COVER PAGE

DCP Protocol #: UWI2016-08-01

Local Protocol #: CPRC #2016LS183 / UW17010 / UAB 1788 / 28UCS2019

Pilot Study of Daily Exemestane in Women with Complex Atypical Hyperplasia of the Endometrium / Endometrial Intraepithelial Neoplasia or Low Grade Endometrial Cancer

Consortium Name: **University of Wisconsin Chemoprevention Consortium**
Name of Consortium Principal Investigator: **Howard H Bailey, MD**
University of Wisconsin Carbone Cancer Center
600 Highland Ave.
CSC K4/654
Madison, WI 53792-6164
Telephone: (608)263-8624
Fax: (608)299-3765
E-mail: hhb@medicine.wisc.edu

Organization Name: Masonic Cancer Center, University of Minnesota
Protocol Principal Investigator: Britt Erickson, MD
Gynecologic Oncology
OB/GYN & Women's Health
420 Delaware St. SE MMX 395
Minneapolis, MN 55455
Telephone: 612-626-6283
Fax: 612-626-0665
Email: bkeric@umn.edu

Organization: University of Wisconsin
Investigator: Lisa Barroilhet, MD
Gynecologic Oncology
600 Highland Ave
H4/638 Clinical Science Center
Telephone: 608-265-2319
Fax: N/A
E-mail: barroilhet@wisc.edu

Organization: University of Alabama at Birmingham
Investigator: Rebecca Arend, MD
Gynecologic Oncology
619 19th Street South
176F Rm 10250
Birmingham, Alabama 35249
Telephone: 205-934-4986
Fax: 205-975-6174
E-mail: rarend@uabmc.edu

Organization: **Investigator:**	E.O. Ospedali Galliera Andrea De Censi, MD Division of Medical Oncology 16128 Genova, Italy Telephone: +39 010 5634501 Fax: +39 010 57481090 E-mail: andrea.decensi@galliera.it
DCP Scientific Monitor:	Goli Samimi, Ph.D., M.P.H. Scientific Monitor Breast and Gynecologic Cancer Research Group Division of Cancer Prevention, NCI, NIH 9609 Medical Center Drive, Rm 5E-336, MSC9783 Bethesda, MD 20892 (For FedEx, use Rockville, MD 20850) Telephone: (240) 276-6582 Fax: (240) 276-7828 Email: goli.samimi@nih.gov
DCP Medical Monitor:	Eva Szabo, MD Chief, Lung & Upper Aerodigestive Cancer Research Group NCI/Division of Cancer Prevention 9609 Medical Center Drive, Room 5E-102, MSC 9781 Bethesda, MD 20892-9781 (For FedEx, use Rockville, MD 20850) Phone: (240) 276-7011 FAX: (240) 276-7848 email: szaboe@mail.nih.gov
Organization: **Statistician:**	University of Wisconsin - Madison Richard Chappell, PhD 610 Walnut St, WARF 207E Madison, WI 53726 Telephone: 608-263-5572 or 608-229-6541 No fax number chappell@biostat.wisc.edu
IND Sponsor:	NCI/Division of Cancer Prevention
IND# **Agent(s)/Supplier**:	[redacted] Exemestane/NCI, Division of Cancer Prevention / Galliera hospital Pharmacy
NCI Contract #	HHSN261201200033I
Protocol Version Date:	November 08, 2021
Protocol Revision or Amendment #	Version 10.0

SCHEMA

Pilot Study of Daily Exemestane in Women with Complex Atypical Hyperplasia of the Endometrium / Endometrial Intraepithelial Neoplasia or Low Grade Endometrial Cancer

Up to 40 post-menopausal women age 45 years and older with diagnosis of complex atypical endometrial hyperplasia/ endometrial intraepithelial neoplasia (CAH/EIN) or low grade (grade 1 or grade 2) endometrial carcinoma who are candidates for hysterectomy.

↓

Pre-screening and Eligibility determination	
For Site in Italy: **1. Prescreening visit:** - Before the diagnostic hysteroscopy, participants will sign a biopsy consent - During the exam, gynecologist will perform the double pass biopsy (one pass for diagnosis and one for research). **2. Screening/pre-baseline visit (day 0):** - If CAH/EIH or low grade endometrial cancer confirmed, participants will sign the main study consent - Perform lab tests for eligibility requirement assessment. - Tampon will be placed by a study nurse. - Send eligibility documents to Consortium Lead Organization (CLO) for eligibility confirmation. **3. Baseline visit (day 1):** - During clinic visit the tampon will be collected - Study drug dispensed. - Establish date of surgery	For Sites in USA: **1. Prior to baseline (pre-surgical) clinic visit** - Pre-Screening by record review/introductory telephone contact - If interested, mail screening consent packet and 2 tampons - Phone call reminder the day before baseline (pre-surgical) clinic visit to place tampon before visit **2. Baseline (pre-surgical) clinic visit (minimum of 22 days prior to planned surgery)** - Obtain written consent - Perform baseline tests and procedures (including tampon removal and biopsy) - Establish date of surgery **3. Confirm eligibility** - Send via courier exemestane with start date instructions and pill diary - Also, send a tampon kit (2 tampons + instructions); tampon to be inserted 8-12 hours before surgery

↓

Day 0 telephone contact (US sites only)

Phone call reminder to start taking exemestane and reminder to note the time taken in the pill diary

↓

Day 1 of exemestane (US sites only)

Participant begins once a day exemestane dosing on day 1, allowing between 21 and 42 days of dosing prior to surgery

↓

Day 15 (±2), of exemestane

Study coordinator or designee contacts participant via telephone to assess adverse effects/toxicity

↓

Day before Surgery	
For Site in Italy: Participant visits the center for symptoms assessment and concomitant medications review. Tampon will be placed by a study nurse. Remind to bring pill diary and medication bottle next day.	For Sites in USA: Study coordinator contacts participant via telephone to remind her to insert the tampon 8-12 hours before surgery and to bring exemestane bottle and pill diary with her to the hospital

↓

Final study visit - Day of surgery

Obtain research blood tests
Reconcile exemestane dosing
Remove research tampon intraoperatively
Procure surgical pathology tissue

↓

Follow up contact on or before first post-surgical follow-up (only if adverse events were ongoing at the time of surgery)

Study coordinator contacts participant regarding any ongoing exemestane attributed toxicity

The following research specimens will be collected for each enrolled patient:

1. Tissue from research biopsy and surgical specimen will be obtained for each enrolled participant
2. Samples from tampon collection pre and post treatment
3. Blood samples pre and post treatment – for estradiol, progesterone and pharmacokinetic levels in plasma

Additional archived tissue will be obtained from 30 historic matched controls

Study Endpoints:

Primary: Change in tumor proliferation (measured by change in Ki-67 expression) pre and post exemestane treatment

Secondary:

1. Changes in circulating serum estradiol and progesterone pre and post exemestane treatment
2. Pathological response to exemestane – (regression of CAH/EIN or low grade endometrial carcinoma)
3. Tissue biomarkers
    a. Apoptosis (cleaved caspase 3)
    b. Proliferation (cyclin D1)
    c. Insulin pathway (pAKT, IGF-1R)
    d. Endocrine regulation (ER/PR/AR)
4. DNA mutational analysis through Next Generations Sequencing and methylation status of endometrial tumor
5. Protein and DNA markers via tampon recovery pre and post exemestane treatment
6. Comparison of Ki-67 expression between participants samples and historically matched samples
7. Evaluation of plasma levels of exemestane pre and post treatment

TABLE OF CONTENTS

1. OBJECTIVES

1.1 Primary Objective

The primary objective is to determine if there is a decrease in proliferation index, measured by Ki-67 expression, in complex atypical hyperplasia (CAH)/ endometrial intraepithelial neoplasia (EIN) or low grade (grade 1 and grade 2) endometrial cancer cells from baseline to post-exemestane treatment.

1.2 Secondary Objectives

1. **Circulating serum estradiol and progesterone:**
   Measure pre- and post-treatment circulating serum estradiol and progesterone levels to determine the effect of a daily dose of 25 mg of exemestane for 21-42 days.
2. **Pathological response (regression of CAH/EIN or low grade (grade 1 and grade 2) endometrial carcinoma):**
   Examine pathologic changes in CAH/EIN or low grade (grade 1 and grade 2) endometrial carcinoma from pre-treatment biopsies to final (post-treatment) pathology.
3. **Tissue biomarkers:**
   Using immunohistochemistry, examine differences in the expression of biomarkers from baseline to post-treatment for the following cellular pathways:
   a) Apoptosis (cleaved caspase 3)
   b) Proliferation (cyclin D1)
   c) Insulin pathway (pAKT, IGF-1R)
   d) Endocrine regulation (ER/PR/AR)
4. **DNA mutational analysis through Next Generation Sequencing and methylation status of endometrial tumor:**
   Analyze DNA from CAN/EIN or low grade (grade 1 and grade 2) endometrial carcinoma for specific genetic mutations, microsatellite instability and methylation status in order to correlate exemestane response to mutational status.
5. **Protein markers via tampon recovery before and after treatment:**
   Perform pre- and post-treatment proteomic analysis of vaginal proteins from tampon recovery to identify biomarkers that may predict response to exemestane treatment.
6. **DNA markers via tampon recovery:**
   Analyze vaginal DNA from tampon recovery to determine if tumor DNA can be detected vaginally. If tumor DNA can be detected vaginally, this could represent an innovative, non-invasive method for detecting endometrial cancer or predicting treatment response.
7. **Safety and adverse effects of treatment:**
   Evaluate safety and adverse effects of the treatment by CTCAE 4.0 toxicity scale.
8. **Comparison of Ki-67 expression changes between study subjects and a historical cohort.**
   Participants will be matched with a historical nonrandomized control group. The control group will provide a reference for how Ki-67 may change based on differences in specimen collection (endometrial biopsies versus surgical specimen) and time between biopsy and surgery, independent of exemestane exposure.
9. **Evaluation of the levels of exemestane in the plasma samples pre and post treatment.**
   Comparison of pharmacokinetic (PK) levels of plasma exemestane pre-and post-treatment.

2. BACKGROUND

Rationale/Hypothesis: Endometrial cancer is the most common gynecologic malignancy in the U.S. with over 60,000 new cases predicted in 2016[1]. It is increasing in frequency, most likely as a consequence of increasing rates of obesity. The standard of care remains hysterectomy, which, given the comorbidities of this patient population (diabetes mellitus, obesity, cardiovascular disease), is associate with significant perioperative morbidity and cost[2]. Like breast cancer, endometrial cancer is a hormonally sensitive disease. Specifically, it is estrogen responsive and in a percentage of women, can be treated with progesterone therapy. However, progesterone therapy is not always effective and therefore is only recommended as primary therapy in women who are not surgical candidates or in women who desire fertility preservation. In a large systematic review of progestin therapy in fertility preservation, durable response to therapy was noted in only 53% of women, suggesting a need for improved therapies [3].Therefore, we are in need of a non-surgical, low side effect treatment for endometrial carcinoma and its precursors. Moreover, given its increase in frequency, a chemopreventive strategy would be helpful in reducing the burden of disease.

Exemestane, an aromatase inhibitor (AI), is used for the primary chemoprevention of breast cancer in high-risk populations, as well as in the upfront and adjuvant treatment of women with advanced and local disease, respectively. [4] It has also been used off label for the treatment of advanced endometrial carcinoma and leiomyosarcoma as well as in the adjuvant treatment of high risk endocrine responsive premenopausal breast cancer in combination with LHRH agonists.[5,6] Given its anti-estrogen effects, it holds promise as a potential therapeutic or chemopreventive intervention for women with (or at high-risk of developing) endometrial cancer. In the present pilot study, we hypothesize that short-term exposure (21-42 days) of patients with low grade endometrial carcinoma and CAH/EIN to exemestane will result in significant reduction in tumor proliferation, as measured by a decrease in Ki-67 expression.

Excess estrogen, progesterone and endometrial carcinoma: Obesity is proposed to contribute to endometrial cancer through multiple mechanisms, of which excess exposure to estrogen relative to progesterone and metabolic disturbances, such as diabetes and metabolic syndrome, play critical roles among postmenopausal women. Data suggests that endometrial cancers develop over many years from progressively more severe endometrial proliferation. Accordingly, there are multiple potential approaches that may reduce the incidence of endometrial cancer including endocrine chemoprevention, agents that correct metabolic disturbances, and weight reduction. Notably, the 1994 WHO classification of simple and complex hyperplasia with or without atypia has been since replaced by the newer 3-tier system of: 1- benign (benign endometrial hyperplasia) 2- premalignant (endometrial intraepithelial neoplasia) and 3- malignant (adenocarcinoma).[7,8] For this proposal, endometrial intraepithelial neoplasia (EIN) will be synonymous with complex atypical hyperplasia (CAH) and endometrial hyperplasia (EH).

Traditionally endometrial endometrioid adenocarcinoma has been described in a 3-tier system: grade 1, grade 2, and grade 3. With an improved molecular understanding these tumors, the 3 tier system can be separated into low-grade and high-grade endometrial cancer.[56, 57] Low-grade tumors (grade 1 and grade 2) are usually early stage, have a better prognosis and are associated with estrogen exposure. High grade tumors (grade 3 as well as uterine serous and clear cell tumors) are aggressive tumors with higher rates of metastases, poor prognosis and are often unrelated to estrogen exposure.[58, 59]

Excess estrogen exposure is strongly linked to the development of low-grade endometrial cancer and its precursors. Ten years of excess estrogen has been shown to increase risk 10 fold [9], and prospective data demonstrate that increased serum estrogen levels double the risk when comparing the highest to the lowest serum level groups[10]. Consistent with these findings, obesity, reproductive, and menstrual factors linked to endometrial cancer risk are proposed to be mediated through increased levels of estrogen. Recent data from a health maintenance organization suggest that breast cancer survivors who have received aromatase inhibitors, which lower circulating estrogen levels, are associated with reduced risk for endometrial cancer

compared to women who received tamoxifen [11].

Endometrial cancer precursors, particularly if less severe than endometrial intraepithelial neoplasia, frequently do not progress to endometrial cancer, suggesting that risk of endometrial cancer may be highly modifiable. In support of this, administering exogenous progesterone is highly effective in treating endometrial cancer precursors and useful in reversing low grade endometrial cancer. For example, oral medroxyprogesterone (MPA) (Provera) is approved to "reduce the incidence of endometrial hyperplasia" in the presence of estrogen replacement therapy, an approach validated by the Women's Health Initiative study. Oral progestins such as MPA and norethindrone (NET) (Aygestin) have also been successfully used to treat endometrial hyperplasia in the absence of estrogen replacement therapy [12]. Additionally, an intrauterine form of progestin, levonorgestrel (LNG) (Mirena) has demonstrated some efficacy in endometrial hyperplasia treatment.[13,14] While numerous trials have demonstrated that progestins are a good option for treatment of endometrial hyperplasia, resistance to progestin has been reported in 12 to 53% of treated women. The development of resistance is associated with various factors including patient characteristics, such as age, co-morbidities, and molecular characteristics [15]. Further, use of exogenous progesterone after menopause may be undesirable because it increases breast cancer risk, whereas use of AIs lowers risk of both endometrial and breast cancer. Given that obesity is a major risk factor for both endometrial and breast cancer, the use of AIs to reduce circulating estrogen levels among women at elevated risk of endometrial cancer may be a promising approach for reducing risk of both cancers.

