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. (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

<table>
<thead>
<tr>
<th>Schema</th>
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<tbody>
<tr>
<td><strong>RANDOMIZE</strong></td>
</tr>
<tr>
<td><strong>Initial Blinded Phase Oxybutynin</strong></td>
</tr>
<tr>
<td><strong>2.5 mL</strong> p.o. BID for 42 days***</td>
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<tr>
<td><strong>Placebo 2.5 mL</strong> p.o. BID for 42 days***</td>
</tr>
<tr>
<td><strong>Oxybutynin 5.0 mL</strong> p.o. BID for 42 days***</td>
</tr>
<tr>
<td><strong>Placebo 5.0 mL</strong> p.o. BID for 42 days***</td>
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<tr>
<th>Optional Unblinded Phase</th>
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<tbody>
<tr>
<td><strong>Oxybutynin 2.5 mL</strong>* p.o. BID for 42 days</td>
</tr>
<tr>
<td><strong>Oxybutynin 5.0 mL</strong>* p.o. BID for 42 days</td>
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</tbody>
</table>

* 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.

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Update #01
3.1 **Patient Selection**

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

3.2 **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.

3.3 **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.

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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, eluxadoline, and potassium chloride], androgens, estrogens, progesterone analogs, gabapentin, SSRI/SNRI anti-depressants, 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.

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; 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