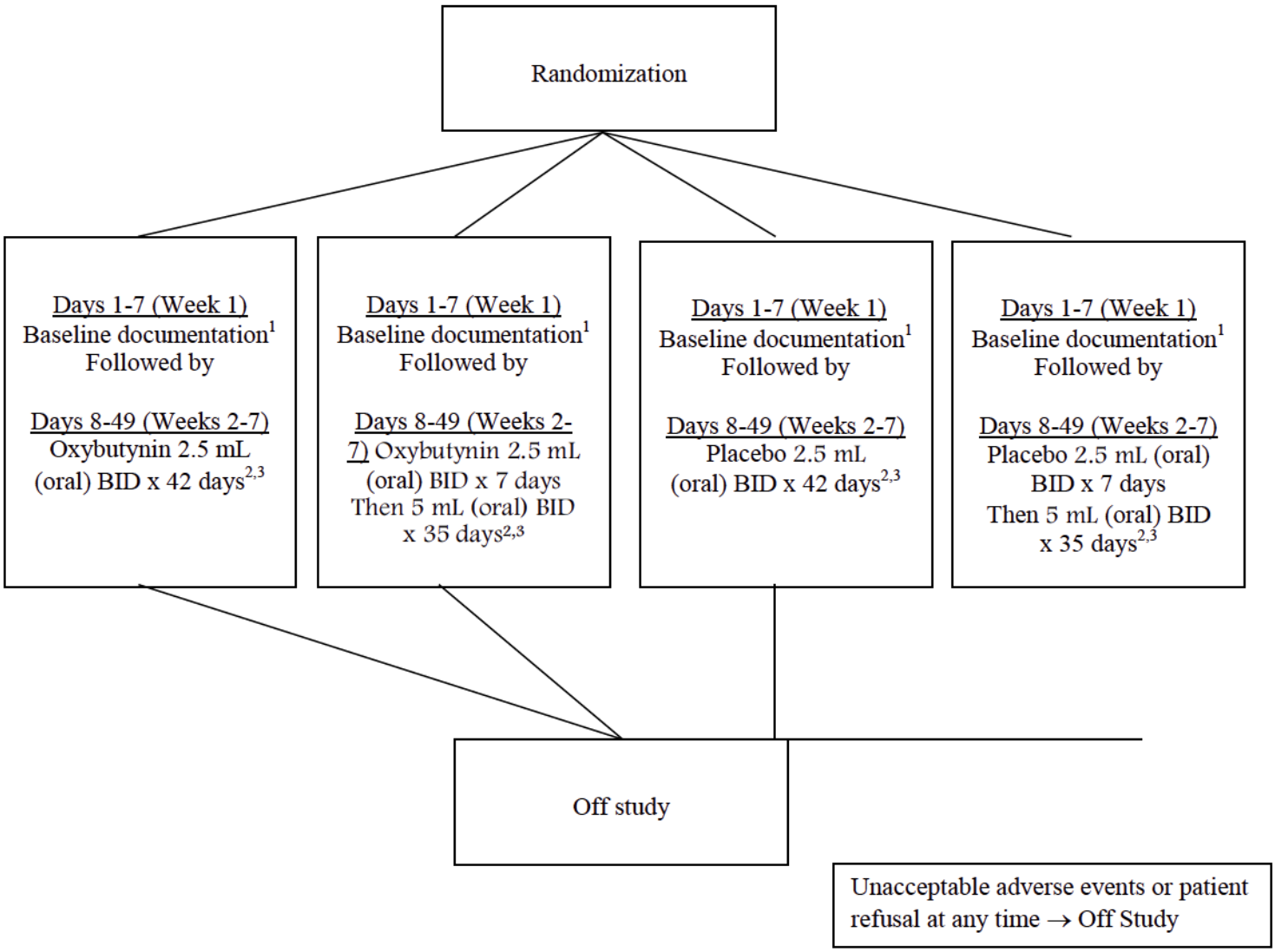
Document History	Effective Date
Pre-activation ACCRU	October 28, 2016
Activation ACCRU	December 9, 2016
Amendment 1	June 23, 2017
Amendment 2	September 08, 2017

Index

Schema

[redacted]

Schema



[1]Baseline symptom documentation.
[2]Unacceptable adverse events (adjust dose per section 8).
[3]Questionnaires will continue to be administered after treatment initiation and for the duration of the study.

Cycle 1 = 7 days
Cycle 2 = 7 days
Cycle 3 = 7 days
Cycle 4 = 7 days
Cycle 5 = 7 days
Cycle 6 = 7 days
Cycle 7 = 7 days

Generic name: Oxybutynin chloride Brand name(s): Ditropan Availability: Biologics	Generic name: Placebo Brand name(s): Placebo Availability: Biologics

1.0 Background

1.1 The Hot Flash Problem

Vasomotor symptoms (VMS) continue to be the most common symptom associated with menopause and are experienced by about 75% of menopausal women. (Stearns V, et. al., 2002; Garcia C and Freeman E, 2004) The mean duration of VMS is 7-9 years; however, over 30% of women may experience moderate to severe VMS for 10 or more years. Stearns V, et. al., 2002) For women who are breast cancer survivors, the risk of long-term VMS is greater, as chemotherapy may result in premature ovarian function cessation. In addition, endocrine therapy is associated with hot flashes. Over 50% of women on tamoxifen and 34-58% of women on aromatase inhibitors (AIs) experience hot flashes. (Molina JR, et al., 2005; Loprinzi CL et al., 2000; Morales AJ et al., 1994)

VMS are not only disruptive and distressing to women, they are associated with a significant economic burden, both in term of medical costs and lost productivity. It has been reported that menopausal symptoms may be more severe in breast cancer survivors compared with healthy women experiencing natural menopause. (Carpenter JS, et. al., 2002)

The most effective treatment for VMS, offering a 80-90% reduction, is estrogen and/or progesterone based therapy.Molina JR, et al., 2005; Bertelli G et al., 2002; MacGregor CA et al., 2005; World Almanac and Book of Facts, 2005; Notelovitz M, et. al., 2000) However, hormonal therapy is not recommended for women with a history of hormone-responsive cancers, including breast cancer. (Stuenkel CA et. al., 2015) The most effective non-hormonal therapies (antidepressants and anticonvulsants) offer about a 50% reduction in VMS. (Loprinzi CL et. al., 2000; Barton DL et al., 2010; Loprinzi CL et. al., 2009) However, these agents do have some unwanted side effects including dizziness, dry mouth, trouble sleeping, somnolence, nausea, and sexual dysfunction. (Barton D, Loprinzi CL, 2004) Furthermore, despite the potential efficacy of antidepressants for the management of VMS, these drugs have been shown to inhibit the CYP2D6 enzyme system, which plays an essential role in the metabolic activation of tamoxifen. In women being treated with tamoxifen, use of CYP2D6 inhibitors has been shown to decrease the plasma concentrations of active tamoxifen metabolites and potentially decrease the anti-cancer efficacy of tamoxifen.(Hemeryck A, Belpaire FM, 2002; Jin Y, et. al., 2005; Borges S, et. al., 2006) Therefore, additional non-estrogenic treatment options for women with breast cancer and therapy-induced VMS would be welcomed. Options that do not interfere with tamoxifen metabolism are especially needed, as some women with breast cancer require endocrine therapy with tamoxifen or AIs for extended periods of time (up to 10 years).