Exemestane (6-methylenandrosta-1,4-diene-3,17-dione) is a type I, 3rd generation, steroidal aromatase inhibitor, which means it directly competes with androgens for the enzyme active site, causing irreversible inactivation of the aromatase enzyme. This is in contrast to type II non-steroidal AIs (such as letrozole and anastrozole), which prevent androgens from reversibly binding the enzyme through the heme moiety of the enzyme. [17,18] After binding to aromatase, exemestane is converted into intermediate active metabolites, which covalently bind to the enzyme causing degradation and inactivation, also known as “suicide inhibition”[19]. The primary active metabolite of exemestane is 17B-hydroexemestane (17-BHE), which has been shown to have a high affinity for androgen receptors. It has been suggested that variability in clinical response to treatment with exemestane could be due to differences in P450 enzymes between patients. [20]

Exemestane is absorbed orally, with maximum plasma concentrations reached within 2 hours. Multiple trials have found that, although doses up to 800mg daily were tolerated, the most favorable effects were observed at the 25mg daily dosing. [21,22] Greater than 98% reduction of estrogen synthesis has been demonstrated *in vivo* at this dose [23]. A single dose can reduce levels of estrogens up to 95% for 2-3 days. [24] Exemestane is distributed extensively in peripheral tissues and it has a mean terminal elimination half-life of 24 hours. [18]

Exemestane has been studied extensively in the neoadjuvant, adjuvant, chemopreventive, and metastatic setting of ER+ breast cancer. It has been studied alone as well as in combination with or compared to non-steroidal 3rd generation AIs (anastrozole) as well as tamoxifen. In the neoadjuvant setting, Fontein et al enrolled 102 women with ER+ untreated breast cancer. In this phase II trial, women received exemestane for 6 months prior to surgery. 68% of women had a clinical response to treatment and rates of breast conservation surgery increased by nearly 10% suggesting a true anti-tumor effect of exemestane. [25] In the chemoprevention setting, the randomized, placebo-controlled, double blind Mammary Protocol 3 (MAP.3) trial of 4,560 women at high risk for developing breast cancers, 11 invasive breast cancers where detected in those women receiving exemestane compared to 32 invasive cancers detected in those receiving placebo (0.19% vs 0.55%; HR 0.35; 95% CI 0.18 - 0.70; p= 0.002) [26]. Studies are currently underway in stage 0-II breast cancer patients to determine whether less than a daily dose of exemestane results in non-inferior reduction in estrogen levels compared with daily dosing to assess whether adverse events can be reduced using this strategy.

Since estrogen levels are associated with the progression of hyperplasia to cancer, estrogen reduction by aromatase inhibition is a viable treatment option for women with hyperplasia. In the case series of 5 infertile premenopausal women presenting with endometrial hyperplasia with or without atypia, Li et al has observed no hyperplasia after 3 months of treatment with letrozole. [27] Barker et al reported retrospective outcomes of 16 of the postmenopausal women with EH or endometrial carcinoma who were not surgical candidates, treated with either anastrozole or letrozole.[28] After three years of treatment, the eight patients with endometrial hyperplasia and the four patients with localized endometrial cancer experienced mean reduction in endometrial thickness of 82% and 67%, respectively, but 4 patients with metastatic endometrial carcinoma patients experienced no change in endometrial thickness. Burnett et al, were able to effectively restore well differentiated endometrium in two women with grade 1 endometrial cancer using MPA and anastrozole (one patient was treated for 3 months and the other for 6 months) in order to maintain fertility[29]. In a more recent non-randomized prospective study, Smith et al reported that five of 12 (41%) patients with grade 1 or 2 endometrial carcinoma demonstrated a significant decrease in the cellular proliferation marker, Ki-67 following daily letrozole treatment for 3 weeks prior to surgery. No study has yet to evaluate if exemestane could cause regression of endometrial pre-cancer or cancer.

The strong link between estrogen levels and endometrial carcinoma, and the role of aromatase inhibitors in reducing circulating estrogen levels suggests that aromatase inhibitors should be used as a treatment for women with endometrial hyperplasia or low grade endometrial cancer. This drug could also be employed as a chemopreventive agent in women at high risk for developing endometrial cancer. Furthermore, treatment with aromatase inhibitors provides a strong added value potentially decreasing risk of breast cancer in this high-risk (obese) population.

2.1 CAH/EIN and Low Grade Endometrial Cancer

A pilot study is proposed to address, whether a daily dose of 25mg of exemestane is effective in decreasing the proliferation marker Ki-67 in CAH/EIN and low grade (grade 1 and grade 2) endometrial cancer. The data generated from this pilot study, including pathologic response, hormone levels, genomics, proteomics and immunohistochemical biomarkers, will help guide potential future studies to determine optimal exemestane dosage scheduling as well as combination therapies for CAH/EIN and low grade endometrial cancer.

2.2 Exemestane

Exemestane is an aromatase inhibitor initially approved by the FDA in 1999 for the treatment of advanced breast cancer in postmenopausal women whose disease has progressed following tamoxifen therapy. On October 5, 2005, it was approved by the FDA for the adjuvant treatment of postmenopausal women with estrogen-receptor positive early breast cancer who have received two to three years of tamoxifen and are switched to exemestane for completion of a total of five consecutive years of adjuvant hormonal therapy. Standard approved dosing is 25 mg by month per day continuously.

Adverse Reactions: Early breast cancer: Adverse events occurring in ≥10% of patients in any treatment group (exemestane vs. tamoxifen) were hot flashes (21.2% vs. 19.9%), fatigue (16.1% vs. 14.7%), arthralgia (14.6% vs. 8.6%), headache (13.1% vs. 10.8%), insomnia (12.4% vs. 8.9%), and increased sweating (11.8% vs. 10.4%). Discontinuation rates due to AEs were similar between exemestane and tamoxifen (6.3% vs. 5.1%). Incidences of cardiac ischemic events (myocardial infarction, angina, and myocardial ischemia) were exemestane 1.6%, tamoxifen 0.6%. Incidence of cardiac failure: exemestane 0.4%, tamoxifen 0.3%.

Advanced breast cancer: Most common adverse events were mild to moderate and included hot flashes (13% vs. 5%), nausea (9% vs. 5%), fatigue (8% vs. 10%), increased sweating (4% vs. 8%), and increased appetite (3% vs. 6%) for exemestane and megestrol acetate, respectively.

2.3 Rationale for CAH/EIN and Low Grade Endometrial carcinoma Prevention with Exemestane

The majority of circulating estrogen comes from the pre-menopausal ovary. However, many other extra-ovarian tissues use the enzyme aromatase to convert androgens into estrogens thereby increasing local and circulating estradiol levels. Adipose tissue has high aromatase levels, and thus has been found to contribute significantly to the level of circulating estrogen.

As our understanding of the aromatase enzyme pathway has increased, so has our ability to develop novel AIs with potentially lower side effect profiles. Aromatase is a cytochrome p450 enzyme, which is responsible for the conversion of androgens (specifically testosterone and androstenedione) into estrogens (specifically estradiol and progesterone, respectively)[16]. Blocking the aromatase enzyme therefore lowers circulating estrogen levels, which may have an anti-proliferative effect on the endometrium.

Increasing evidence suggests that tobacco and alcohol use are risk factors in the development of intraepithelial neoplasia and cancer. In addition, tobacco and alcohol use may adversely affect agent intervention, for example by altering the safety profile or metabolism of a drug. Standardized assessments of tobacco and alcohol use during clinical trials will aid in understanding the potential relationship between the use of these products and clinical endpoints or cancer prevention biomarkers. Therefore, NCI, DCP is including assessment of tobacco and alcohol use at baseline (pre-surgical) clinic visit and Surgery, to determine the potential impact of tobacco and alcohol use on 1) treatment toxicity and symptom burden, and 2) the efficacy of treatment intervention.

3. SUMMARY OF STUDY PLAN

Study Plan: This is a multi-center, phase IIA, single-arm 'window of opportunity' pilot study of 25 mg per day of exemestane for 21 to 42 days in patients undergoing hysterectomy for CAH/ EIN or low grade endometrial cancer (grade 1 or grade 2). Tissue from participant's research endometrial biopsy will be used for pre-surgical biomarker analysis. The tissue obtained from surgical excision will be used for post-treatment biomarker analysis.

Study recruitment will occur in gynecology oncology clinics at participating institutions. A lead gynecologic oncology surgeon has been identified at each site. Up to 40 patients will be accrued for this pilot study. An age, disease and body mass index (BMI) matched historical comparator cohort will also be identified in order to compare changes in the primary outcome, Ki-67 expression between biopsy and surgical specimen in an untreated cohort.

For the U.S. based sites, prior to the baseline (pre-surgical) clinic visit, a pre-screening telephone contact will be completed to determine interest and basic eligibility for the study. If the participant gives verbal consent, study materials will be mailed to them. Materials will include a full study consent form to read through prior to their visit as well as 2 tampons (one to be inserted prior to the baseline (pre-surgical) clinic visit and other one as back up) and instructions for inserting the tampon (appendix D).

At the baseline (pre-surgical) clinic visit, participants will meet the study team to discuss and sign the informed consent form. The study team (including the research coordinator and the treating gynecologic oncologist) will review their medical history, conduct physical examination and review of concomitant medications. Participants will also have baseline laboratory tests. These tests include Complete Blood Count (CBC) with differential and platelets, Comprehensive Metabolic Panel (CMP), Estradiol, Progesterone and Follicle Stimulating Hormone (FSH) in all women 45-55 years old and in women 56-59 years old if they report less than 2 years of amenorrhea to confirm the post-menopausal status. Additionally,

blood will be drawn for exemestane pharmacokinetics. This research blood sample for exemestane pharmacokinetics will be destroyed if the participant does not qualify for the study.

Because this is a window of opportunity study, the study period will be limited to the time between the initial pre-surgical visit and definitive surgery (hysterectomy). In order to reduce number of visits for the study participants and to start treatment in a timely fashion, all eligibility tests will be performed at the baseline (pre-surgical) clinic visit. Being able to acquire an adequate endometrial biopsy specimen is an important part of eligibility given that the primary endpoint of this study compares Ki-67 expression between pre and post treatment tissue. Therefore, an endometrial biopsy for research purposes will be performed at the baseline (pre-surgical) clinic visit during the standard pelvic exam. Laboratory tests will also be performed at the baseline (pre-surgical) clinic visit, either before or after the physical exam and endometrial biopsy. The vaginal tampon, which was inserted by participant prior to the baseline (pre-surgical) clinic visit, will be removed during the pelvic exam. If the participant is subsequently deemed ineligible (either due to inadequate biopsy tissue, laboratory values or physical exam results), the endometrial biopsy samples of the participant will be destroyed and her tampon will be destroyed.

Although attempts will be made to contact all participants prior to their baseline (pre-surgical) visit, the study can also be presented at their baseline (pre-surgical) visit. If interested, the participants will sign the consent form and then undergo study procedures (research biopsy, lab tests, etc) on the day of their baseline (pre-surgical) visit. In this case, participants will not have a tampon sample collection as part of their baseline (pre-surgical) visit. This will not be considered a protocol deviation. If participants are willing to return for an additional visit, they will be permitted to return for a biopsy and tampon collection within 1-2 weeks of signing consent form.

For E.O. Ospedalli Galliera (EOG) site only, participants will be approached to participate prior to their actual diagnosis of CAH/EIN/low grade endometrial cancer. Standard of care in this region includes a visit with a gynecologic oncologist and subsequent hysteroscopy with biopsies when patients have postmenopausal bleeding and a high suspicion for pre-invasive or invasive disease. Therefore, the research team will meet the potential participants for a prescreening visit before the diagnostic hysteroscopy. Patients will sign a pre-screening consent on this day before the procedure. During the examination, the surgeon will perform one diagnostic biopsy and one research only biopsy. If CAH/EIN/low grade EC is confirmed then participants will sign the main study consent. If the patient does not meet the CAH/EIN/low grade EC diagnosis the research tissue samples will be destroyed. On the day before the baseline (pre-surgical) clinic visit the team will obtain written consent for study participation. A tampon will be placed by a study nurse. Lab tests for eligibility will be collected. Eligibility documents will be submitted to CLO for verification. On the day of the pre-surgical clinic visit, the study nurse will remove the tampon and place in cold PBS. The study drug will be dispensed to the participant at this visit after receiving the eligibility confirmation from CLO. If the lab test results are not within study required parameters, the patient will be deemed ineligible and the tampon will be removed and discarded during this clinic visit.

Participants who meet eligibility requirements will begin oral exemestane daily for at least 21 days (no longer than 42 days) with a dose of 25 mg/day by mouth (PO) until the day prior to surgery.

The day the participant begins taking exemestane is considered Day 1 of the study. The study team will make telephone contacts to the participants on

- Day 0/1 as a reminder to start exemestane
- Day 15 (±2 days) to assess for adverse events and other symptoms, and review medication changes.

- One day prior to surgery to assess for adverse events and other symptoms and review medications. In addition, the participants will be reminded to insert a tampon 8-12 hours before surgery.

Participants will be encouraged to contact the investigator or study coordinator with any new symptoms or concerns at any time during the trial.

Participants will place a tampon 8-12 hours before surgery. For US based sites, a tampon kit will be mailed to the participants. The study agent will be mailed along with an additional tampon kit. The kit will include 2 tampons (one to be inserted prior to surgery and one as back up) and instructions to insert the tampon (appendix D).

For EOG site only, the participants will come back to the clinic the day before surgery and have the second tampon placed by a study nurse.

Surgery must occur between Days 22-43 of the study. On the day of surgery, participants will undergo a physical exam, laboratory tests (Complete Blood Count (CBC) with differential and platelets, Comprehensive Metabolic Panel (CMP), estradiol and progesterone), and an additional blood draw for plasma levels of exemestane. In addition, adverse events and concomitant medications will be reviewed. At the time of surgery, the self-inserted tampon will be removed by the surgeon.

Following surgery, and after completion of necessary standard of care surgical pathology, an additional section of the tumor (up to 1x1x1 cm) will be collected, cut in half and snap frozen as per institutional policy and stored for genetic analysis. If there is not a visible lesion, a random 1x1x1 cm area from the endometrium will be selected. This can be smaller if the pathology team needs to review more of the endometrium. The amount and location of the sample is at the investigators clinical discretion. In addition, ten unstained 5µm formalin fixed paraffin embedded (FFPE) slides will be obtained from the primary tumor surgical specimen for IHC biomarker analysis.

For EOG site only, follow-up at the standard of care post-operative visit will be performed in order to collect long-term safety information of the study treatment, whether or not the participant has any ongoing adverse events at the surgery visit.

If any reported adverse events attributed to the study agent are ongoing on the day of surgery, the participant will be contacted by the study team on or before the post-operative visit to perform safety assessments for ongoing adverse events or symptoms.

The study participants will be matched with a historical nonrandomized control group based on age (± 5 years), disease type and BMI (>20-24, 25-30, > 30). Historical samples (no more than 5 years old) will be identified through pathologic databases that exist at all participating sites. Medical records will be reviewed to ensure correct matching. The pre-surgical and post-surgical tissue samples, within 42 days of each other, will be obtained from each historical subject. All subjects will be de-identified. IHC analysis of Ki-67 expression will be performed on the pre-surgical and post-surgical samples.

4. PARTICIPANT SELECTION

In the U.S. based sites, whenever feasible, potential participants will be pre-screened for the study and contacted by the study team prior to their planned baseline (pre-surgical) clinic visit. The advantage of this is to introduce the study concept to the potential participant and allow her to place a tampon for specimen collection prior to her baseline (pre-surgical) clinic visit. If the participant gives verbal consent over the phone for the screening portion of the study, a pre-study packet will be mailed to her. This packet will

contain an informed consent form for her review and 2 commercially available tampons (one to be inserted in her vagina 8-12 hours before her baseline (pre-surgical) clinic visit and one for back up) along with instructions on how to insert a tampon (Appendix D). The tampon will be removed during the baseline (pre-surgical) clinic visit by the physician at the time of the pelvic exam. If the participant is eligible and agrees to take part in the study, the tampon will be processed and the resultant protein and DNA will serve as a pre-treatment sample. If the participant is either not eligible or refuses to sign the study consent, the tampon will be discarded. If a subject was unable to place a tampon prior to their baseline (pre-surgical) clinic visit, she will still be eligible for participation in this study.
For EOG site only, the patient will be approached for study participation when they first present with postmenopausal bleeding.

4.1 Inclusion Criteria

Eligible participants must meet the following requirements:

4.1.1 Females with a histologically proven CAH/ EIN or low grade (grade 1 or grade 2) endometrial carcinoma (EC) for which surgery is planned. The pathologic report from the referring facility will be used to determine pathologic eligibility. This report must be within 45 days of their baseline (pre-surgical) clinic visit.

4.1.2 No prior treatment for CAH/EIN/EC

4.1.3 Age ≥45 years

4.1.4 Post-menopausal confirmed with one the following criteria:

- ≥ 60 years of age
- age 56 to 59 years of age with **≥ 2 years** of amenorrhea
- age 56 to 59 years of age with **< 2 years** of amenorrhea and FSH within institutional post-menopausal range.
- age 45 to 55 years of age with FSH within institutional post-menopausal range.

The Ki-67 expression changes based on menopausal status and specifically varies based on what phase of the menstrual cycle the sample is collected. Therefore, in order to eliminate this source of variability, only postmenopausal women will be included in this trial. In addition, exemestane is currently approved for use in post-menopausal women only.

4.1.5 ECOG performance status ≤1 (appendix A)

4.1.6 Participants must have normal organ and marrow function as defined below:

- Hemoglobin ≥ 9 g/dL
- Serum creatinine ≤ 1.5× upper limit of normal or calculated creatinine clearance ≥ 60 mL/min using Cockcroft-Gault equation for patients with creatinine levels > 1.5× Institutional ULN
- Total bilirubin ≤ 1.5× ULN OR direct bilirubin ≤ 1× ULN,
- AST and ALT ≤ 2.5× ULN
- Hematologic function: WBC ≥ 3000/mcl;
- platelets ≥ 100,000/mcl.

4.1.7 Able and willing to take oral medications.

4.1.8 Ability to understand and the willingness to sign a written informed consent document.

4.1.9 BMI > 20

4.2 Exclusion Criteria

Criteria for Exclusion: Participants will be excluded from the study for the following reasons:

4.2.1 Participants who had curatively treated invasive malignancies for which all treatments ended within 1 year prior to the study (with the exception of basal cell or squamous cell carcinoma of the skin),

4.2.2 Not a surgical candidate or surgery is not scheduled within 43 days from starting the study drug.

4.2.3 Receiving any other investigational agents.

4.2.4 Any gastrointestinal condition causing malabsorption or obstruction (e.g. celiac sprue, gastric bypass surgery, strictures, adhesions, history of small bowel resection, blind loop syndrome).

4.2.5 Has been on any hormonal treatment (including progestin-containing IUD) for CAH/EIN or low grade (grade 1 or grade 2) endometrial carcinoma in last 3 months.

4.2.6 Use hormone replacement therapy (including systemic or topical estrogen, progesterone, or testosterone based medication) or/and phytoestrogen supplements (i.e. black cohosh) or has been on progestin (including progestin containing IUD), tamoxifen or aromatase inhibitor within the prior 3 months.

4.2.7 Concomitant use of strong CYP3A4 inducers such as rifampicin, phenytoin, carbamazepine, phenobarbital or St. John's wort as these may significantly reduce the availability of exemestane.

4.2.8 Known hypersensitivity to exemestane or its excipients.

4.2.9 Known intercurrent illness or psychiatric illness/social situations that will limit compliance with study requirements.

4.2.10 Evidence or high suspicion of metastatic disease at enrollment.

4.2.11 Women with severe bone density issues/osteoporosis (defined as any medical treatment for osteoporosis, and/or a T-score of -2.5 or lower, and/or history of fracture of the hip or spine).

4.2.12 Unwilling or unable to undergo research biopsy during the baseline (pre-surgical) clinic visit, or inadequate research biopsy obtained during the baseline (pre-surgical) clinic visit (determined by the gynecologic oncologist at the time of the subject's pelvic exam).

4.3 Inclusion of Women and Minorities

Study entry is open to post-menopausal women regardless of race or ethnic background. While there will be every effort to seek out and include minority women, the patient population is expected to be similar to that of the general population of newly diagnosed CAH/EIN and low grade(grade 1 or grade 2) endometrial cancer at the participating institutions.

Women of childbearing potential are not eligible for the study. Refer to section 4.1.4.

4.4 Recruitment and Retention Plan

University of Minnesota (UMN): The University of Minnesota Gynecologic Oncology team sees approximately 100 new low grade (grade 1 and grade 2) endometrial cancers or CAH/EIN patients yearly. Approximately 30 patients will be screened for the current trial.

University of Wisconsin (UWI): The University of Wisconsin estimates that based on historical low grade endometrial cancer patients or CAH/EIN patients that are seen each year in clinic, they will see approximately 10 eligible patients each month for this study. Approximately 30 patients will be screened for the current trial.

University of Alabama (UAB): The University of Alabama at Birmingham anticipates seeing approximately 100 new low grade endometrial cancers or CAH/EIN patients yearly based on historical numbers. Approximately 30 patients will be screened for the current trial.

E. O. Ospedali Galliera (EOG): E. O. Ospedali Galliera anticipates seeing approximately 100 new low grade endometrial cancers or CAH/EIN patients yearly based on historical numbers. Approximately 30 patients will be screened for the current trial.

Each site will review the gynecologic oncologists' clinic patient list to identify potential participants. Through a review of the medical record, the study team will determine if a patient is eligible and contact them for interest in the study. Review of medical records prior to consenting to the research study is very minimum risk of harm to the potential study participants and involves no study related procedures for which written consent is normally required outside of the research context.
A study specific flyer can be provided to the contacted patients as a means to give them a brief understanding of the study.

The principal investigator at each of the sites are gynecologic oncologist and will have a team of other gynecologic oncologists helping to identify participants for the study. Each site will have a lead study coordinator trained on the study related procedures to carry out the tasks for the study. Sites will be encouraged to have back up coordinators to help the lead coordinator.

5. AGENT ADMINISTRATION

Exemestane will be self-administered on an outpatient basis. Reported AEs and potential risks are described in Section 6.2.

5.1 Dose Regimen and Dose Group

Exemestane 25 mg per day is taken by mouth once a day (participant self-administers) for at least 21 days but not to exceed 42 days prior to surgery. The last dose is taken on the day before surgery.

5.2 Exemestane Administration

Exemestane will be dispensed by an investigational pharmacist or appropriate study staff at the participating organization (PO) and then self-administered by the participant at home. Depending on when the surgery is scheduled, the participant will be given 1 or 2 bottles of the study agent. Each bottle contains 30 tablets of exemestane. After confirmation of eligibility, the agent will be mailed to the participants via courier.

Exemestane is a 25 mg tablet to be taken by mouth following a meal once daily at approximately the same time each day. If the dose is missed by more than 8 hours, the patient will skip that dose and take the next scheduled dose at the usual time.

The patient will be provided with a daily pill diary to record the time of administration, side effects, and any missed doses. The patient will be instructed to bring the pill diary and study drug bottles (including any empties) on the day of surgery.

5.3 Run-in Procedures

Not applicable

5.4 Contraindications

Exemestane tablets are contraindicated in patients with a known hypersensitivity to the drug or to any of the excipients. Refer to package insert for an accurate list.

5.5 Concomitant Medications

All medications (prescription and over-the-counter), vitamin and mineral supplements, and/or herbs taken by the participant will be documented on the concomitant medication CRF until the time of surgery and will include start and stop date, dose and route of administration, and indication. Medications taken for a procedure should also be included. Medications given prior to surgery or in the hospital as part of the standard surgical protocol will not be documented as concomitant medications. However, any medications given to treat an adverse or unexpected event following surgery will be documented.

Exemestane is extensively metabolized by CYP3A4, but co-administration of ketoconazole, a potent inhibitor of CYP3A4, has no significant effect on exemestane pharmacokinetics. Significant pharmacokinetic interactions mediated by inhibition of CYP isoenzymes therefore appear unlikely, and are acceptable to be taken while on study. Co-medications that induce CYP3A4 (e.g., rifampicin, phenytoin, carbamazepine, phenobarbital, or St. John's wort) may significantly decrease exposure to exemestane. Therefore, participants on CYP3A4 inducers will not be enrolled in the study and participants should not take CYP3A4 inducers while on study.

5.6 Dose Modification

Dose modification is not applicable for this study. However if a participant is unable to tolerate exemestane, it will be discontinued. Any grade 3 or greater adverse event (based on CTCAE v4.0), grade 2 heart failure, grade 2 rash (paputopustular, acneiform, maculo-papular, etc.) covering 10-30% of the body surface area (BSA) and grade 2 thromboembolic event (DVT requiring medical intervention) that is at least possibly related to exemestane will result in permanent discontinuation.

5.7 Adherence/Compliance

Participants will be considered compliant for secondary "per protocol" statistical analysis if they have taken ≥ 80% of their exemestane doses based on a tablet count and review of the participant completed pill diary.

6. PHARMACEUTICAL INFORMATION

6.1 Exemestane (IND # [redacted] NCI, DCP)

Exemestane is a steroidal, suicide inhibitor of aromatase, the principal enzyme that converts androgens to estrogens. Exemestane is approved in the US for adjuvant treatment of postmenopausal women with estrogen receptor-positive early breast cancer (EBC) after receiving 2−3 years of prior tamoxifen therapy and for treatment of advanced breast cancer in postmenopausal women whose disease has progressed following tamoxifen therapy. Though not officially approved for cancer prevention, exemestane administered to postmenopausal women at moderately increased risk of breast cancer (≥60 years; Gail five-

year risk score >1.66%; prior atypical ductal or lobular hyperplasia or lobular carcinoma *in situ*; or ductal carcinoma *in situ* with mastectomy) resulted in a 65% relative risk reduction of invasive breast cancer compared with placebo treatment after three years of follow-up in the MAP.3 trial[50]. NCI, DCP is continuing to evaluate exemestane for estrogen-dependent cancer prevention such as CAH/EIN.

Exemestane (25 mg) is provided as an oral tablet for once daily administration after a meal and is packaged as 30 tablets per bottle. The compound is a white to slightly yellow powder that is practically insoluble in water but freely soluble in organic solvents (methanol, *N*,*N*-dimethylformamide). Each tablet contains 25 mg exemestane; inactive ingredients may vary based on commercial source of generic materials, but may include mannitol, copovidone, crospovidone, silicified microcrystalline cellulose, sodium starch glycolate, magnesium stearate, titanium dioxide, polyethylene glycol 400 or 8000, and hypromellose, polysorbate 80, polydextrose, triacetin, and povidone K30.

Exemestane (Aromasin, Pfizer) for E.O. Galliera will be purchased by the Hospital Pharmacy as an oral tablet for once daily administration after a meal and will be packaged as 30 tablets per bottle specifically labeled for the trial. Each tablet contains 25 mg exemestane; inactive ingredients may vary based on commercial source of generic materials, but may include silica colloidal hydrated, crospovidone, hypromellose, magnesium stearate, mannitol, microcrystalline cellulose, sodium starch glycolate, polysorbate; *coating*: hypromellose, polyvinylalcohol, simeticone, macrogol, sucrose, magnesium carbonate light, titanium dioxide, methyl parahydroxybenzoate, cetyl esters wax, talc and carnauba wax.

6.2 Reported Adverse Events and Potential Risks

According to the exemestane US prescribing information, treatment-emergent adverse events (TEAEs) more commonly reported by EBC patients treated with exemestane compared with placebo were (in order of frequency): hot flashes (33%), alopecia (15%), hypertension (15%), depression (10%), diarrhea (10%), dermatitis (8%), headache (7%), and myalgia (6%). TEAEs similarly or less commonly reported by EBC patients treated with exemestane compared with placebo were (in order of frequency): arthralgia (29%), increased sweating (18%), insomnia (14%), nausea (12%), fatigue (11%), abdominal pain (11%), dizziness (10%), edema (6%), and anxiety (4%). Elevations of alkaline phosphatase (14–15%), bilirubin (5–7%), and creatinine (6%) were more commonly seen in patients receiving exemestane than tamoxifen or placebo. Though rare, cardiac ischemic events (myocardial infarction, angina, and myocardial ischemia) were elevated in EBC patients treated with exemestane (1.6%) compared with tamoxifen (0.6%) [51].

6.3 Availability

Exemestane will be supplied by NCI, DCP. E.O. Ospedali Galliera will obtain exemestane through the hospital pharmacy which will purchase it from the Pfizer local vendor.

6.4 Agent Distribution

Exemestane will only be released by NCI, DCP (hospital pharmacy, vendor for Galliera) after documentation of CIRB approval of the DCP-approved protocol and consent is provided to DCP and the collection of all essential documents is complete (see DCP website for description of essential documents). These essential documents should be submitted to the CLO for processing. When a site has submitted all of the required documents, the DCP's regulatory contractor will issue drug shipment authorization for that site. No study agent will be shipped to a site until the drug shipment authorization has been issued and a study initiation visit or teleconference has been completed.