1.2 Oxybutynin for Hot Flashes

Oxybutynin is an anticholinergic agent that can be taken orally (as short or long-acting formulations) or transdermally. Oxybutynin is primarily metabolized by CYP3A4, and has no known inhibitory effect on CYP2D6, making it a therapeutic option for women concurrently using tamoxifen if is found to be effective for VMS management. Oxybutynin is FDA approved for overactive bladder symptoms. Due to the observation that patients treated for overactive bladder with oxybutynin experienced decreased sweating, a prospective, placebo-controlled trial of oxybutynin was conducted to assess its efficacy in the treatment of hyperhydrosis. (Wolosker N et. al., 2012) This trial demonstrated improvement in palmar and axillary hyperhydrosis in >70% of patients. Side effects were minor (dry mouth the most common), and quality of life was also found to be improved.

There are data to suggest efficacy of oxybutynin in the treatment of VMS unresponsive to other treatments. (Sexton T et. al., 2007) In a retrospective review of a prospectively collected database, Sexton et al identified 52 patients with moderate-to-severe hot flashes that received treatment with

oxybutynin. Of these, >90% had refractory symptoms, with 27% of patients having tried at least 3 previous lines of therapy, including SSRIs, SNRIs, gabapentin, clonidine and hormone therapy. Seventy percent of patients treated with oxybutynin had a partial or excellent response, and more than half of patients continued treatment for at least six months. More than 90% of patients received 5 mg twice daily (BID) or less, although more "excellent responses" were seen in patients that took 5 mg BID. Although 62% of patients reported mild to moderate side effects, only 12% discontinued oxybutynin due to side effects. Dry mouth was the most common side effect (48%), followed by nausea (12%), cognitive/emotional symptoms (8%), blurred vision (2%) and constipation (2%). No clear correlation between dose and frequency of side effects or treatment discontinuation was noted.

In addition, a prospective, double-blind clinical trial was developed to address the utility of oxybutynin for treating menopause-related VMS. While the results of this clinical trial were not published when this current protocol was conceived (only an internet report was available from 2007; LaGuardia KD, 2007 patent), a published report of this trial appeared in late 2016 (Simon JA, 2016). This report revealed that higher doses of oxybutynin than are being studied in the current trial (i.e. 3 times the lowest dose in this current trial) resulted in significant reductions ($P<.001$) in both of the primary endpoints (daily frequency of moderate to severe VMS and daily severity of all VMS) in the 12th week compared to baseline. This was at the cost of higher toxicity in the treatment arm, including over 50% of patients reporting mouth dryness, as compared to 5% in the placebo arm. In addition, there was more dyspepsia (12% versus 1%), and diarrhea (10% vs 0%), leading to 7% of patients discontinuing treatment. The authors of this publication recommended that lower doses of oxybutynin be studied for treating hot flashes, akin to what is outlined in the current trial. In addition, the current trial will be using a short-acting formulation, allowing for further dose reductions in the event of excess toxicity.

2.0 Goals

2.1 Primary

2.11 To determine whether oxybutynin can diminish hot-flash activity in women with a history of breast cancer or in women who have a concern about taking estrogen for fear of breast cancer.

2.2 Secondary

2.21 To perform a dose-response evaluation of two oxybutynin doses.

2.22 To determine the toxicity of oxybutynin in the study population.

2.23 To assess the impact of hot-flash activity on overall quality of life and to examine whether oxybutynin can diminish this impact on quality of life.

3.0 Patient Eligibility

3.1 Inclusion Criteria

3.11 Age ≥ 18 years.

3.12 Women with history of breast cancer, DCIS, or LCIS (currently without evidence of malignant disease) **OR** a concern about taking estrogen for fear of breast cancer.

3.13 Bothersome hot flashes (defined by their occurrence of ≥ 28 times per week and of sufficient severity to prompt the patient to seek therapeutic intervention).

3.14 Presence of hot flashes for >30 days prior to study entry.

3.15 Ability to complete questionnaire(s) by themselves or with assistance.

3.16 ECOG Performance Status (PS) = 0, 1. (Form is available on the ACCRU web site https://www.accru.org/accru/forms/NonProtocolSpecificForms/index.html).

3.17 Ability to provide informed written consent.

3.18 Life expectancy ≥6 months.

3.19a Willing to work with the enrolling institution for follow-up (during the Active Monitoring Phase of the study).

3.2 Exclusion Criteria

3.21 Any of the following current (≤4 weeks prior) or planned therapies:

- Antineoplastic chemotherapy (anti-HER2 agents allowed)
- Androgens
- Estrogens (any delivery route)
- Progestogens
- Tamoxifen, raloxifene and aromatase inhibitors are allowed, but patient must have been on a constant dose for at least 28 days and must not be expected to stop the medication during the study period
- SSRIs/SNRIs, when being used for hot flash management or other indications such as depression, is allowed, assuming the dose will remain unchanged for the study duration
- Gabapentin/pregabalin, when being used for hot flash management (use for other indications, such as pain, is allowed, assuming the dose will remain unchanged for the study duration)
- Clonidine
- Agents with known potent anticholinergic activity as listed on Appendix VII. Agents with mild-moderate anticholinergic activity are allowed.

3.22 Prior use of oxybutynin during the period in which patient has had hot flashes.

3.23 Any of the following because this study involves an investigational agent whose genotoxic, mutagenic and teratogenic effects on the developing fetus and newborn are unknown:

- Pregnant women
- Nursing women

3.24 History of any of the following contraindications to oxybutynin:

- Uncontrolled gastroesophageal reflux disease (GERD) despite appropriate therapy. If patient has history of GERD, but symptoms are well-controlled with medical treatment, patient is eligible.
- Ulcerative colitis
- Narrow-angle glaucoma
- Urinary retention
- Hypersensitivity to oxybutynin or any other components of the product
- Current uncontrolled hyperthyroidism
- Coronary heart disease (angina or prior myocardial infarction)
- Congestive heart failure
- Symptomatic cardiac arrhythmias
- Current uncontrolled hypertension
- Myasthenia gravis
- Dementia

4.0 Test Schedule

Tests and procedures	Active Monitoring Phase				
	≤ 60 days prior to registration	End of week 1 (baseline)	Daily during baseline week and during treatment (x7 weeks)	End of each treatment week	End of treatment (end of study)
History and exam, weight, height, ECOG PS	X				
Hot Flash Diary[2,4] (Appendix IV)			X[3]		
Patient Questionnaire: Symptom Experience Questionnaire[2] (Appendix V)		X[3]		X[3]	
Hot Flash Daily Interference Scale[2] (Appendix VI)		X[3]			X[3]
Nurse/CRA phone contact (Appendix VIII)		X[1]		X[1]	

[1]Nurse/CRA to call patient at ends of weeks 1, 2, 3, 4, 5, 6 and 7 (AE assessment does not need to be done for end of week 1 call, however a form MUST be entered for forms tracking purposes). The CRA/Nurse Phone Call Script (Appendix VIII) may be used to assist in data collection.
[2]Patient questionnaire booklets must be used.
[3]Patient questionnaire booklets should be returned to the investigator at the end of the 1st and 7th study weeks. The patient should be supplied with addressed/stamped envelopes for returning the booklets.
[4]Patient will be encouraged to carry a small notepad with them during the day to keep track of hot flashes and enhance accuracy of recording on Hot Flash Diary.

5.0 Stratification Factors:

5.1 Age: 18 - 49 vs ≥50.

5.2 Current tamoxifen use: Yes vs no.

5.3 Current aromatase inhibitor use: Yes vs no.

5.4 Duration of flash symptoms (months): <9 vs ≥9.

5.5 Average frequency of hot flashes per day: 4 - 9 vs ≥10.

6.0 Registration/Randomization Procedures

6.1 Registration Procedures

6.11 To register a patient, access the ACCRU web page at [redacted] click on "Training Page" and enter the registration/randomization application. The registration/randomization application is available 24 hours a day, 7 days a week. Back up and/or system support contact information is available on the Web site. If unable to access the Web site, call the Academic and Community Cancer Research United (ACCRU) Registration Office at [redacted] between the hours of 8 a.m. and 4:30 p.m. Central Time (Monday through Friday).

The instructions for the registration/randomization application are available using the Help button. Prior to initiation of protocol treatment, this process must be completed in its entirety and a ACCRU subject ID number must be available as noted in the instructions. It is the responsibility of the individual and institution registering the patient to confirm the process has been successfully completed prior to release of the study agent. Patient registration via the registration/randomization application can be confirmed in any of the following ways:

- Contact the ACCRU Registration Office [redacted]. If the patient was fully registered, the ACCRU Registration Office staff can access the information from the centralized database and confirm the registration.
- Refer to "Instructions for Remote Registration" in section "Finding/Displaying Information about A Registered Subject."

6.12 Documentation of IRB approval must be on file with ACCRU before an investigator may register any patients. Approvals should be uploaded through the online ACCRU Regulatory Management System (ARMS).

In addition to submitting initial IRB approval documents, ongoing IRB approval documentation must be on file with ACCRU (no less than annually). Approvals should be uploaded through the online ACCRU Regulatory Management System (ARMS). If the necessary documentation is not submitted in advance of attempting patient registration, the registration will not be accepted and the patient may not be enrolled in the protocol until the situation is resolved.

Submission of annual IRB approvals to ACCRU is required until the study is closed through your IRB.

6.13 Prior to accepting the registration/randomization, the registration/randomization application will verify the following:

- IRB approval at the registering institution
- Patient eligibility
- Existence of a signed consent form
- Existence of a signed authorization for use and disclosure of protected health information

6.14 Treatment cannot begin prior to registration and must begin ≤ 30 days after registration.

6.15 Pretreatment tests/procedures (see Section 4.0) must be completed within the guidelines specified on the test schedule.

6.16 Treatment on this protocol must commence at an ACCRU institution under the supervision of a health care professional.

6.17 Study drug is available on site.

6.18 Patient questionnaire booklet is available on site; copies are not acceptable for this submission.

6.2 Randomization Procedures

6.21 The factors defined in Section 5.0, together with the registering membership, will be used as stratification factors.

6.22 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 which balances the marginal distributions of the stratification factors between the treatment groups (Pocock SJ, Simon R, 1975).

- Oxybutynin 2.5 mL BID x 42 days
- Oxybutynin 2.5 mL BID x 7 days followed by 5 mL BID x 35 days
- Placebo 2.5 mL BID x 42 days
- Placebo 2.5mL BID x 7 days followed by placebo 5mL BID x 35 days

6.3 Procedures for Double-Blinding the Treatment Assignment

6.31 At the time that the site has registered/randomized the patient , the Registration Office will contact the designated site contact person with the assigned treatment as follows:

- Oxybutynin 2.5mL oral BID x 42 days
- Oxybutynin 2.5 mL oral BID x 7 days followed by 5 mL oral BID x 35 days
- Placebo 2.5mL oral BID x 42 days
- Placebo 2.5 mL oral BID x 7 days followed by placebo 5 mL oral BID x 35 days

The name of this person and his/her contact information will be entered on the Enrollment Form. This contact person may not be involved in assessing adverse events or any other outcome measure. The institutional pharmacist or designated contact person will maintain records that identify the patient and his/her corresponding treatment assignment.

7.0 Protocol Treatment

7.1 The patient will be instructed *not* to take any study medication for the first seven days but to complete their daily questionnaire [redacted] during this baseline period. At the end of the week, patients will complete Symptom Experience Form [redacted] and Hot Flash Daily Interference Scale [redacted]. For the subsequent six weeks, patients will be instructed to take their study medication as illustrated below.

- Oxybutynin 2.5mL oral BID Days 8 through 49 total of 42 days)
- Oxybutynin 2.5 mL oral BID Days 8 through 14 (total of 7 days) → 5 mL oral BID Days 15 through 49 (total of 35 days)
- Placebo 2.5 mL oral BID Days 8 through 49 (total of 42 days)
- Placebo 2.5mL oral BID Days 8 through 14 (total of 7 days) → 5 mL oral BID Days 15 through 49 (total of 35 days)

7.2 At study entry, the patient will be given the following two booklets:

- Double-Blind Week 1 (Baseline) that contains a Patient Instruction Sheet, Hot Flash definitions, a daily Hot Flash Diary, Symptom Experience Questionnaire, and a Hot Flash-Related Daily Interference Scale.
- Double-Blind (Weeks 2-7) which contains Patient Instruction Sheet, Hot Flash Definitions, six daily Hot Flash Diaries, six Symptom Experience Questionnaires, and one Hot Flash-Related Daily Interference Scale.

Procedures for completing and returning the booklets are to be carefully explained. Patient will be encouraged to carry a small notepad with them during the day to keep track of hot flashes and enhance accuracy of recording on Hot Flash Diary.

7.21 The page labeled "First Study Week (Baseline)" should be filled out during the first seven days following study entry, to document the patient's baseline hot flashes [redacted]

7.22 The next pages labeled "Week 2" should be filled out during the second seven days after study entry and so on for weeks 3-7 [redacted]

7.23 Evaluation procedures

7.231 Each patient will be contacted by telephone at weekly intervals during the study weeks to document compliance, encourage completion of the questionnaires and address problems. Phone calls may be omitted in those weeks in which the patient is seen at the institution responsible for her primary care. The information obtained must be recorded on the Nurse/CRA Evaluation form in the forms packet.

7.232 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.

7.3 Premature discontinuation of study

7.31 If the patient decides to discontinue the study medication because of unacceptable side effects, she is to call the study nurse. The patient should be asked to complete diaries/questionnaires to date and send them in. The patient can then be taken off study.

7.32 Patients wishing to discontinue the study medication because of perceived lack of benefit should be encouraged, whenever possible, to complete the study arm, since the full effect of treatment may not be evident for six weeks.

7.33 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.

7.4 Procedures at end of study.

7.41 Patients need to be contacted on their last scheduled day of the randomized, blinded study. It should be assured that the patient has completed her questionnaires. Then the patient should be told which dose of oxybutynin they were receiving and subsequently given the choice of whether she would like to continue with oxybutynin off study (or start it if she was on the placebo). No further data submission is required.

7.42 If the patient chooses not to continue (or start) oxybutynin after the 7-week randomized period, then this is fine.

7.51 7.5 Breaking Codes in Double–Blinded StudiesThe treatment code may not be broken prior to study completion except for emergnecies. In the event of an emergency, call the ACCRU Registration Office at [redacted] to break the code on Monday through Friday, [redacted] Central Time. If the code must be broken after hours, assume the patient was assigned to active treatment and treat accordingly. Place a call to the ACCRU Registration Office and leave a message informing them of the need to un-blind a patient. Provide your contact information so that ACCRU Registration Office personnel can return the call the next business day.