The request for study agent to be shipped to each site will be generated by the CLO using the DCP clinical drug request form (NIH-986) (US only). At the time of study initiation, the CLO will request complete shipping contact information for the site's investigational pharmacy. If the site does not have an investigational pharmacy, the complete shipping contact information for the person responsible for study

agent accountability at the site will be requested. DCP guidelines require that the agent be shipped directly to the institution or site where the agent will be administered. DCP does not permit the transfer of agents between institutions (unless prior approval from DCP is obtained). The CLO will submit study agent requests to:

John Cookinham
MRIGlobal DCP Repository
1222 Ozark Street
North Kansas City, MO 64116
Phone: (816) 360-3805
FAX: (816) 753-5359
Emergency Telephone: (816) 360-3800

Exemestane will be purchased by the Hospital Pharmacy of E.O. Ospedali Galliera from Pfizer, local vendor. Pfizer is the only authorized dealer for Liguria region. The tablet will be packaged and labeled specifically for the trial.

Carla Elda Angela Fraguglia
Director of Hospital Pharmacy
E.O. Ospedali Galliera
Corso Mentana, 10
16128 - Genova

6.5 Agent Accountability

The investigator, or a responsible party designated by the investigator, must maintain a careful record of the inventory and disposition of all agents received from DCP or vendor using the NCI Drug Accountability Record Form (DARF). The investigator is required to maintain adequate records of receipt, dispensing and final disposition of study agent. Include on receipt record from whom the agent was received and to whom study agent was shipped, date, quantity and batch or lot number. On dispensing record, note quantities and dates study agent was dispensed to and returned by each participant. POs can use the computerized inventory system if available on site and provide the updated copy of computerized DARF upon request by CLO monitors.

6.6 Packaging and Labeling

Exemestane will be packaged by NCI, DCP. E.O. Ospedali Galliera will obtain packaged medication from local vendors. The costs of drug purchasing are covered by the study specific budget.

6.7 Storage

Study drug will be stored in a secure location at controlled room temperature, 25°C (77ºF) with excursions permitted between 15°–30°C (59°–86°F).

6.8 Registration/Randomization

CLO will be informed about the expected date and time of the scheduled baseline (pre-surgical) clinic visit as soon as it has been scheduled. This will happen after the verbal telephone consent is obtained to dispense the tampon kit to the potential participant.
Once a participant has signed a study informed consent form and has satisfied all eligibility criteria:

- Fax (608-299-3765) or email (prevention@uwcarbone.wisc.edu) the participant's eligibility checklist signed by Investigator and copy of the signed consent form to CLO.

- CLO will verify eligibility documents are complete and then give confirmation to dispense the study medication. The following documents should be sent:
  - Informed consent form
  - Eligibility questionnaire
  - Clinical safety/eligibility lab report
  - Pre-study diagnostic biopsy report
  - Medical/surgical history worksheet
  - Concomitant medication log
  - Physical exam
- PID will be assigned sequentially to all participants who sign consent at the PO and will designate the recruitment site, the study and the participant.
- As soon as a subject has been determined to be eligible, the CLO will email a confirmation of accrual to the study coordinator at the participating institution. If a confirmation is not received within two hours, the coordinator should contact the CLO to confirm that eligibility documents were received.
- For EOG site, the confirmation is due within 24 hours because of the different time zone.

6.9 Blinding and Unblinding Methods

This is not a blinded study.

6.10 Agent Destruction/Disposal

At the completion of investigation, all unused study agent will be returned to NCI, DCP Repository according to the DCP "Guidelines for AGENT RETURNS" and using the DCP form "Return Drug List".

7. CLINICAL EVALUATIONS AND PROCEDURES

7.1 Schedule of Events

Evaluation/ Procedure	Pre-screening Contact	Baseline (pre-surgical) clinic Visit (Day -30 to Day 0)	Day 1	Day 15 Phone Contact (±2 Days)	1 Day Prior to Surgery Phone Contact (-2 Days)	Final Study Visit Surgery Day 22 - 43	Follow up contact on or before 1st Post-Surgery Follow-up[1]
Verbal telephone consent (Biopsy consent*)	X						
Informed consent		X					
Mailing tampon and consent form (US only)	X						
Reminder for tampon insertion (US Only)		X[2]			X		
Assess eligibility	X[3]	X					
Medical history		X					
Review of concomitant medications		X		X	X	X	X
Baseline symptoms		X					
Adverse events				X	X	X	X
Physical exam with ECOG score		X				X	
Demographics		X					
Vitals including height, weight and BMI		X				X[4]	
CBC/Diff/Plt		X				X	
Comprehensive Metabolic Panel (CMP) or Equivalent[5],		X				X	
Estradiol and Progesterone[6]		X				X	
Research blood draw[7]		X				X	
Serum FSH level for confirmation of post-menopausal status, if applicable[8]		X					
Endometrial biopsy[9]	X*	X					
Tampon insertion by research team*		X*			X*		
Surgical pathologic samples of endometrium						X	
Vaginal cell collection via tampon (inserted 8-12 hours before appointment/surgery)		X	X*			X	
Mailing study agent / (Dispense study agent*)		X[10]	X*				
Telephone reminder to start study agent			X[11]				
Start study agent			X				
Collect study agent						X	
Review pill diary/record and assess compliance				X	X	X	
Reminder for last dose					X		
Tobacco and Alcohol Assessments		X[12]				X[12]	

* Procedures only applicable to E. O. Ospedalli Galliera (EOG) site.

1. Phone call or in person contact is only performed if there are any unresolved AEs (with a possible, probable or definite attribution to the study agent) on the day of surgery. For EOG Site only: AEs for long term effects of study treatment will be assessed at this follow up visit.
2. Reminder phone call for tampon insertion a day prior to baseline (pre-surgical) clinic visit.
3. Assess diagnosis based on available pathology report and age of the participant (US only)
4. Height will not be recorded on the day of surgery. Previously recorded height will be considered for BMI calculation

5. Comprehensive metabolic panel consists of albumin, alkaline phosphatase (ALP), alanine aminotransferase (ALT), aspartate aminotransferase (AST), blood urea nitrogen (BUN), calcium, creatinine, glucose, electrolytes (CO2, Cl, Na, K), total bilirubin, and total protein
6. Research samples for estradiol and progesterone are ordered and processed through each institution's clinical laboratory with CBC and CMP
7. Research blood draws–plasma PK of exemestane will be drawn using the study kit sent to sites.
8. Serum FSH test for all women that are 45-55 years old and for women that are 56-59 years old and **< 2 years** of amenorrhea.
9. EOG site will determine eligibility using the pathology report obtained after the biopsy.
10. Exemestane will be mailed once eligibility is determined at or following baseline (pre-surgical) clinic visit.
11. Telephone reminder to start study drug can be done on Day 1 or Day 0. This is to make sure the participant starts taking the study agent at the planned date.
12. Appendix E – administer the baseline version of tobacco and alcohol assessments at baseline visit, administer the follow-up version of tobacco and alcohol assessments at surgery visit.

7.2 Pre-Screening and Initial Patient Contact

The study coordinator or designee will prescreen upcoming clinic visits for women aged 45 years or older with newly diagnosed CAH/EIN or low grade (grade 1 or grade 2) endometrial cancer (EC) by reviewing the outside hospital referral pathology report. The report is available in the electronic medical record as part of the referral process to a gynecologic oncologist.

Telephone contact will be made, introducing the concept of the protocol using the telephone consent form (Appendix B). If the patient expresses interest, verbal consent to participation in the tampon collection will be obtained and, a kit will be mailed. The kit will include 2 commercially available plastic applicator vaginal tampons and instructions (Appendix D) along with the informed consent form for review. She will be instructed to place the tampon in her vagina for 8–12 hours before coming to the baseline (pre-surgical) clinic visit. If the patient has trouble inserting the first tampon she can use the second tampon in the kit. If her visit is in the afternoon, she will be instructed to place the tampon the morning of her visit. Informed consent form will be signed in person before any study related procedures are conducted at the baseline (pre-surgical) clinic visit. The tampon will be removed by the gynecologic oncologist during the standard pelvic exam.

The tampon will be processed at each institution and sent to the University of Minnesota for protein and DNA extraction and analysis per section 10.2. If a subject was unable to place a tampon prior to their baseline (pre-surgical) clinic visit, they will still be eligible for participation in this study trial. Every effort should be made to collect the tampon; however, if this is not feasible, the patient is still eligible for participation and a protocol deviation will not be filed.

For E.O. Ospedalli Galliera site only, participants will be approached to participate prior to their actual diagnosis of CAH/EIN/low grade endometrial cancer. Standard of care in this region includes a visit with a gynecologic oncologist and subsequent hysteroscopy with biopsies when patients have postmenopausal bleeding and a high suspicion for pre-invasive or invasive disease. Therefore, the research team will meet the potential participants for a prescreening visit before the diagnostic hysteroscopy. Patients will sign a pre-screening consent on this day before the procedure. During the examination, the surgeon will perform one diagnostic biopsy and one research only biopsy. If CAH/EIN/low grade EC is confirmed then participants will sign the main study consent. If the patient does not meet the CAH/EIN/low grade EC diagnosis the research tissue samples will be destroyed.

On the day before the baseline (pre-surgical) clinic visit the team will obtain written consent for study participation. A tampon will be placed by a study nurse. Lab tests for eligibility will be collected. Eligibility documents will be submitted to CLO for verification by email.

7.3 Baseline (pre-surgical) clinic Visit

A written informed consent form will be signed before any study related procedures (specifically blood draws and biopsy) are conducted at the baseline (pre-surgical) clinic visit.

The following procedures will be performed to determine eligibility (within 30 days of starting exemestane):

- Review of diagnostic pathology report, medical history, concomitant medications, and baseline symptoms
- Physical exam with vitals including height, weight, and BMI as well as ECOG performance score.
- Endometrial biopsy will be performed to ensure an adequate amount of tissue for IHC and genetic analysis. If a biopsy is not feasible, or if insufficient tissue is obtained (noted by the physician at the time of biopsy), the subject will not be eligible for this trial, as comparative IHC is the primary outcome for the study.
    - This biopsy is done for research purposes only.
    - Endometrial biopsies will be performed in the gynecologic oncology clinic by the gynecologic oncologist. This is a common outpatient procedure, which is performed during the pelvic/speculum exam (part of the standard pre-surgical physical exam). With the speculum in place, the physician will pass an endometrial pipelle through the cervix and then sample endometrial cells through standard biopsy techniques. This procedure is similar to a Pap smear in terms of sample acquisition except instead of scraping cells from the cervix, a straw-sized pipelle is passed through the cervix and cells are aspirated from the endometrium.
    - No additional sedation or monitoring is required for this procedure.
    - Two biopsy “passes” with the endometrial pipelle will be performed. The first specimen will be formalin-fixed, paraffin embedded (FFPE), and sent to the University of Minnesota for IHC analysis and central pathologic review . The second specimen will be placed directly into a stabilizing agent (AllProtect) for genetic analysis.
    - This sample will be destroyed if the participant does not meet eligibility criteria

Note that the subjects will consent to the study prior to their physical examination. It is important to minimize discomfort to the study subjects and therefore we plan to perform the research-related endometrial biopsy at the same time as the standard pre-operative pelvic/speculum exam. This is done to avoid the discomfort of having multiple pelvic exams and to reduce the number of visits for the study participant.

For participants who would like to delay their decision regarding participating until after discussion with the physician, written consent can be signed on the day of baseline (pre-surgical) clinic visit and the participant can come back to the clinic to get the research biopsy and have the tampon collected.

Being able to acquire an adequate endometrial biopsy specimen is an important part of eligibility given that the primary endpoint of this study compares Ki-67 expression between pre- and post-treatment tissue. If the participant is subsequently deemed ineligible based on the laboratory values, the endometrial biopsy samples will be destroyed. We anticipate this will happen infrequently, as biopsies will only be performed in women who have been found otherwise eligible up until this point.

Additionally, the following procedures will performed at the baseline (pre-surgical) clinic visit:

- Baseline laboratory tests for eligibility will include CBC with a Differential, a complete metabolic profile (CMP) and a serum FSH level in all women 45-55 years old and in women 56-59 years old if they report less than 2 years of amenorrhea to confirm the post-menopausal status to confirm post-menopausal status.
    - **For EOG site only** this can be performed 1 day prior to the pre-surgical clinic visit after the participant is consented.
- Baseline research blood sample to measure plasma pharmacokinetics of exemestane. If participant does not meet eligibility criteria this sample will be destroyed. Additionally, estradiol, and progesterone levels will be measured for the clinical laboratory.
    - **For EOG site only** this can be performed 1 day prior to the pre-surgical clinic visit after the participant is consented.
- Demographic information such as age and race/ethnicity.
- Appendix E: baseline tobacco and alcohol assessment questionnaires will be administered.
    - **For EOG site only** this can be performed 1 day prior to the pre-surgical clinic visit after the participant is consented.
- The vaginal tampon will be removed during the pelvic examination.
    - **For EOG site only**, the study nurse will remove the tampon and place in cold PBS.
    - If the lab test results are not within study required parameters, the tampon will be removed and discarded during the baseline (pre-surgical) clinic visit.

Patients meeting criteria set forth in the protocol will pass the screening phase of the trial. Eligibility will be confirmed at the Contract Lead Organization (CLO). E.O. Ospedali Galliera, can submit the documents for confirmation of eligibility day before the baseline (pre-surgical) clinic visit to account for the difference in time zones and timely verification of eligibility.

Once a surgery date is scheduled, patients will begin daily oral exemestane for at least 21 days (but not longer than 42 days) prior to surgery. Exemestane and pill diary will be mailed to the subject so that they can begin taking this medication at home. The day the patient begins taking study drug is considered Day 1 of the study.

E.O. Ospedali Galliera can dispense the study drug to the participant at this visit after receiving the eligibility confirmation from CLO.

Once enrolled, subjects will also be given an additional tampon to be placed by the subject 8-12 hours before surgery. They will be supplied with 2 tampons (one to place 8-12 hours before surgery and one extra in case they are unable to place it correctly the first time) along with the instructions (Appendix D).

Participants will be compensated $150.00 for additional time and effort associated with being in the study including the endometrial biopsy as well as tampon collection. Since the regulations in Italy do not permit for research participants to be compensated with money, no compensation will be provided to the participants enrolled at E.O. Ospedali Galliera.

On the day of the pre-surgical clinic visit, the study nurse will remove the tampon and place in cold PBS. The study drug will be dispensed to the participant at this visit as well. If the lab test results are not within study required parameters, the patient will be deemed ineligible and the tampon will be removed and discarded during this clinic visit

7.4 Day 15 Phone Contact

Participants will be contacted by telephone at Day 15 (±2) of exemestane treatment by the study coordinator or designated study team member. The purpose of this contact is to query for exemestane-associated side effects/adverse events, review of the pill diary to confirm compliance, review any new or changes to medications and answer any questions the participant may have. It will be reiterated that the participant should continue exemestane daily with the last dose the day before surgery. In addition, the participant will be reminded to place the tampon (provided to her at the baseline (pre-surgical) clinic visit) 8-12 hours before the surgery.