7.52 See section 7.41 regarding unblinding patients at end of treatment.

8.0 Dosage Modification Based on Adverse Events

8.1 During 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 or placebo doses will be adjusted as follows:

Dose modifications for adverse events	
Low Dose	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	If symptoms occur during first 7 days of treatment, proceed as for the low-dose group. If symptoms occur on or after day 8 of treatment, 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 persist, the drug will be discontinued and patient will be asked to complete questionnaires to date and then be taken off study.

9.0 Ancillary Treatment/Supportive Care

9.1 All ancillary treatments as appropriate for symptom control and cancer therapy may be administered as clinically indicated with the exception of treatment for hot flashes. Although at the time of study entry, patients with current or planned therapy with antineoplastic chemotherapy, androgens, estrogens, or progestational agents are not eligible for this study, if, during the conduct of this study any of these agents become clinically appropriate, they may then be given (record reason clearly on the Nurse/CRA Work Sheet, [redacted]). If these agents are started, then the patient data will be censored at that point.

10.0 Adverse Event (AE) Reporting and Monitoring

The site principal investigator is responsible for reporting any/all serious adverse events to the sponsor as described within the protocol, regardless of attribution to study agent or treatment procedure. The sponsor/sponsor-investigator is responsible for notifying FDA and all participating investigators in a written safety report of any of the following:

- Any suspected adverse reaction that is both serious and unexpected.
- Any findings from laboratory animal or *in vitro* testing that suggest a significant risk for human subjects, including reports of mutagenicity, teratogenicity, or carcinogenicity.

- Any findings from epidemiological studies, pooled analysis of multiple studies, or clinical studies, whether or not conducted under an IND and whether or not conducted by the sponsor, that suggest a significant risk in humans exposed to the drug.
- Any clinically important increase in the rate of a serious suspected adverse reaction over the rate stated in the protocol, package insert, or Investigator's Brochure (IB).

Definitions

Adverse Event
Any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

Suspected Adverse Reaction
Any adverse event for which there is a reasonable possibility that the drug caused the adverse event.

Expedited Reporting
Events reported to sponsor within 24 hours, 5 days or 10 days of study team becoming aware of the event.

Routine Reporting
Events reported to sponsor via case report forms

Events of Interest
Events that would not typically be considered to meet the criteria for expedited reporting, but that for a specific protocol are being reported via expedited means in order to facilitate the review of safety data (may be requested by the FDA or the sponsor).

10.1 Adverse Event Characteristics

CTCAE term (AE description) and grade: The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP web site: (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm)

a. Adverse event monitoring and reporting is a routine part of every clinical trial.

b. Identify the grade and severity of the event using the CTCAE version 4.0.

c. Determine whether the event is expected or unexpected (see Section 10.2).

d. Determine if the adverse event is related to the study intervention (agent, treatment or procedure) (see Section 10.3).

e. Determine whether the event must be reported as an expedited report. If yes, determine the timeframe/mechanism (see Section 10.4).

f. Determine if other reporting is required (see Section 10.5).

g. Note: All AEs reported via expedited mechanisms must also be reported via the routine data reporting mechanisms defined by the protocol (see Sections 10.6 and 18.0).

Each CTCAE term in the current version is a unique representation of a specific event used for medical documentation and scientific analysis and is a single MedDRA Lowest Level Term (LLT).

NOTE: A severe AE, as defined by the above grading scale, is NOT the same as serious AE which is defined in the table in Section 10.4.

10.2 Expected vs. Unexpected Events

Expected events - are those described within the Section 15.0 of the protocol, the study specific consent form, package insert (if applicable), and/or the investigator brochure, (if an investigator brochure is not required, otherwise described in the general investigational plan).

Unexpected adverse events or suspected adverse reactions are those not listed in Section 15.0 of the protocol, the study specific consent form, package insert (if applicable), or in the investigator brochure (or are not listed at the specificity or severity that has been observed); if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan.

Unexpected also refers to adverse events or suspected adverse reactions that are mentioned in the investigator brochure as occurring with a class of drugs but have not been observed with the drug under investigation.

10.3 Assessment of Attribution

When assessing whether an adverse event is related to a medical treatment or procedure, the following attribution categories are utilized:

Definite - The adverse event *is clearly related* to the agent(s).
Probable - The adverse event *is likely related* to the agent(s).
Possible - The adverse event *may be related* to the agent(s).
Unlikely - The adverse event *is doubtfully related* to the agent(s).
Unrelated - The adverse event *is clearly NOT related* to the agent(s).

Events determined to be possibly, probably or definitely attributed to a medical treatment suggest there is evidence to indicate a causal relationship between the drug/device and the adverse event.

*Report any clinically important increase in the **rate** of a serious suspected adverse reaction (at your study) site over that which is listed in the protocol or investigator brochure as an expedited event.

*Report an expected event that is greater in severity or specificity than expected as an expedited event

*An investigational agent/intervention might exacerbate the expected AEs associated with a commercial agent. Therefore, if an expected AE (for the commercial agent) occurs with a higher degree of severity or specificity, expedited reporting is required.

A list of known/expected AEs is reported in the investigator brochure, package insert or the literature, including AEs resulting from a drug overdose.

10.331 Death

- Any death occurring within 30 days of the last dose, regardless of attribution to an agent/intervention under an IND/IDE requires expedited reporting within 24-hours.

- Any death occurring greater than 30 days with an attribution of possible, probable, or definite to an agent/intervention under an IND/IDE requires expedited reporting within 24-hours.

- **Reportable categories of Death**

    - Death attributable to a CTCAE term.

    - Death Neonatal: A disorder characterized by cessation of life during the first 28 days of life.

    - Death NOS: A cessation of life that cannot be attributed to a CTCAE term associated with Grade 5.

    - Sudden death NOS: A sudden (defined as instant or within one hour of the onset of symptoms) or an unobserved cessation of life that cannot be attributed to a CTCAE term associated with Grade 5.

    - Death due to progressive disease should be reported as **Grade 5 "Neoplasms benign, malignant and unspecified (including cysts and polyps) – Other (Progressive Disease)"** under the system organ class (SOC) of the same name. 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.

10.332 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.

- All secondary malignancies that occur following treatment with an agent under an IND/IDE to be reported. Three options are available to describe the event:

    - Leukemia secondary to oncology chemotherapy (e.g., Acute Myeloid Leukemia [AML])

    - Myelodysplastic syndrome (MDS)

    - Treatment-related secondary malignancy

- Any malignancy possibly related to cancer treatment (including AML/MDS) should also be reported via the routine reporting mechanisms outlined in each protocol.

10.333 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.

10.335 Pregnancy

Prior to obtaining private information about a pregnant woman and her infant, the investigator must obtain consent from the pregnant woman and the newborn infant's parent or legal guardian before any data collection can occur. A consent form will need to be submitted to the IRB for these subjects if a pregnancy occurs. If informed consent is not obtained, no information may be collected.

In cases of fetal death, miscarriage or abortion the mother is the patient. In cases where the child/fetus experiences a serious adverse event other than fetal death, the child/fetus is the patient.

NOTE: When submitting ACCRU Adverse Event Report reports for "Pregnancy", "Pregnancy loss", or "Neonatal loss", the potential risk of exposure of the fetus to the investigational agent(s) or chemotherapy agent(s) should be documented in the "Description of Event" section. Include any available medical documentation.

10.4 Expedited Reporting Requirements for Studies using Commercial Agent(s) ONLY

Expedited Reporting Requirements for Adverse Events that Occur in a Non-IND/IDE trial within 30 Days of the Last Administration of a Commercial Agent [1, 2]

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)
NOTE: Investigators **MUST** immediately report to the sponsor **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 ofexisting 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 sponsor within the timeframes detailed in the table below.

<table>
<tr><th>Hospitalization</th><th>Grade 1 Timeframes</th><th>Grade 2 Timeframes</th><th>Grade 3 Timeframes</th><th>Grade 4 & 5 Timeframes</th></tr>
<tr><td>Resulting in Hospitalization ≥ 24 hrs</td><td colspan="3">7 Calendar Days</td><td rowspan="2">24-Hour / 3 Calendar Days</td></tr>
<tr><td>Not resulting in Hospitalization ≥ 24 hrs</td><td colspan="2">Not required</td><td>7 Calendar Days</td></tr>
</table>

Expedited AE reporting timelines are defined as:

- "24-Hour / 3 Calendar Days" - The AE must initially be reported within 24 hours of learning of the AE, followed by a complete expedited report within 3 calendar days of the initial 24-hour report.
- "7 Calendar Days" - A complete expedited report on the AE must be submitted within 7 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 3 calendar days for:

- All Grade 4, and Grade 5 AEs

Expedited 7 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

Follow site-specific reporting guidelines.

Commercial agent expedited reports must be submitted to the FDA via MedWatch.3500A http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM048334.pdf or http://www.fda.gov/AboutFDA/ReportsManualsForms/Forms/ListFormsAlphabetically/default.htm

Instructions for completing the MedWatch 3500A: http://www.fda.gov/downloads/Safety/MedWatch/HowToReport/DownloadForms/UCM387002.pdf Submit copies to the ACCRU SAE Coordinator via fax [redacted]. The ACCRU SAE Coordinator will forward to (insert sponsor name).

10.5 Other Required Reporting

10.51 Unanticipated Problems Involving Risks to Subjects or Others (UPIRTSOS) in general, include any incident, experience, or outcome that meets **all** of the following criteria:

1. Unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;

2. Related or possibly related to participation in the research (in this guidance document, possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and

3. Suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

Some unanticipated problems involve social or economic harm instead of the physical or psychological harm associated with adverse events. In other cases, unanticipated problems place subjects or others at increased *risk* of harm, but no harm occurs.

Note: If there is no language in the protocol indicating that pregnancy is not considered an adverse experience for this trial, and if the consent form does not indicate that subjects

should not get pregnant/impregnate others, then any pregnancy in a subject/patient or a male patient's partner (spontaneously reported) which occurs during the study or within 120 days of completing the study should be reported as a UPIRTSO.

If the event meets the criteria for an UPIRTSO, submit to your IRB as required by your institutional policies.

10.52 Baseline and Adverse Events Evaluations

Adverse event evaluations will be evaluated by the weekly questionnaires. If patients have significant toxicities, they will also be assessed with weekly phone calls.

10.53 **Case Report Forms** - Academic and Community Cancer Research United (ACCRU)

Submit the following AEs not specified in Section 10.5 (paper or electronic, as applicable)

10.521 Grade 2 AEs deemed *possibly, probably, or definitely* related to the study treatment or procedure.

10.522 Grade 3 and 4 AEs regardless of attribution to the study treatment or procedure.

10.523 Grade 5 AEs (Deaths)

10.5231 Any death within 30 days of the patient's last study treatment or procedure regardless of attribution to the study treatment or procedure.

10.5232 Any death more than 30 days after the patient's last study treatment or procedure that is felt to be at least possibly treatment related must also be submitted as a Grade 5 AE, with a CTCAE type and attribution assigned.

10.54 The Academic and Community Cancer Research United (ACCRU) Routine AE Data Submission Policy does not apply, as this study does not collect AE attribution. Submit Grade 2 or greater AEs via the AE Log when AEs experienced by the patient are not specified in Section 10.5.

11.0 Treatment Evaluation

11.1 During the seven-day baseline symptom documentation and the treatment periods of this study, patients will be instructed to complete a daily "Hot Flash Diary" [redacted] at roughly the same time each day to document severity and frequency of hot flashes. Patients will also complete a weekly "Symptom Experience Questionnaire [redacted] to document possible side effects.

12.0 Descriptive Factors

12.1 Duration of tamoxifen therapy (years): 0, <1, 1-5, >5

12.2 Duration of AI therapy (years). : 0, <1, 1-5, >5

12.3 Duration of hot flashes (years). : <1, 1-5, >5

13.0 Treatment/Follow–up Decision at Evaluation of Patient

13.1 A patient is deemed *ineligible* if after registration, it is determined that at the time of registration, the patient did not satisfy each and every eligibility criteria for study entry. The patient may continue treatment off-protocol at the discretion of the physician as long as there are no safety concerns, and the patient was properly registered. The patient will go directly off study.

- If the patient received treatment, all data up until the point of confirmation of ineligibility must be submitted.
- If the patient never received treatment, on-study material must be submitted.

13.2 A patient is deemed a *major violation*, if protocol requirements regarding treatment in cycle 1 of the initial therapy are so severely violated that evaluability for primary end point is questionable. All data up until the point of confirmation of a major violation must be submitted. The patient will go directly to the event-monitoring phase of the study. The patient may continue treatment off-protocol at the discretion of the physician as long as there are no safety concerns, and the patient was properly registered.

13.3 A patient is deemed a *cancel* if he/she is removed from the study for any reason before any study treatment is given. On-study material and the End of Active Treatment/Cancel Notification Form must be submitted. No further data submission is necessary.

14.0 Body Fluid Biospecimens - Not Applicable

15.0 Drug Information

Drug Package Insert: The most current version of the package insert will be maintained in the study folder on the ACCRU website.

The study drug is IND exempt because:

- The drug product is lawfully marketed in the United States.
- The investigation is not intended to be reported to FDA as a well-controlled study in support of a new indication and there is no intent to use it to support any other significant change in the labeling of the drug.
- In the case of a prescription drug, the investigation is not intended to support a significant change in the advertising for the drug.
- The investigation does not involve a route of administration, dose, patient population, or other factor that significantly increases the risk (or decreases the acceptability of the risk) associated with the use of the drug product (21 CFR 312.2(b)(1)(iii)).
- The investigation is conducted in compliance with the requirements of §312.7 (i.e., the investigation is not intended to promote or commercialize the drug product).

15.1 Oxybutynin chloride

15.11 Formulation: Oxybutynin chloride is available as immediate release tablets of 5mg or oral syrup of 5mg/5mL. Extended release (XL) tablets of 5, 10 and 15 mg are also available. For the current study, we will use the oxybutynin chloride syrup 5 mg/5 mL, supplied in 473 mL bottles.

Each 5 mL, for oral administration, contains 5 mg of oxybutynin chloride. In addition, the following inactive ingredients are present: Artificial raspberry flavor; citric acid, USP; D&C Yellow No. 10; FD&C Blue No. 1; glycerin, USP; liquid sugar; methylparaben, NF; propylene glycol, USP; sodium citrate, USP and sorbitol solution, USP.

The drug will be provided to the patient free-of-charge.