7.5 One Day (-2 days) Prior to Surgery

The study coordinator or designee will again contact the participant and remind her to insert the tampon in her vagina 8-12 hours before the surgery and to bring her exemestane bottle(s) with any leftover tablets and the pill diary with her on the day of surgery. If her surgery is in the afternoon, she will be instructed to place the tampon the morning of her visit. Also, a review of exemestane associated side effects/adverse events, review of the pill diary to confirm compliance and review any new or changes to medications.
For EOG site only, the participant would return to clinic for this visit. The research nurse will place the tampon for surgery visit.

7.6 Final Study Visit – Day of Surgery

The surgical procedure will be standard of care and not altered based on participation.

The following research procedures will occur prior to surgery:

- Physical exam with vitals including height, weight and body mass index
- Medical/ surgical history review and update
- Review of concomitant medications and adverse events.
- Laboratory tests will include CBC with a differential, CMP, estradiol and progesterone.
- Appendix E: follow-up tobacco and alcohol assessment questionnaires will be administered.
- The vaginal tampon, which was placed by the participant 8-12 hours before surgery will be removed in the operating room by the surgeon prior to the surgical procedure. Attempt should be made to obtain tampon specimen at day of surgery visit even if baseline sample was not obtained.
- Research blood sample to obtain plasma pharmacokinetics of exemestane

At the time of surgery, once the patient is under anesthesia the vaginal tampon will be removed and processed in the same way as the pre-treatment tampon. The tampon will be processed at each institution and the resultant cells and washings will be frozen and shipped on dry ice to the University of Minnesota for DNA and protein extraction per section 10.2.

The surgical pathologic specimen (the uterus) will be processed as is the usual standard at each institution. A portion of the FFPE tumor block will be collected and batch shipped to UMN at the end of the study to be cut into 10 unstained 5µm slides. If the FFPE block cannot be sent due to limited amount of tumor, then 10 unstained 5µm slides will be cut and the slides will be shipped to UMN. An additional section of the tumor, up to 1x1x1cm, will be collected after removal of the uterus or from the pathology lab, cut in half and snap frozen as per institutional policy for genetic and protein analysis. If there is not a visible lesion, select a random 1x1x1 cm from the endometrium, or smaller if the pathology team needs to review more of the endometrium. This is done at the investigators clinical discretion. This tumor section will also be batch shipped to UMN at the end of the study. The tumor biopsy specimens, the FFPE blocks and the

unstained slides will be sent to the University of Minnesota (UMN) for proteomics, DNA analysis, histologic review, and IHC.

The study coordinator or designee will collect the exemestane supply and completed drug log.

7.7 Follow-up Contact

The final study visit will coincide with the day of surgery unless there are any unresolved AEs (with a possible, probable or definite attribution to the study agent) on the day of surgery. The unresolved AEs will be assessed via telephone call during the postoperative period, before or on the day of the 1st post-surgical follow-up visit. AEs that occurred after surgery will not be recorded.

For EOG site only, follow-up at the standard of care post-operative visit will be performed in order to collect long-term safety information of the study treatment, whether or not the participant has any ongoing adverse events at the surgery visit.

8. CRITERIA FOR EVALUATION AND ENDPOINT DEFINITION

8.1 Primary Endpoint

Estrogen stimulates the proliferation of endometrial cells; we hypothesize that blocking the enzyme aromatase will lead to less estrogen available to stimulate the growth of pre-cancer and cancerous endometrial cells. Thus, exemestane treatment should lead to decreased levels of Ki-67, an important marker of cellular proliferation.

Unlike in breast cancer, proliferation indices in endometrial cancer are not well study and a threshold that predicts ongoing response to Aromatase Inhibitor therapy does not yet exist. Choosing a threshold at which to power this study would be arbitrary. Our goal is to help begin to establish these important biomarkers in endometrial cancer. Therefore, the primary endpoint of the study is the absolute change in proliferation index (Ki-67) expression in CAH/EIN or low grade (grade 1 and grade 2) endometrial cancer cells from baseline to post-exposure. We will evaluate the change from baseline to post-exposure in absolute change in percent Ki-67 using one-sample Student's t-test or Wilcoxon signed-rank test, as appropriate. Immunohistochemistry will be performed at the UMN Histology and IHC Laboratory and then read by Dr. Mahmoud Khalifa.

Tissue collected from the research biopsy and surgical specimen will be fixed in 10% neutral buffered formalin and processed into paraffin blocks. Antigen retrieval is performed on slides using a 6.0 pH buffer in a steamer, followed by a cool down period. Slides are rinsed in water followed by immersion in 1x Tris-buffered saline/0.1% Tween-20 (TBST). Subsequent steps are automated using an IHC staining platform (Nemesis, Biocare). Endogenous peroxidase activity is quenched by slide immersion in 3% hydrogen peroxide solution followed by TBST rinse. A serum-free blocking solution is placed on sections. Blocking solution is removed and slides are incubated in primary antibody diluted in 10% blocking solution/90% TBST followed by TBST rinse. A two step polymer detection (Novalink, Leica) is used according to manufacturer's instruction. Following the detection, the slide is rinsed with TBST and diaminobenezie is applied followed by TBST rinse. Slides are then counterstained with CAT Hematoxylin (Biocare) rinsed, dehydrated and coverslipped.

8.2 Secondary Endpoints

8.2.1 Circulating serum estradiol and progesterone:

Evaluate pre and post treatment circulating serum estradiol and progesterone levels to determine the effect

of a daily dose of 25 mg of exemestane for 21-42 days.

8.2.2 Pathological response (regression of CAH/EIN and low grade (grade 1 and grade 2)endometrial carcinoma):
Examine pathologic changes in CAH/EIN or carcinoma from pre-treatment biopsies to final pathology. Ultimately, the goal of any pharmacologic intervention will be regression of CAH/EIN and low grade endometrial carcinoma to a normal endometrium. Given that the average time for regression for progesterone therapy is approximately 6 months[3], we do not anticipate that 3 weeks of exemestane therapy will result in high levels of tumor regression. However, we do anticipate that there may be some change in histology. All preoperative biopsy specimens and postoperative surgical specimens will undergo H&E staining. Central pathology review will be performed by Dr. Mahmoud Khalifa at the University of Minnesota. Review will be in accordance with the updated pathologic criteria[32].

8.2.3 Tissue biomarkers:
Examine biomarker differences in pre and post treatment samples with regards to expression (measured by immunohistochemistry) of markers of these cellular functions or pathways.

a) Apoptosis (cleaved caspase 3)
b) Proliferation (cyclin D1)
c) Insulin pathway (pAKT, IGF-1R)
d) Endocrine regulation (ER/PR/AR)

Estradiol induces the production of IGF-1 and the expression of IGF-1 receptor (IGF-1R) is higher in the endometrium of patients with CAH/EIN and endometrial cancer compared to normal endometrium[30] [31]Thus, our hypothesis is that by using exemestane to reduce the levels of systemic estradiol, this will lead to lower levels of IGF-1 and reduced IGF-1R expression. Activation of IGF-1R by IGF1 leads to phosphorylation of AKT through the PI3K/AKT pathway, which in turn causes accumulation of nuclear cyclin D1, leading to increased mitosis and cellular proliferation in addition to having a potent anti-apoptotic effect. Therefore, reducing IGF-1R activation by decreasing estradiol will lead to decreased pAKT, cell cycle arrest, and increased apoptosis. We hypothesize that exemestane will not only show a decrease in cellular proliferation as evidenced by a decrease in Ki-67, but a decrease in the cell cycle regulatory protein, cyclin D1, and lead to an increase in cleaved caspase 3, which is a marker of apoptosis. We also hypothesize that due to exemestane's inhibition of androgen binding sites and subsequent effects on hormone levels, there may be a change in hormone receptors (estrogen, progesterone and androgen receptors), as measure by IHC. The following biomarkers, all of which are commercially available, will be assessed: Cyclin D1, cleaved caspase 3, pAKT, IGF-1R, ER-alpha, PR, AR. Staining technique will be as above.

8.2.4 DNA mutational analysis through Next Generation Sequencing and methylation status of endometrial tumor and vaginal DNA:
Analyze DNA from the CAH/EIN or low grade endometrial carcinoma for specific genetic mutations, microsatellite instability and hypermethylation in order to correlate exemestane response to mutational status. Additionally, vaginal DNA (recovered from tampon collection) will be analyzed for presence of tumor mutations or hypermethylation.

8.2.4.1 Tumor genetics: As evident by the recent TCGA analysis of >350 endometrial carcinomas, endometrioid tumors have frequent mutations in a variety of genes including PTEN, CTNNB1, PIK3CA, KRAS, and POLE[33]. Furthermore, the TCGA categorized endometrial carcinoma into 4 prognostically significant groups characterized by; 1) POLE hotspot mutations and endometrioid morphology; 2) microsatellite instable (MSI) tumors with mutated PTEN and endometrioid morphology; 3) microsatellite

stable (MSS) tumors with mutated PTEN and endometrioid morphology; and 4) MSS tumors with mutated TP53, high somatic copy number alteration burden and predominantly serous or mixed morphology. We hypothesize that response to exemestane may correlate with tumor genetics and these described subtypes. We therefore seek to determine the mutational status of all tumors with DNA panel testing to see if this correlates with treatment response. In this context, tumor response will be defined as any decrease in absolute Ki-67 expression by ≥ 5%.

Pre and post treatment specimens will be sent to the MDL for DNA extraction from AllProtect or fresh frozen tissue. Mutation testing will be performed via Next Generation sequencing using a CLIA-validated 62 gene solid tumor panel. This panel includes clinically actionable genes identified from high quality somatic mutation databases including the Dienstmann[52], DOCM[53], MD Anderson Personalized Cancer Therapy, and My Cancer Genome databases. All cases from the TCGA dataset demonstrated at least one mutated gene from this 62-gene panel and the critical genes needed for subtype assessment (POLE, PTEN, TP53) are covered within it. DNA will be extracted using the QIAamp DNeasy Tissue kit (Qiagen. Inc). DNA will be quantified using Qubit reagents (ThermoFisher) and target specific enrichment will be performed using the Fluidigm Access Array microfluidics PCR system. Sample specific barcodes are appended in a second step PCR reaction, pooled, and sequenced on a MiSeq instrument (Illumina). Raw sequencing data is analyzed through a validated custom bioinformatics pipeline[54]. Average coverage is >2000X, and limit of detection sensitivity is 5% variant allele fraction (VAF) for single nucleotide variants (SNV) and 1% VAF for indels.

Microsatellite instability will be assessed using the NCI recommended 5 marker panel[55]. DNA from tumor and matched normal tissue (if available) will be PCR amplified (GeneAmp® PCR Reagent Kit Applied Biosystems) with fluorescently labeled primers for the 5 variable maker regions and separated by capillary electrophoresis (Applied Biosystems 3100 Genetic Analyzer). Cases will be categorized as MSI-high if 3 or more markers are shifted, MSI-low if 1 or 2 markers are shifted, and MSS if zero markers are shifted.

8.2.4.2 DNA Recovery from Tampon Experiments: Given that the endometrium communicates with the vagina through the endocervix, we speculate that we could identify protein and DNA that descend through the endocervix and into the vagina through tampon collection, based on a recently published manuscript on DNA recovery from vaginal tampons for the detection of ovarian cancer[34]. This ovarian cancer detection study focused primary on identifying tumor specific somatic DNA through deep sequencing of vaginal DNA. In this present study, we propose a similar method of DNA collection for cancer detection through tampon recovery.

Tampons will be collected in the clinic or operating room and will be placed into a 50 mL conical polypropylene tube with a screw-top lid into which 30 mL of cold, sterile phosphate buffer saline (PBS) will be added. The tampon can soak in the cold PBS solution for up to 12 hours before agitation. The tube will be mounted on a platform rocker for 30 minutes at 4°C for gentle agitation. The tampon will be carefully removed from the conical tube and inserted into a 35cc syringe. The plunger of the syringe will be slowly depressed to completely compress the tampon, thereby releasing cells and any of the remaining PBS solution from the tampon. The tampon will then be discarded. The PBS solution that was in the initial conical tube with the tampon should be combined with the PBS solution that was compressed out of the tampon to yield approximately 30 mL. This 30 mL cell suspension will be equally divided into two 50 mL conical polypropylene tubes and centrifuged for 10 minutes to pellet the cells. The 14 mL of supernatant from both of the conical tubes will be gently removed by pipet and combined into one conical polypropylene tube. The cell pellets will be re-suspended in the remaining 1 mL of PBS using a disposable glass pipet and transferred to 1.5 mL Eppendorf tubes each and spun for 10 minutes at 3000xg. After separating the cell pellets the remaining 1 mL of supernatant from both tubes will be combined with the supernatant in the 50 mL conical polypropylene tube. This will be frozen and shipped on dry ice to the University of Minnesota.

The cell pellets that remain at the bottom of the two 1.5 mL Eppendorf tube will be frozen and shipped to the University of Minnesota on dry ice.

DNA will be extracted from the cell pellet using a modified protocol and reagents from the QIAamp DNA mini kit (Qiagen) as previously described by Erickson et al[34]. DNA concentration will be quantified using Qubit reagents (ThermoFisher). Extracted DNA will be used to identify genomic alterations observed in tumor DNA. We will modify the 62-gene solid tumor NGS assay (or a subset of genes enriched for mutations in the study population) for this purpose to incorporate unique identifiers (UIDs) as described by Kinde et al.[55]. Our laboratory has extensive experience using amplicon based enrichment on the microfluidics platform for enrichment of targets using NGS. Using a combination of both microfluidic PCR and UIDs, we anticipate capability to detect somatic alterations at least as low as 0.01% in the tampon DNA which will be compared to matched sequencing of the concurrent endometrial biopsy specimen.

8.2.4.3 DNA Methylation

To better define the sensitivity of vaginal DNA methylation in the detection of endometrial cancer, an additional experiment whereby vaginal DNA extracted through tampon collection will be evaluated for hypermethylation. DNA from the corresponding endometrial tumor (low grade endometrial carcinoma or CAH/EIN) will be separately analyzed and the tumor DNA-vaginal DNA pairs will be analyzed for concordance of methylation across 850,000 CpG sites. Vaginal DNA will be extracted per methods already described for the genomics portion of this study from the cell pellets. The same DNA extracted from the cell pellet will be used for NGS. A bisulfite conversion step will be performed as part of the standard Illumina Methylation array protocol, which requires 250 ng minimum DNA input. Vaginal and tumor DNA methylation studies will be performed using the EPIC methylation chip (Illumina Inc.), which evaluates methylation in 850,000 CpG sites that include both promoter and enhancer elements using 500 ng of DNA.