15.12 Preparation and storage:

The local pharmacist will be told the study arm to which the patient was randomized. With this information, the pharmacist will prepare the product and instructions for the patient:

Study arm	Preparation and directions
Oxybutynin 2.5 mL BID for 6 weeks	Put 240 mL (8 fl. oz.) of 5mg/5mL oxybutynin syrup into brown bottle with instructions to take 2.5 mL by mouth BID for 6 weeks.
Oxybutynin 2.5 mL BID for 1 week and then 5.0 mL BID for 5 weeks	Put 473 mL (16 fl. oz.) of 5mg/5mL oxybutynin syrup into brown bottle with instructions to take 2.5 mL by mouth BID for1 week and then 5 mL BID for 5 weeks.
Placebo 2.5 mL BID for 6 weeks	Put 240 mL (8 fl. oz.) of Ora-Sweet SF into brown bottle with instructions to take 2.5 mL by mouth BID for 6 weeks.
Placebo 2.5 mL BID for 1 week and then 5.0 mL BID for 5 weeks	Put 473 mL (16 fl. oz.) of Ora-Sweet into brown bottle with instructions to take 2.5 mL by mouth BID for 1 week and then 5 mL by mouth BID for 5 weeks.

Store at 20º to 25º C (68º to 77º F).

15.13 Known potential toxicities: Common side effects include xerostomia (35-72%), dizziness (up to 17%), constipation (up to 15%), somnolence (up to 14%), nausea (up to 12%), blurred vision (up to 10%), diarrhea (up to 8%), headache (8%), indigestion (up to 6%), gastroenteritis (2%) and dry eyes (3%). Anaphylaxis/hypersensitivity, confusion, seizures and hallucinations have been reported.

15.14 Drug procurement: Each participating ACCRU treating location will order the drug from Biologics, Inc. Fax the Drug Order Request Form (found in the forms packet) to:

[redacted]

Each participating ACCRU treating location will request 5 bottles of oxybutynin and 5 bottles of Ora-Sweet from Biologics at study initiation. This is estimated to be enough for about 15 patients (range from about 6 to about 20, depending on which arms that they are accrued to). If/when resupply is needed, then enough should be ordered to allow the institution to have about 5 bottles of each. If an institution is accruing patients rapidly, then a larger supply can be ordered.

Each site will provide its own syringes and 8 oz. and 16 oz. amber bottles.

Outdated or remaining drug is to be destroyed on-site as per procedures in place at each institution.

15.15 Nursing guidelines:

15.131 Patient may take medication with or without food.

15.132 Monitor for potential mild nausea. Treat accordingly.

15.133 Warn patient of possible somnolence. If patient does experience somnolence, advise her to refrain from driving or operating machinery.

15.134 Stress to patient the importance of avoiding medications listed on Appendix VII. Encourage patient to contact Nurse/CRA before initiation of new medications.

15.135 Warn patient about possible urinary retention. If patience experiences this, she should hold the next dose and contact Nurse/CRA for next steps.

15.2 Placebo

The liquid placebo, Ora-Sweet SF, will also be supplied free-of-charge. No toxicity is expected from the placebo.

15.21 Preparation and Storage

Ora-Sweet SF will be used as the base solution for preparing the placebo doses. Ora-Sweet SF is a flavored sugar-free syrup vehicle available in 473mL (16 oz.) bottles. The product contains glycerin, sorbitol, sodium saccharin, xanthan bum, flavoring agent, and purified water. The solution is buffered with citric acid and sodium citrate and preserved with methylparaben, propylparaben, and potassium sorbate.

Store at controlled room temperature (15º to 30º C, 59º to 86º F). A 473 mL (16 oz.) bottle is to be retained for the preparation of multiple patient's dispenses. After the bottles have been opened for the first time, the site will assign an expiration date of one year, if this expiration date is shorter than the expiration date listed on the bottles.

15.21 Procurement: Refer to Section 15.14 for procurement instructions.

Outdated or remaining drug is to be destroyed on-site as per procedures in place at each institution.

16.0 Statistical Considerations and Methodology

16.1 Study design

16.11 This study is a randomized four-arm, double-blind, placebo-controlled phase III trial to assess the effectiveness and toxicity of oxybutynin as a treatment for hot flashes. Patients will be randomly assigned to oxybutynin at two target doses and placebo arms in 2:2:(1:1) ratios according to the dynamic allocation scheme. Patients assigned to the placebo arms will be equally divided to receive the same dose schedule as each of the two target doses of oxybutynin, so that double-blinding is maintained.

16.12 We will adopt a modified intent-to-treat principle that excludes those patients who will be deemed ineligible, major violation, cancel after randomization or missing all repeated measures of primary endpoint after randomization. All statistical hypothesis testing will be carried out using a two-sided test with a significance level α=0.05.

16.2 Primary and secondary endpoints

16.21 The primary endpoint is the intra-patient changes of weekly hot flash activity from baseline during the treatment period. The hot flash activity will be measured by the weekly average hot flash score (Sloan JA, et. al., 2001), which is a composite entity of both frequency and severity of hot flashes. The daily hot flash score is computed by the grade of severity multiplying the frequency of the same grade hot flashes according to the hot flash diary over a 24 hour period. Taking the average of daily hot flash scores over a week produces the weekly average hot flash score.

16.22 Secondary endpoints: There are a number of secondary endpoints that may be affected by oxybutynin treatment. Due to their exploratory nature, we will not adjust for multiple comparisons when performing these analyses.

16.221 The change of weekly frequency and maximum grade of hot flashes as measured by the Hot Flash Diary during the treatment period.

16.222 The change of frequency and maximum grade of adverse events reported via the CTCAE 4.0 during the treatment period. In particular, dry mouth is of interest.

16.223 The change of severity of symptoms as measured the Symptom Experience Questionnaire from baseline to treatment termination.

16.224 The change of daily interference as measured by the HFRDIS from baseline to treatment termination.

16.225 The intra-patient changes of weekly hot flash activity from baseline during the treatment period between two placebo groups using different dosing.

16.3 Analysis plan

16.31 Primary analysis

16.331 The time-averaged intra-patient changes in hot flash activity from baseline during the treatment period will be compared between treatment and placebo arms using a repeated measures model of weekly hot flash score. Patient baseline characteristics, prognostic factors and actual exposure to oxybutynin (exact dose) may be considered as covariate in the model. Estimates from this model will be used to construct a 95% confidence interval for the mean difference in intra-patient changed of hot flashes between the treatment and placebo arms.

Because our two treatment arms represent different doses of the same drug, we will perform a fixed sequence of up to two hypothesis tests, rather than two simultaneous tests, as would generally be done for studies in which the primary analysis involves two independent hypotheses. This is based on the belief that the treatment effect of oxybutynin, if one exists, will change monotonically with respect to dose. To control the overall type-I error for our primary analysis, we will employ a gatekeeping procedure. In particular, we will first use the time-averaged longitudinal model mentioned above to test the higher dose (2.5mg BID for one week, followed by 5mg BID for five weeks) vs placebo at the level 0.05, using a two-sided alternative. **If and only if** this test is significant, we will test the smaller dose oxybutynin arm (2.5mg BID for 6 weeks) vs placebo, again at the level 0.05, and using a two-sided alternative. If the test of the larger dose arm vs. placebo is not significant, we will not perform the test of the smaller dosing arm

vs. placebo as part of our primary analysis. If both of these tests are significant, we will conclude that the treatment effect of oxybutynin given at the dose 2.5mg BID or higher is significant (i.e. both the lower and higher dosing schedules are associated with a significant treatment effect). If only the higher dose arm test is significant, we will conclude that only the treatment effect for the higher dosing schedule is significant. If the higher dose arm is not found to differ significantly from placebo in the first test, we will conclude that neither of our treatment arms differ significantly from the placebo group. It should be noted that, if the higher dosing arm is not found to differ significantly from the placebo arms, we will still perform the test for the lower dosing arm, but as a secondary analysis, rather than a primary analysis.

16.332 Supplementary analyses will be conducted to incorporate patient characteristics, baseline hot flash score and other baseline risk factors in the repeated measures model. Graphical procedures will include a stream plot of individual scores over time and a plot of average (or median) scores over time for the oxybutynin and placebo arms.

16.32 Secondary analyses

Secondary endpoints will be transformed to a 0-100 point scale where applicable to aid in ease of comparison. This transformation is standard practice in NCCTG Cancer Control trials with numerous secondary endpoints (Sloan JA, Dueck A, 2004).

16.321 The change of frequency and maximum severity of hot flashes during the treatment period between treatment and placebo arms will be compared using repeated measures models. Generalized estimating equations may be used to estimate model parameters, as these are likely to be count and ordinal endpoints.

16.322 The frequency and maximum grade of adverse events reported via the CTCAE version 4 through treatment will be first summarized by descriptive statistics. For each adverse event, Chi-square tests (or Fisher's exact tests) will be used to evaluate the difference between oxybutynin and placebo arms.

16.323 The change of severity of symptoms as measured by the Symptom Experience Questionnaire from baseline to treatment termination will be first summarized by descriptive statistics and then compared across oxybutynin and placebo arms using Wilcoxon rank sum tests (or two sample *t*-tests).

16.324 The change of daily interference as measured by the HFRDIS from baseline to treatment termination will be first summarized by descriptive statistics and then compared across oxybutynin and placebo arms using Wilcoxon rank sum tests (or two sample *t*-tests).

16.325 The time-averaged intra-patient changes in hot flash activity from baseline during the treatment period will be compared between the two placebo arms using a repeated measures model of weekly hot flash score.

16.4 Power and sample size

16.41 Sample size calculations are based on the primary analysis of using a time-averaged repeated measures model to compare oxybutynin and placebo arms. In particular, the number of evaluable patients needed per arm was obtained using Equation 2.4.2 in Diggle et al (2002):

$$m = \frac{2(z_\alpha + z_Q)^2 \sigma^2 [1 + (n-1)\rho]}{nd^2}$$

where z_α and z_Q are the quantiles of standard normal distribution that corresponds to (one-sided) significance level α and type II error Q, σ is the standard deviation, n is the number of repeated measures per subject, ρ is the correlation of repeated measures of weekly hot flash score, and d is the meaningful difference of interest.

16.42 We assume the minimum meaningful difference (*d)* in the time-averaged intra-patient change in hot flash activity from baseline is half of a standard deviation (i.e. d/σ = *0.5*), which is considered a moderate effect size by Cohen (Cohen J, 1988) and which has been described as clinically meaningful (Sloan J, et. al., 2003). A moderate correlation ($\rho = 0.5$) between repeated measures of weekly hot flash score over the six (*n = 6*) weeks is also assumed for the sample size calculation.

16.43 For the two-sided test of the time-averaged hot flash scores at 5% significance level (note, this is two-sided significance, so we use α = 2.5% in the sample size formula above) in the primary analysis, we will need 42 evaluable patients per arm to provide 85% power to detect an effect size of one half standard deviation. The total sample size will be 126 patients, as we have two oxybutynin arms. Assuming that as many as 15% of patients will be lost due to ineligibility, cancellation, or major violations, our target accrual will be 150 patients (50 patients in each active treatment arm and 25 patients in each placebo arm).

16.5 Accrual rate and time to completion

We anticipate accruing approximately 10 evaluable patients per month, based on our previous experience with similar hot flash trials. Thus, we expect to complete the primary accrual within 15 months of study initiation and the double-blind data collection 17 months from study initiation.

16.6 Missing data

16.61 We will examine the mechanisms of missing data if the proportion of missing assessments is not small (>=5%). Graphical presentation, correlation analysis (Kendall's) and logistic regression will be performed to examine whether the missing data mechanism depends on the covariates (patient characteristics and other baseline risk factors), observed patient-reported outcome (PRO) scores, and missing PRO scores.

16.62 If we feel it is reasonable to assume that the missing data mechanism depends on the covariates only (missing completely at random, MCAR) or depends on the covariates and observed PRO scores only (missing at random, MAR) (Little R and Rubin D, 2002), we will enhance the primary analysis to incorporate these covariates in the repeated measures model. Assuming the resulting model includes all observed data and covariates that

explain the missing data mechanism, this should result in unbiased estimates under MCAR and MAR (Fairclough D, 2002).

16.63 If the missing data mechanism depends on not only the covariates and observed PRO scores, but also on the missing HF score (missing not at random, MNAR) (Little R and Rubin D, 2002), we will explore advanced models that consider both longitudinal PRO assessments and missing data mechanism, such as pattern mixture model and selection model (Fairclough D, 2002).

16.64 Simple and multiple imputations will be used as part of sensitivity analysis to examine the dependence of the results on specific assumptions about the PRO scores of individuals with missing assessments. Previous experience with imputation in NCCTG clinical trials have demonstrated that the use of various imputation methods compared to analysis of all available data provides evidence of the degree of robustness of the results relative to the assumptions of the analytical procedure.

16.7 Monitoring

The efficacy and toxicity data for this study will be reviewed semiannually by the Mayo Clinic Data Safety Monitoring Board (DSMB). Early termination of accrual will be considered if there is evidence of unacceptable toxicity.

16.8 Adverse Event Stopping Rule

The stopping rule specified below is based on the knowledge available at study development. We do 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 events that the study team considers to be at least possibly related to study treatment (i.e., an adverse event with attribute specified as “possible,” “probable,” or “definite”) that satisfy the following:

If there are at least 2 events (so that the score is not just 1 versus 0) and a greater than 50% increase in grade 4 or higher non-hematologic adverse events (compared to the control arms) in the first 20 treated patients; or a 25% increase in grade 4 or higher nonhematologic adverse events on the oxybutynin arms compared to the control arms after 20 patients total are accrued.

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.

16.9 Minority accrual

This study will be available to all eligible patients, regardless of race or ethnic origin. There is no information currently available regarding differential effects of oxybutynin in subsets defined by race or ethnicity, and there is no reason to expect such differences to exist. Nonetheless, the planned analyses will, as always, look for differences in treatment effect based on racial groupings.