The proposed experimental design will accomplish several novel goals. First, this design will establish the global methylation pattern of each patient's endometrial carcinoma/EIN which can be statistically compared to the primary study endpoint (Ki-67 response to exemestane treatment) in the context of potentially clinically relevant methylation groups established by the TCGA. Second, the design will allow to rigorously test the sensitivity/limit of detection for specific methylation pattern discrimination in the tampon DNA for underlying carcinoma. Finally, the design will allow for a robust comparison of clinical utility between ultra-sensitive DNA sequencing, methylation analysis, and proteomics to determine which platform is most sensitive for detection of disease.

8.2.5 Protein markers via tampon recovery before and after treatment:

We propose a proteomic analysis of vaginal specimens and endometrial biopsies as an exploratory experiment to determine if response to exemestane correlates with a change in vaginal and endometrial proteins. Proteins identified in this experiment could potentially serve as surrogate biomarkers for exemestane response. We also anticipate discovering a different protein profile in the tampon collected proteins and tissue biopsies of women with CAH/EIN vs. low grade endometrial cancer.

Dr. Skubitz has successfully performed proteomic studies using the Olink platform on serum protein from healthy women and women with ovarian cancer. The methodology that Dr. Skubitz optimized in her preliminary studies will be applied to this study. The concentration of protein in each sample will be determined by using the bicinchoninic acid (BCA) assay. If necessary due to low protein yields in the tampon washings, they will be passed through an Amicon filter (3 kD cut-off) in order to concentrate the proteins. In preliminary studies, the total amount of protein in each 1 mL of tampon washing sample ranged from 65 to 500 ug (i.e. enough for multiple proteomic analyses). We also plan to extract protein from the

cell pellet that is saved from the tampon washing (described in 8.2.6.1) and from tumor biopsies (pre- and post-treatment with exemestane).

For the proteomic pilot studies, we will analyze samples from the first 10 patients that will be sent directly to the University of Minnesota. In particular, we will be analyzing 4 samples from each patient: (i) the PBS tampon washing pre-treatment, (ii) the cell pellet from the tampon washing pre-treatment, (iii) the PBS tampon washing post-treatment with exemestane, and (iv) the cell pellet from the tampon washing post-treatment with exemestane.

The rationale for using the PBS rinse of the tampon as well as the cell pellet from the tampon is four-fold.

1. The PBS rinse from the tampon is a rich source of protein that contains proteins that are secreted from the uterus (and endometrium), cervix, and vagina by the patient over the time period that the tampon was placed in her vagina. These proteins will be absorbed by the tampon (along with blood proteins and cells that are shed). In our previous studies, we found a sufficient amount of protein in the PBS rinse to perform protein based assays. .
2. The number of cells that are present in the cell pellet from the tampon may not be sufficient for us to perform the genomic studies and the proteomic studies. If the genomic study would take priority, then we would not have a sufficient amount of protein to conduct proteomics. Thus, we do not want to limit the proteomic portion of this study to just the cell pellet.
3. The proteins that are present in the PBS rinse may not be the same as those that are in the cell pellet. Thus, if were to limit this study to the identification of proteins present only in the cell pellet, we may miss proteins that could serve as candidate biomarkers for early stage endometrial cancer.
4. The proteomic results that we obtain from the PBS rinse will play a significant role in future applications for the detection of early stage endometrial cancer. In particular, we anticipate that women in the near future will be able to perform an at home self-administered vaginal swab, and then send the swab into a lab for proteomic detection of biomarkers for specific gynecological diseases. The PBS rinse is the closest we have come to this test becoming a reality.

We anticipate that the samples will contain varying amounts of blood, so we will use commercially available platforms that were specifically designed to be used with serum or plasma samples. There are currently two major companies that have products that would be amenable to the identification of protein biomarkers in serum samples: Olink and SomaLogic. Olink technology was initially designed to quantify the levels of proteins in sera and/or plasma using Proximity Extension Assays. (See their website at https://www.olink.com/) Thus, the Olink platform is well suited to handle the endometrial samples, which contain high amounts of blood proteins. The unique technology behind the Olink® Target 96 panels enables high-throughput, multiplex immunoassays that measure 92 proteins across 96 samples simultaneously using only one microliter of serum, or plasma. The Olink panels have also been used on other type of biological samples. We have searched their lists of more than 1500 proteins that they can measure in their 13 commercially available "Target 96" panels. We found >100 proteins that fall into the category of "proliferation" (which is the focus of this project) on five of their panels. Since each panel measures 92 proteins, this will result in generating data for the levels of 92 x 5 = 460 proteins. This is far better than we could expect from MS experiments that are contaminated with blood proteins.

We propose to: 1-Determine the feasibility of using the Olink panels by running one panel (Immuno-Oncology) to analyze the tampon washing samples, since we are not certain of the dilution of protein that will yield optimal results. We will extract protein from the 20 tampon washing cell pellets and use various dilutions of the tampon washing cell pellet lysates and supernatants. We will place aliquots of the diluted samples into a 96-well microtiter plate from the 40 tampon washing samples (10 pre-treatment supernatants, 10 post-treatment supernatants, 10 pre-treatment cell pellets, and 10 post-treatment cell

pellets). We will provide these samples to the University of Minnesota Genomics Center, whose staff will run the samples as a fee-for-service. - send Olink ~50 ug of protein from the 40 tampon washing samples (10 pre-surgery supernatant, 10 post-surgery supernatant, 10 pre-surgery cell pellets, and 10 post-surgery cell pellets). 2- Once optimal dilutions have been determined, we will be able to test the other 4 Olink panels that are relevant to this study as a fee-for-service.

SomaLogic technology was also initially designed to quantify the levels of proteins in sera and/or plasma. However, SomaLogic uses technology based on aptamers to quantify protein levels in many types of samples (See their website at https://somalogic.com/). Their technology allows for the quantification of 7000 proteins simultaneously from 75 ul of protein at 0.2 ug/ul.

We propose to: 1- Send SomaLogic ~10 ug of protein from the 40 tampon washing samples (10 pre-treatment supernatants, 10 post-treatment supernatants, 10 pre-treatment cell pellets, and 10 post-treatment cell pellets). 2- As a fee-for-service, have SomaLogic run the 40 samples on their SomaScan platform.

Once we have the data back from Olink and SomaLogic, we will be able to analyze the data to identify proteins that are differentially expressed between the tampon supernatants and cell pellet lysates, the pre- and post-treatment samples from the same patient, as well as those proteins that are differentially expressed between the women whose tumors respond to Exemestane treatment and those whose tumors do not respond.

Since the Olink and SomaLogic platforms are not compatible with denatured proteins, it will not be possible to use either platform to analyze the protein extracts from the biopsies (which were extracted in AllPrep reagent for recovery of DNA and protein) or tumor tissues. The tissue sample extracts can be used for other protein experiments, such as validation of the proteins identified in the tampon washing samples by Western immunoblotting.

Option 3 of this project is to analyze a subset of the samples from the remaining 30 patients by proteomic techniques in a similar manner to those outlined above for Patients #1-10. In particular, based on the results that we obtain from the Proteomic Pilot study using 10 patients and 40 samples, we will be able to limit our next set of experiments to the one sample type (tampon washing or tampon cell pellet) that provided the best results, instead of analyzing all of the remaining 120 samples (i.e. 30 remaining patients x 4 samples each). For example, we would omit a sample type(s) that did not yield sufficient protein after removal of the highly abundant proteins. Or we may omit the sample type(s) that did not show any significant differences in proteins identified or quantified between the pre-treatment and the post-treatment. We may also decide to limit the samples to cases where the women responded to treatment. Thus, we will limit Option #3 to the analysis of an additional 30 samples. Thus, the cost of performing the experiments in Option #3 would cost the same as the experiments outlined in the Proteomic Pilot study. The data from these experiments will allow us to make comparisons between the sample sets and validate our results.

8.2.6 Safety and adverse effects of treatment:
Evaluate safety and adverse effects of the treatment by CTCAE 4.0 toxicity scale.

8.2.7 Comparison of Ki-67 expression changes between subjects and a historical cohort
The reason a historic cohort will be studied is to provide the context in which to assess the effects of exemestane in reducing Ki-67 from baseline to post-exposure to exemestane. Specifically, there may be a change in Ki-67 expression from pretreatment biopsy to final surgical specimen in the historical control cohort suggesting that time alone (between biopsy and surgery) or potentially differences in tissues

acquisition (biopsy versus surgical specimen) may have an impact on Ki-67 expression.

The study participants will be matched with a historical nonrandomized control group based on age (+/- 5 years), disease type and BMI (>20-24, 25-30, > 30). This control group will provide a reference for how Ki-67 may change based on time (specifically time between biopsy and surgery which has to be within 42 days) or differences in specimen collection (endometrial biopsies versus surgical specimen), independent of exemestane exposure.

8.2.8 Evaluation of the levels of exemestane in the plasma samples pre and post treatment
Comparison of pharmacokinetic (PK) levels of plasma exemestane pre-and post treatment will analyzed at Cancer Pharmacology Laboratory (CP Laboratory) at University of Wisconsin Carbone Cancer Center (UWCCC). The plasma samples collected during the baseline (pre-surgical) clinic visit and before surgery will be processed as mentioned in section 10.2.4 at each participating center and batch shipped to CP Laboratory for analysis.

8.3 Off-Agent Criteria
Participants may stop taking exemestane for the following reasons: completed the protocol-prescribed intervention, AE or serious adverse event (SAE), noncompliance, contraindicated medications, medical contraindication or surgery is not performed within 21 to 42 days of the first dose of exemestane. Any participant discontinuing exemestane prior to 1 day before surgery will be instructed to bring the exemestane bottles and the completed pill diary to her next appointment. A final study visit will occur at the participant's first post-surgical visit.

8.4 Off-Study Criteria
Participants may go 'off-study' for the following reasons: surgery and the final study visit has occurred, AE/SAE, lost to follow-up, non-compliance, contraindicated medication, medical contraindication, withdrawal of consent, death, determination of ineligibility (including screen failure).

8.5 Study Termination
NCI, DCP as the study sponsor has the right to discontinue the study at any time.

9. CORRELATIVE/SPECIAL STUDIES
Not Applicable

10. SPECIMEN MANAGEMENT

10.1 Laboratories
See lab manual for more detailed instructions.

10.1.1 Tissue samples
Endometrial biopsy tissue sample at baseline (pre-surgical) clinic visit

- First pass will immediately go into formalin and within 24 hours a Formalin Fixed Paraffin Embedded (FFPE) block will be made. Blocks will be shipped on frozen ice packs to prevent melting of the FFPE block.
- Second pass will be placed in a stabilizing agent (AllProtect) and stored at 4°C and then shipped on frozen ice packs.

Hysterectomy Tumor tissue sample at surgery

- Section snap-frozen and stored at -70/-80°C. Remove up to 1x1x1 cm of tumor and cut in half. If there is not a visible lesion, select a random 1x1x1 cm area from the endometrium. This can section can be smaller if the pathology team needs to review more of the endometrium. The amount and location of removal of specimen is at the investigators clinical discretion. This should be snap frozen and shipped on dry ice.
- A portion of the formalin fixed paraffin embedded block, which was collected as standard of care per institutional pathology guidelines, will be sent to the University of Minnesota and cut into 10 unstained 5µm slides. If the FFPE block cannot be sent due to limited amount of tumor, then 10 unstained 5µm slides will be cut and the slides will be shipped to UMN. Blocks will be shipped on ice to prevent melting of the paraffin.

Historical matched controls from repository:

- Identify a list of potential matched controls from the repository for each site that will satisfy the matching criteria mentioned in section 3 of the protocol.
- For each matched control, two samples will be collected, first from the pre-surgical biopsy remnant tissue and the second from the surgical tissue. This tissue can be sent as a block or cut into 10 unstained 5µm slides.
- All blocks or slides will be shipped at the end of study.
- If slides are sent, they should NOT be cut until the time of shipment.

Tissue analysis will be performed at the University of Minnesota (UMN) as detailed below. Specimens from the University of Wisconsin and University of Alabama will shipped by an overnight carrier to the Biorepository laboratory at the University of Minnesota:

Biorepository & Laboratory Services
Attn: Tyler Colgan
420 Delaware St SE
C338 Mayo Memorial Building
MMC 76
Minneapolis, MN 55455-0341

There the samples will be logged in and then transferred to the appropriate laboratory within the University of Minnesota. Please contact the lab prior to shipping/mailing, to inform the lab that a specimen is on the way: Tyler Colgan: colga007@umn.edu

10.1.2 Blood

Clinical labs (CBC with differential, Comprehensive Metabolic Panel, FSH, estradiol, and progesterone level) will be sent to the clinical laboratories at each institution for processing.

Plasma for exemestane concentration will be shipped to:

CP Laboratory
University of Wisconsin Hospital and Clinics
Room K4/559
600 Highland Ave.
Madison, WI 53792-5669

10.1.3 Tampon

The day before baseline (pre-surgical) clinic visit and surgery, the participant will be provided tampons for insertion. The tampon will be removed during the baseline (pre-surgical) clinic visit by the physician at the time of the pelvic exam and during surgery.

10.2 Collection and Handling Procedures

The UWCCC CP Laboratory will prepare sample kits for each subject enrolled on the study, which will include tampons, endometrial pipelles and two 6mL green top tubes for collecting the pharmacokinetic samples.

10.2.1 Vaginal Tampon (baseline (pre-surgical) clinic visit and day of surgery) - Tampons will be collected in the clinic or operating room and immediately will be placed into a 50 mL conical polypropylene tube with a screw-top lid into which 30 mL of cold, sterile phosphate buffer saline (PBS) will be added. The tampon can soak in the cold PBS solution for up to 12 hours before agitation. The tube will mounted on a platform rocker for 30 minutes at 4°C for gentle agitation. The tampon will be carefully removed from the conical tube and inserted into a 35cc syringe. The plunger of the syringe will be slowly depressed to completely compress the tampon, thereby releasing cells and any of the remaining PBS solution from the tampon. The tampon will then be discarded. The PBS solution that was in the initial conical tube with the tampon should be combined with the PBS solution that was compressed out of the tampon to yield approximately 30 mL. This 30 mL cell suspension will then be equally divided into two 50 mL conical polypropylene tubes and centrifuged for 10 minutes to pellet the cells. Remove 14 mL of supernatant from both of the conical tubes by gently pipetting and combine into one 50 mL conical polypropylene tube. The cell pellets will be re-suspended in the remaining 1 mL of PBS using a disposable glass pipet and transferred to 1.5 mL Eppendorf tubes each and spun for 10 minutes at 3000xg. After separating the cell pellets the remaining 1 mL of supernatant from both tubes will be combined with the supernatant in the 50 mL conical polypropylene tube. The supernatant and two cell pellets that remain at the bottom of the two 1.5 mL Eppendorf tubes will be stored at -70/ -80°C until it is sent to the UMN for analysis after the surgical tampon is collected at the below mentioned address.