17.0 Pathology Considerations/Tissue Biospecimens – Not applicable

18.0 Records and Data Collection Procedures

18.1 Submission Timetable

Initial Material(s)

CRF	**Active-Monitoring Phase** (Compliance with Test Schedule Section 4.0)
Institutional Contacts	≤2 weeks after registration
On-Study Form	≤2 weeks after registration
Off Treatment	Submit ≤4 weeks after registration if withdrawal/refusal occurs prior to beginning protocol therapy
Patient Status: Baseline	≤ 4 weeks after registration

1. Submit to the ACCRU Operations Office, [redacted].

Test Schedule Material(s)

CRF	Active-Monitoring Phase (Compliance with Test Schedule Section 4.0)	
	At each evaluation during treatment	At end of treatment
Nurse/CRA Evaluation	X	X
Adverse Events: Solicited	X	X
Adverse Events: Other	X	X
Patient Questionnaire Booklet[1]	X	
Patient Questionnaire Booklet Compliance[2]	X	
Off Treatment		X
Patient Status: Treatment	X	X
Week 1 QOL Status[4]	X	
Week 2-7 QOL Status		X
Deviation Form[3]	X	X
Lost to Follow-up	X[3]	X
Consent Withdrawal/Consent Withdrawal: QOL	X[3]	X[3]

1. Patient questionnaire booklets (Double-Blind Week 1 (Baseline) and Double-Blind Weeks 2-7) **must** be used; copies are not acceptable for this submission. Submit to [redacted].
2. This form must be completed **only** if the patient questionnaire booklets (Double-Blind Week 1 (Baseline) and Double-Blind Weeks 2-7) contain absolutely **NO** patient provided assessment information. Submit to [redacted]
3. Submit only if applicable.
4. Submit at end of week 1.

19.0 Budget

19.1 Each site should review the test schedule (Section 4.0), taking into account local and regional coverage policies, to determine which items are standard of care and which are research at their site. Refer to the payment synopsis for funding provided per accrual for covering study costs, as well as any additional invoiceables that may be allowed.

19.2 Tests to be research funded: None.

19.3 Other budget concerns: Oxybutynin and placebo will be provided free of charge.

20.0 References

Barton DL, Lavasseur BI, Sloan JA, et al: Phase III, Placebo-Controlled Trial of Three Doses of Citalopram for the Treatment of Hot Flashes: NCCTG Trial N05C9. J Clin Oncol28:3278-83, 2010.

Barton D, Loprinzi CL: Making sense of the evidence regarding nonhormonal treatments for hot flashes. Clinical Journal of Oncology Nursing 8:39-42, 2004.

Bertelli G, Venturini M, Del Mastro L, et al: Intramuscular depot medroxyprogesterone versus oral megestrol for the control of postmenopausal hot flashes in breast cancer patients: a randomized study. Ann Oncol 13:883-8, 2002.

Borges S, Desta Z, Li L, et al: Quantitative effect of CYP2D6 genotype and inhibitors on tamoxifen metabolism: Implication for optimization of breast cancer treatment. Clin Pharmacol Ther 80:61-74, 2006.

Carpenter JS, Johnson D, Wagner L, et al: Hot flashes and related outcomes in breast cancer survivors and matched comparison women. Oncol Nurs Forum 29:E16-25, 2002.

Cohen J: Statistical power analysis for the behavioral sciences. New Jersey, Lawrence Erlbaum Associates, Inc., 1988.

Diggle P, Heagerty P, Liang K-Y, et al: Analysis of Longitudinal Data (ed 2nd). Oxford, England, Oxford University Press, 2002.

Fairclough D: Design and Analysis of Quality of Life Studies in Clinical Trials. Boca Raton, Florida, Chapman & Hall / CRC, 2002.

Gracia C, Freeman E: Acute consequences fo the menopausal trasition: the rise of common menopausal symptoms. Endocrinol Metab Clin North Am 33:675-89, 2004.

Hemeryck A, Belpaire FM: Selective serotonin reuptake inhibitors and cytochrome P-450 mediated drug-drug interactions: an update. Curr Drug Metab 3:13-37, 2002.

Hsu J, Berger R. Stepwise confidence intervals without multiplicity adjustment for dose-response and toxicity studies. J Amer Stat Assoc 94:468-82, 1999.

Jin Y, Desta Z, Stearns V, et al: CYP2D6 genotype, antidepressant use, and tamoxifen metabolism during adjuvant breast cancer treatment. J Natl Cancer Inst 97:30-9, 2005.

Laguardia KD, inventor. Treatment of hot flashes using muscarinic receptor antagonists such as oxybutynin [patent]. 2007 http://www.google.com/patents/WO2007143486A2?cl=en. Accessed August 11, 2016.

Little R, Rubin D: Statistical Analysis with Missing Data (ed 2). Hoboken, New Jersey, John Wiley & Sons, Inc, 2002.

Loprinzi CL, Diekmann B, Novotny PJ, et al: Newer antidepressants and gabapentin for hot flashes: a discussion of trial duration. Menopause, 16:883-7, 2009.

Loprinzi CL, Kugler JW, Sloan JA, et al: Venlafaxine in management of hot flashes in survivors of breast cancer: a randomised controlled trial. Lancet 356:2059-63, 2000.

MacGregor CA, Canney PA, Patterson G, et al: A randomised double-blind controlled trial of oral soy supplements versus placebo for treatment of menopausal symptoms in patients with early breast cancer. Eur J Cancer 41:708-14, 2005

Molina JR, Barton DL, Loprinzi CL: Chemotherapy-induced ovarian failure: manifestations and management. Drug Safety 28:401-16, 2005

Morales AJ, Nolan JJ, Nelson JC, et al: Effects of replacement dose of dehydroepiandrosterone in men and women of advancing age. J Clin Endocrinol Metab 78:1360-7, 1994

Notelovitz M, Lenihan JP, McDermott M, et al: Initial 17beta-estradiol dose for treating vasomotor symptoms. Obstet Gynecol 95:726-31, 2000.

Pocock SJ, Simon R. Sequential Treatment Assignment with Balancing for Prognostic Factors in the Controlled Clinical Trial. Biometrics 31:103-115, 1975.

Sexton T, Younus J, Perera F, et al: Oxybutynin for refractory hot flashes in cancer patients. Menopause 14:505-509, 2007.

Simon JA, Gaines T, LaGuardia KD, for the Extended-Release Oxybutynin Therapy for VMS Study Group. Extended-release oxybutynin therapy for vasomotor symptoms in women: a randomized clinical trial. Menopause 2016;23 (11):1-8.

Sloan JA, Dueck A: Issues for statisticians in conducting analyses and translating results for quality of life end points in clinical trials. J Biopharm Stat 14:73-96, 2004.

Sloan JA, Loprinzi CL, Novotny PJ, et al: Methodologic lessons learned from hot flash studies. J Clin Oncol 19:4280-90, 2001.

Sloan J, Symonds T, Vargas-Chanes D, et al: Practical guidelines for assessing the clinical signficiance of health-related quality of life changes within clinical trials. Drug Info J 37:23-31, 2003.

Stearns V, Ullmer L, Lopez JF, et al: Hot flushes. Lancet 360:1851-61, 2002.

Stuenkel CA, Davis SR, Gompel A, et. al. Treatment of Symptoms of the Menopause: An Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab 2015 Nov;100(11):3975-4011. doi: 10.1210/jc.2015-2236. Epub 2015 Oct 7.

Westall P, Krishen A: Optimally weighted, fixed sequence and gatekeeper multiple testing procedures. . J Stat Plan Inference 99:25-40, 2001.

Wolosker N, de Campos JR, Kauffman P, et al: A randomized placebo-controlled trial of oxybutynin for the initial treatment of palmar and axillary hyperhidrosis. J Vasc Surg 55:1696-700, 2012.

World Almanac Books: Top-selling medicinal herbs in the US, 1999-2003. The world almanac and book of facts, 2005. New York (NY): St. Martin’s Press; c2005.