Biorepository & Laboratory Services
Attn: Tyler Colgan
420 Delaware St SE
C338 Mayo Memorial Building
MMC 76
Minneapolis, MN 55455-0341

10.2.2 Tumor biopsy specimens (baseline (pre-surgical) clinic visit) - At the baseline (pre-surgical) clinic visit, participants will undergo an endometrial biopsy in clinic to ensure adequate tissue for IHC and genetic analysis as well as to confirm pathology. All biopsy samples will be sent to the UMN for proteomics, DNA analysis, central pathology review, and IHC. This biopsy will be done for research purposes only and is routinely performed during a pelvic/speculum exam in gynecologic oncology clinics without additional anesthesia, sedation or monitoring. Two biopsy "passes" with an endometrial pipelle will be performed. The first will be formalin-fixed, paraffin embedded (FFPE), and sent to UMN for central pathology review and IHC analysis. The first pass will be made go into formalin and within 24 hours a Formalin Fixed Paraffin Embedded (FFPE) block will be made. Blocks will be shipped on ice to UMN for central pathology review and IHC analysis. The second pass will be placed in a stabilizing agent (AllProtect) stored at 4 °C and then shipped on frozen ice packs.

10.2.3 Surgical Samples - The surgical pathologic specimen (the uterus) will be processed as is the usual standard at each institution. A portion of the FFPE tumor block will be collected and batch shipped to UMN

to be cut into 10 unstained 5µm slides. If the FFPE block cannot be sent due to limited amount of tumor, then 10 unstained 5µm slides will be cut and the slides will be shipped to UMN. Blocks and slides will be shipped on frozen ice packs to prevent melting of the paraffin. An additional section of the tumor (up to 1x1x1 cm) will be collected, cut in half and snap frozen to -70/-80°C for genetic sequencing. If there is not a visible lesion, select a random 1x1x1 cm area from the endometrium. This section can be smaller if the pathology team needs to review more of the endometrium. The amount and location of the sample is at the investigators clinical discretion. This tumor section will also be batch shipped to UMN on dry ice.

10.2.4 Research Blood Samples - At each pharmacokinetic time point (baseline and Day 22-43 (Day of surgery - drawn before the surgery), blood will be drawn to fill one 6mL heparinized tube. The tubes will be centrifuged for 10 minutes at 4°C to separate plasma. The plasma will be divided into 2 cryovial tubes. The 2 cryovial tubes will be labeled with the labels provided in the kit. The participants' number, initials, and date of processing will be added to the labels. The cryovial tubes will be frozen at -70/-80°C, and save for transport to the UWCCC CP Laboratory.

10.3 Shipping Instructions

All samples will be shipped in compliance with the International Air Transport Association (IATA) Dangerous Goods Regulations. Kits with pre-printed Fed-Ex billing labels will be provided to each participating institution. For E.O. Osepdali Galliera, the supply required for the study will be obtained locally and not provided by CP lab. The samples will be shipped in batches of 4 participants.

10.3.1 Methods for shipping tissue

Tissue Samples are shipped (Monday-Thursday) for next day delivery to the Biorepository lab at the University of Minnesota. Tissue samples will not be shipped the day before major university holidays.

10.3.2. Methods for shipping the plasma pharmacokinetics samples:

Once the patient has completed the study, ship the carton containing the pharmacokinetic samples for one patient to the address below. If multiple patients are completing the study, samples from multiple patients can be combined in one shipment. Please note this address is for the pharmacokinetic samples ONLY. Tissue samples should be sent to the address above at UMN.

CP Laboratory
University of Wisconsin Hospital and Clinics
Room K4/559
600 Highland Ave
Madison, WI 53792-5669

Call the CP Laboratory to inform them of a shipment (608) 263-5369 or email the CP Laboratory mailing list 3plab@lists.medicine.wisc.edu

Use the express courier service indicated by the shipping label contained in the kit. Closely follow all special shipping instructions outlined in the kit instruction packet.

Ship the PK samples only on Monday, Tuesday or Wednesday to ensure safe arrival during the week. Do not ship the day before a holiday.

Fill the styrofoam cooler with dry ice and put all of the blood samples into the cooler. Place the cooler into the shipping box in which you received the kit.

10.4 Tissue Banking

Biologic specimens collected during the conduct of each clinical trial that are not used during the course of the study will be considered deliverables under the contract and thus the property of the NCI. At study completion, NCI reserves the option to either retain or relinquish ownership of the unused biologic specimens. If NCI retains ownership of specimens, the contractor shall collect, verify and transfer the requested biologic specimens from the site to a NCI-specified repository or laboratory at NCI's expense.

11. REPORTING ADVERSE EVENTS

DEFINITION: AE means any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. An AE can therefore be any unfavorable and unintended sign), symptom, or disease temporally associated with participation in a study, whether or not related to that participation. This includes all deaths that occur while a participant is on a study.

Please note that all abnormal clinical laboratory values that are determined to be of clinical significance based on a physician's assessment are to be reported as AEs. Those labs determined to be of no clinical significance or of unknown clinical significance (per the physician's assessment) should not be reported as AEs. Any lab value of unknown clinical significance should continue to be investigated/followed-up further for a final determination, if possible.

A list of AEs that have occurred or might occur can be found in §6.2 Reported Adverse Events and Potential Risks, as well as the Investigator Brochure or package insert.

11.1 Adverse Events

11.1.1 Reportable AEs

All AEs that occur after the informed consent is signed and baseline assessments are completed (including run-in) must be recorded on the AE CRF (paper and/or electronic) whether or not related to study agent and stop at the beginning of surgery. EOG site must also record on the AE CRF all the AEs that occur after the pre-screening informed consent is signed and screening assessments are completed.
All SAEs, including all hospitalizations, during the study period will be reported as per DCP SAE reporting procedures, with the following exception;

i. Hospitalization for planned surgery will not be reported. However, if this hospitalization event lasts longer than the usual period at the institution (as determined by the Site Principal Investigator or Sponsor), it will be reportable as an SAE. Adverse events (AEs) relevant to the prolongation of this hospitalization will also be collected and reported on AE CRFs.

11.1.2 AE Data Elements:

The following data elements are required for AE reporting.

- AE verbatim term
- NCI Common Terminology Criteria for Adverse Events version 4.0 (CTCAE v4.0) AE term (MedDRA lowest level term)
- CTCAE (MedDRA) System Organ Class (SOC)
- Event onset date and event ended date
- Treatment assignment code (TAC) at time of AE onset
- Severity grade
- Attribution to study agent (relatedness)
- Whether or not the event was reported as a SAE
- Whether or not the subject dropped due to the event
- Outcome of the event

11.1.3 Severity of AEs

11.1.3.1 Identify the AE using the CTCAE version 4.0. The CTCAE provides descriptive terminology (MedDRA lowest level term) and a grading scale for each AE listed. A copy of the CTCAE can be found at http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

AEs will be assessed according to the grade associated with the CTCAE term. AEs that do not have a corresponding CTCAE term will be assessed according to the general guidelines for grading used in the CTCAE v4.0. as stated below.

CTCAE v4.0 general severity guidelines:

Grade	Severity	Description
1	Mild	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
2	Moderate	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL)*.
3	Severe	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL**.
4	Life-threatening	Life-threatening consequences; urgent intervention indicated.
5	Fatal	Death related to AE.

ADL

*Instrumental ADL refers to preparing meals, shopping for groceries or clothes, using the telephone, managing money, *etc*.

**Self-care ADL refers to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

11.1.4 Assessment of relationship of AE to treatment

The possibility that the AE is related to study agent will be classified as one of the following: not related, unlikely, possible, probable, and definite.

11.1.5 Follow-up of AEs

All AEs, including lab abnormalities that in the opinion of the investigator are clinically significant, will be followed according to good medical practices and documented as such.

11.2 Serious Adverse Events

11.2.1 DEFINITION: Regulations at 21 CFR §312.32 (revised April 1, 2014) defines an SAE as any untoward medical occurrence that at any dose has one or more of the following outcomes:

- Death
- A life-threatening AE
- Inpatient hospitalization or prolongation of existing hospitalization

- A persistent or significant incapacity or substantial disruption of the ability to perform normal life functions
- A congenital anomaly or birth defect
- Important medical events that may not be immediately life-threatening or result in death or hospitalization should also be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient and may require intervention to prevent one of the other outcomes.

11.2.2 Reporting SAEs to DCP

11.2.2.1 The Lead Organization and all Participating Organizations will report SAEs on the DCP SAE Report Form found at http://prevention.cancer.gov/clinical-trials/clinical-trials-management/protocol-information-office/pio-instructions-and-tools/2012-consortia.

11.2.2.2 Contact the DCP Medical Monitor by phone or email (email preferable) within 24 hours of knowledge of the event.

Eva Szabo, MD
Chief, Lung & Upper Aerodigestive Cancer Research Group
NCI/Division of Cancer Prevention
9609 Medical Center Drive, Room 5E-102, MSC 9781
Bethesda, MD 20892-9781 (For FedEx, use Rockville, MD 20850)
Phone: (240) 276-7011
FAX: (240) 276-7848
email: szaboe@mail.nih.gov

Include the following information when calling the Medical Monitor:

- Date and time of the SAE
- Date and time of the SAE report
- Name of reporter
- Call back phone number
- Affiliation/Institution conducting the study
- DCP protocol number
- Title of protocol
- Description of the SAE, including attribution to drug

11.2.2.3 The Lead Organization and all Participating Organizations will email written SAE reports to DCP's Regulatory Contractor CCS Associates, Inc. (CCSA; phone: 650-691-4400) at safety@ccsainc.com as well as DCP medical monitor simultaneously within 48 hours of learning of the event using the fillable PDF SAE Report Form.

11.2.2.4 The DCP Medical Monitor and CCSA regulatory and safety staff will determine which SAEs require FDA submission as IND safety reports.

11.2.2.5 The Lead Organization and all Participating Organizations will comply with applicable regulatory requirements related to reporting SAEs to the IRB/IEC.

11.2.3 Follow-up of SAE

Site staff should send follow-up reports as requested when additional information is available. Additional information should be entered on the DCP SAE Report Form in the appropriate format. Follow-up information should be sent to DCP as soon as available. Any SAE will be followed-up until resolution as per the GCP practice.

11.3 Suspected Unexpected Serious Adverse Reaction

An adverse event or suspected adverse reaction is considered by the sponsor and/or study investigator as being unexpected, serious and as having a reasonable possibility of a causal relationship with the study drug. At EOG site, in case of SUSAR (Suspected Unexpected Serious Adverse Reaction) the Pharmacovigilance Unit performs the regulatory notification to EudraVigilance and to the local EC in order to comply with the current European regulatory requirements.

12. STUDY MONITORING

12.1 Data Management

All of the procedures outlined in the University of Wisconsin Chemoprevention Consortium standardized Data Management Plan (approved 09/23/2019) will be followed in this protocol. Please refer to this document for additional details on data management procedures. The University of Wisconsin Carbone Cancer Center's OnCore database will be the database of record for the protocol and subject to NCI and FDA audit. OnCore is a web-based clinical trials database. Data entry will be performed by the CLO where staff is trained in OnCore and applicable regulatory requirements such as 21 CFR: Part 11. Data from the OnCore database will be transferred to Federal Security Compliant formats for transmission to DCP according to pre-established DCP standards and procedures.

12.2 Case Report Forms

In lieu of a CRF set, a System Variable Attribute Report (SVAR) will be used to document all questions and data elements to be collected in the database for this protocol. The NCI/DCP approved SVAR will be used to create the electronic data entry pages in the OnCore database. Amendments to the SVAR will be submitted to the DCP Protocol Information Office for review and approval. Data will be extracted from source documents submitted by the PO.

12.3 Source Documents

To standardize the collection of study data, the CLO will provide the PO's with protocol specific Visit Guides and Source Document Worksheets to ensure that all required data elements are captured. These documents will be used to supplement data collected on primary clinical source documents. All data reported must be documented either on a separate source document found in the participant's medical record or on the Visit Guides and Source Document Worksheets. All source documents must be signed by the study team member that collected or elicited the information in the source documents. Source documents will be submitted to the CLO (either by fax, or e-mail) for entry into the OnCore database within 10 business days of each study contact. Primary clinical source documents will be de-identified and relabeled with the participant's PID number prior to submission. Documents containing participant personally identifiable information that has not been completely obscured cannot be accepted and will be returned to the site.

12.4 Data and Safety Monitoring Plan

All of the procedures outlined in the University of Wisconsin Chemoprevention Consortium standardized Data and Safety Monitoring Plan (approved 03/20/2018) as well as the Master Data and Safety Monitoring

Plan will be followed in this protocol. The UW Chemoprevention Consortia Data and Safety Monitoring Committee meet every 6-12 months to review all data from ongoing consortium studies.

12.5 Sponsor or FDA Monitoring

The NCI, DCP (or their designee), pharmaceutical collaborator (or their designee), or FDA may monitor/audit various aspects of the study. These monitors will be given access to facilities, databases, supplies and records to review and verify data pertinent to the study.

12.6 Record Retention

Clinical records for all participants, including CRFs, all source documentation (containing evidence to study eligibility, history and physical findings, laboratory data, results of consultations, *etc*.), as well as IRB records and other regulatory documentation will be retained by the Investigator in a secure storage facility in compliance with Health Insurance Portability and Accountability Act (HIPAA), Office of Human Research Protections (OHRP), Food and Drug Administration (FDA) regulations and guidance, and NCI/DCP requirements, unless the standard at the site is more stringent. The records for all studies performed under an IND will be maintained, at a minimum, for two years after the approval of a New Drug Application (NDA). For NCI/DCP, records will be retained for at least three years after the completion of the research. NCI will be notified prior to the planned destruction of any materials. The records should be accessible for inspection and copying by authorized persons of the Food and Drug Administration. If the study is done outside of the United States, applicable regulatory requirements for the specific country participating in the study also apply.

12.7 Cooperative Research and Development Agreement (CRADA)/Clinical Trials Agreement (CTA)

Not Applicable

13. STATISTICAL CONSIDERATIONS

13.1 Study Design/Description

This is a multi-center, phase IIA, single-arm 'window of opportunity' pilot study of 25 mg per day exemestane for 21 to 42 days in patients undergoing planned surgery for CAH/EIN or low grade endometrial cancer, with an age, disease and BMI-matched comparator cohort, obtained from each institution's biobank,

We plan to enroll up to 40 patients over 12-18 months at an accrual rate of 2-3 patients per month. Although all subjects will have CAH/EIN or low grade endometrial cancer based on their referral biopsy, we anticipate that some subjects will not have CAH/EIN or low grade endometrial cancer on central pathology review, thus making them ineligible for final analysis[43]. Additionally, tissue samples may not be adequate for measuring Ki-67 expression. We therefore anticipate that approximately 25% of subjects will not be eligible for final analysis. This will result in 30 evaluable patients, the effective sample size for the study.

13.2 Randomization/Stratification

In the absence of randomized placebo controls, we will obtain age, disease and BMI matched comparator cohort from each institution's biobank. The historical samples from each matched control will need to be obtained within 42 days of each other in order to be consistent with the study participants. This matching will be one-to-one. A comparison of Ki-67 expression between subjects on this study and historic controls is not a primary goal of the study. The primary outcome is the overall change in Ki-67 expression between pre and post-treatment of each subject. The reason a historic cohort will be studied is to provide the context in which to assess the effects of exemestane in reducing Ki-67 from baseline to post-exposure to

exemestane. Specifically, there may be a change in Ki-67 expression from pretreatment biopsy to final surgical specimen in the historical control cohort suggesting that time alone (between biopsy and surgery) or potentially differences in tissues acquisition (biopsy versus surgical specimen) may have an impact on Ki-67 expression.

13.3 Accrual and Feasibility

Each participating organization sees over 100 new patients annually with diagnosis of CAH/EIN or low grade endometrial carcinoma. It is planned to enroll up to 40 participants over 12 to 18 months from the three participating clinical sites to ensure 30 evaluable patients.

13.4 Primary Objective, Endpoint(s), Analysis Plan

The primary objective is to determine if there is a decrease in proliferation index, measured by percent Ki-67 expression, in CAH/EIN or low grade endometrial cancer cells from baseline to post-exposure. Therefore, the primary endpoint is the absolute change in Ki-67 expression in endometrial cancer cells from baseline to post-exposure. We will evaluate the change from baseline to post-exposure in absolute change in Ki-67 using one-sample Student's t-test or Wilcoxon signed-rank test, as appropriate. In addition, we will evaluate the change relative to the change recorded in the historic cohort.

Ki-67 values for patients with endometrial cancer are available in prior research[44]. When the patients from this paper are limited to those with low grade cancers, the mean (standard deviation) of the decrease from baseline was 7.2 (7.5) among the treated patients. Given an SD of 7.5, the table below shows the detectable effect sizes (defined as the mean change divided by the standard deviation of the change) and mean changes for a one-sided test for significance level α=0.05 and various power (1-β) levels for the primary endpoint given the effective sample size of 30. For example, using an 0.05 level one-sided one-sample Student t-test, we would be able to detect an effect size of 0.50, which corresponds to a mean decrease of 3.8, with 0.85 power.

	Power		
	0.80	0.85	0.90
Effect Size	0.46	0.50	0.55
Mean Decrease	3.5	3.8	4.1

The mean decreases in this table are smaller than the mean difference in the treatment group for those with low grade endometrial cancer in the prior research with letrozole[44]. We are including CAH/EIN in addition to low grade endometrial cancer in the current study and therefore it is not unreasonable to expect a lesser treatment effect for these patients with a less severe form of the disease. For these reasons, we feel there is a need to power for smaller differences.

It is estimated that 50% of the patients will have CAH/EIN and 50% will have low grade endometrial cancer. For subgroups each with 15 patients, using a 0.05 level one-sided one-sample Student t-test, and assuming the same standard deviation as above, there will be power of 0.8-0.9 to detect a mean decrease ranging from 5.1-6.0. Because of the nature of the study being exploratory, we are not making adjustment for multiplicity of testing in subgroups defined by CAH/EIN vs low grade carcinoma.

13.5 Secondary Objectives, Endpoints, Analysis Plans

The secondary objectives are to examine and test change in circulating serum estradiol and progesterone, histology, and tissue biomarkers. Additionally, we will correlate response with tumor DNA mutations, and

protein and DNA markers via tampon recovery. Therefore, the secondary endpoints are the changes in circulating serum estradiol and progesterone levels, in tissue biomarkers such as apoptosis as measured by cleaved caspase 3 level, proliferation as measured by cyclin D1 level, and insulin pathway as measured by pAKT and IGF-1R levels, and hormone receptor changes as measured by ER, PR and AR.

All tumors will be sequenced via Next Generation Sequencing panel testing and also be tested for microsatellite instability. Results of tumor genetic testing will be correlated with exemestane response as defined by the change in KI-67 expression.

As an exploratory endpoint, we will attempt to identify the genetic mutation of the primary tumor by performing Next Generation Sequencing of tampon collected DNA. Additionally, vaginal proteomic analysis will also be performed via tampon collection and correlated with tumor response to exemestane as defined by the change in KI-67 expression[45,46].

To evaluate the reliability of methylation measurement assayed on the 850K EPIC chip, an intraclass correlation coefficient (ICC) will be calculated for each CpG site using the technical replicates (using 4 blinded duplicate measurements). We aim to classify the CpG sites into multiple reliability groups, by modeling the distribution of ICC values using a mixture distribution.

The degree of methylation will be determined using Illumina GenomeStudio software. The methylation score for each CpG will be represented as a beta (β) value calculated by dividing the fluorescence intensity of the methylated allele by the sum of the intensities of the methylated allele and unmethylated allele. β-values may take any value between 0 (non-methylated) and 1 (completely methylated). Background subtraction will be conducted with the GenomeStudio software using built-in negative control bead types on the array. An average normalization will also applied in GenomeStudio to minimize scanner-to-scanner variation using ~90 normalization probe pairs included on the array, which target housekeeping regions with no underlying CpG sites. These probes will be used to independently calculate normalization values in the green and red channels so that all samples have the same average intensity.

We will identify individual DNA methylation sites (β values as independent variables) in the 850K EPIC chip that are either overexpressed or underexpressed in endometrial tumor DNA by focusing on the tails of distribution of the β values. We will evaluate whether those individual methylation sites can be detected in the matched tampon DNA. We realize that this study is not powered to comprehensively identify all individual DNA methylation markers in endometrial cancer and will perform these analyses to potential targets that can be confirmed in future studies.

Vaginal and tumor DNA methylation studies will be performed; the signals from methylated (M) and unmethylated (U) bead types will be used to calculate $\beta = M/(U + M)$ for the 850,000CpG sites that the EPIC methylation chip evaluates. Correlations will be tested between vaginal and tumor DNA methylation at each CpG site, adjusting for covariates, possibly including age. Linear mixed models adjusting for covariates such as age and histology (CAH/EIN vs grade 1/2) will be used to test for relationships between vaginal DNA methylation at CpG sites and the primary endpoint, change in Ki-67. A False Discovery Rate (FDR) q-value of 0.05 will be applied to adjust for multiplicity in these tests; where an FDR is not appropriate, a Bonferroni correction will be used.

13.6 Reporting and Exclusions

As noted above, we anticipate that approximately 25% of patients will not have CAH/EIN or low grade endometrial carcinoma on central pathology review or their tissue samples will not be adequate for measuring Ki-67 expression, thus making them unevaluable for final analysis[43]. This will result in 30 evaluable patients, the effective sample size for the study. These cases will be considered random loss, and will be excluded from analysis. Otherwise, all cases will be included in the analysis regardless of

compliance with the protocol treatment. All cases that received any amount of exemestane will be included in the analysis of toxicity as indicated below.

13.7 Evaluation of Toxicity
All participants will be evaluable for toxicity from the time of their first dose of exemestane using CTCAE version 4.0. The incidence and severity of adverse events will be summarized with frequency and proportion.

13.8 Evaluation of Response
Pathological response, i.e. regression of endometrial hyperplasia and carcinoma in pre-treatment biopsies to final surgical tissue samples, will be summarized with frequency and proportion. All of the participants who met the eligibility criteria, with the exception of those who did not receive study agent, will be included in the main analysis. Random dropouts will be excluded. Data will be examined for non-random dropouts. An appropriate sensitivity analysis will be conducted in the case of missing data.

13.9 Interim Analysis
There is no planned interim analysis of the primary endpoint of the study. Safety data will be monitored periodically by the consortium's data and safety monitoring committee.

13.10 Ancillary Studies
Not Applicable

14. ETHICAL AND REGULATORY CONSIDERATIONS

14.1 Form FDA 1572
Prior to initiating this study, the Protocol Lead Investigator at the Lead or Participating Organization(s) will provide a signed Form FDA 1572 stating that the study will be conducted in compliance with regulations for clinical investigations and listing the investigators, at each site that will participate in the protocol. All personnel directly involved in the performance of procedures required by the protocol and the collection of data should be listed on Form FDA 1572.

14.2 Other Required Documents
14.2.1 Current (within two years) CV or biosketch for all study personnel listed on the Form FDA 1572 and Delegation of Tasks form for the Lead Organization and all Participating Organizations.

14.2.2 Current medical licenses (where applicable) for all study personnel listed on Form FDA 1572 and Delegation of Tasks form for the Lead Organization and all Participating Organizations.

14.2.3 Lab certification (*e.g.*, CLIA, CAP) and lab normal ranges for all labs listed on Form FDA 1572 for the Lead Organization and all Participating Organizations.

14.2.4 Documentation of training in "Protection of Human Research Subjects" for all study personnel listed on the FDA Form 1572 and Delegation of Tasks form for the Lead Organization and all Participating Organizations.

14.2.5 Documentation of Federalwide Assurance (FWA) number for the Lead Organization and all Participating Organizations.

14.2.6 Signed Investigator's Brochure/Package Insert acknowledgement form

14.2.7 Delegation of Tasks form for the Lead Organization and all Participating Organizations signed by the Principal Investigator for each site and initialed by all study personnel listed on the form

14.2.8 Signed and dated NCI, DCP Financial Disclosure Form for all study personnel listed on Form FDA 1572 for the Lead Organization and all Participating Organizations

14.3 Institutional Review Board Approval

Prior to initiating the study and receiving agent, the Investigators at the Lead Organization and the Participating Organization(s) must obtain written approval to conduct the study from the CIRB. Should changes to the study become necessary, protocol amendments will be submitted to the DCP PIO according to DCP Amendment Guidelines. The DCP-approved amended protocol must be approved by the CIRB prior to implementation

14.4 Informed Consent

All potential study participants will be given a copy of the IRB-approved Informed Consent to review. The investigator will explain all aspects of the study in lay language and answer all questions regarding the study. If the participant decides to participate in the study, he/she will be asked to sign and date the Informed Consent document. The study agent(s) will not be released to a participant who has not signed the Informed Consent document. Subjects who refuse to participate or who withdraw from the study will be treated without prejudice.

Participants must be provided the option to allow the use of blood samples, other body fluids, and tissues obtained during testing, operative procedures, or other standard medical practices for further research purposes. If applicable, statement of this option may be included within the informed consent document or may be provided as an addendum to the consent. A Model Consent Form for Use of Tissue for Research is available through a link in the DCP website.

Prior to study initiation, the informed consent document must be reviewed and approved by NCI, DCP, the Consortium Lead Organization, and the IRB at each Organization at which the protocol will be implemented. Any subsequent changes to the informed consent must be approved by NCI, DCP, the Consortium Lead Organization's IRB, and then submitted to each organization's IRB for approval prior to initiation.

14.5 Submission of Regulatory Documents

All regulatory documents are collected by the Consortia Lead Organization and reviewed for completeness and accuracy. Once the Consortia Lead Organization has received complete and accurate documents from a participating organization, the Consortium Lead Organization will forward the regulatory documents to DCP's Regulatory Contractor:

Paper Document/CD-ROM Submissions:
Regulatory Affairs Department
CCS Associates, Inc.
2001 Gateway Place, Suite 350 West
San Jose, CA 95110
Phone: 650-691-4400
Fax: 650-691-4410
E-mail Submissions:
regulatory@ccsainc.com

Regulatory documents that do not require an original signature may be sent electronically to the Consortium Lead Organization for review, which will then be electronically forwarded to DCP's Regulatory Contractor.

14.6 Other

This trial will be conducted in compliance with the protocol, Good Clinical Practice (GCP), and the applicable regulatory requirements.

15. FINANCING, EXPENSES, AND/OR INSURANCE

The costs of all procedures for this protocol are paid for by the study contract with the exception of the costs associated with surgical treatment at the end of the study. In the event that a participant is physically injured as a result of participating in this research, there is no provision for compensation for medical care for the injury. Participants will be compensated $150.00 for additional time and effort associated with the endometrial biopsy and tampon collection. Since the regulations in Italy does not permit for research participants to be compensated with money, no compensation will be provided to the participants enrolled at E.O. Ospedali Galliera.

According to Directive 2001/20/EC implemented in Italy with Law Decree 211/2003, this clinical trial is covered by a study specific insurance. The study drug will be provided by the E.O. Ospedali Galliera Pharmacy and will be covered by the study budget.

REFERENCES

1. Siegel RL, Miller KD, Jemal A: Cancer statistics, 2016. CA Cancer J Clin 66:7-30, 2016
2. Walker JL, Piedmonte MR, Spirtos NM, et al: Laparoscopy compared with laparotomy for comprehensive surgical staging of uterine cancer: Gynecologic Oncology Group Study LAP2. J Clin Oncol 27:5331-6, 2009
3. Gunderson CC, Fader AN, Carson KA, et al: Oncologic and reproductive outcomes with progestin therapy in women with endometrial hyperplasia and grade 1 adenocarcinoma: a systematic review. Gynecol Oncol 125:477-82, 2012
4. Visvanathan K, Hurley P, Bantug E, et al: Use of pharmacologic interventions for breast cancer risk reduction: American Society of Clinical Oncology clinical practice guideline. J Clin Oncol 31:2942-62, 2013
5. Lindemann K, Malander S, Christensen RD, et al: Examestane in advanced or recurrent endometrial carcinoma: a prospective phase II study by the Nordic Society of Gynecologic Oncology (NSGO). BMC Cancer 14:68, 2014
6. Thanopoulou E, Thway K, Khabra K, et al: Treatment of hormone positive uterine leiomyosarcoma with aromatase inhibitors. Clin Sarcoma Res 4:5, 2014
7. Parkash V, Fadare O, Tornos C, et al: Committee Opinion No. 631: Endometrial Intraepithelial Neoplasia. Obstet Gynecol 126:897, 2015
8. Baak JP, Mutter GL, Robboy S, et al: The molecular genetics and morphometry-based endometrial intraepithelial neoplasia classification system predicts disease progression in endometrial hyperplasia more accurately than the 1994 World Health Organization classification system. Cancer 103:2304-12, 2005
9. Grady D, Gebretsadik T, Kerlikowske K, et al: Hormone replacement therapy and endometrial cancer risk: a meta-analysis. Obstet Gynecol 85:304-13, 1995
10. Potischman N, Hoover RN, Brinton LA, et al: Case-control study of endogenous steroid hormones and endometrial cancer. J Natl Cancer Inst 88:1127-35, 1996
11. Chlebowski RT, Schottinger JE, Shi J, et al: Aromatase inhibitors, tamoxifen, and endometrial cancer in breast cancer survivors. Cancer 121:2147-55, 2015
12. Apgar BS, Greenberg G: Using progestins in clinical practice. Am Fam Physician 62:1839-46, 1849-50, 2000
13. Abu Hashim H, Ghayaty E, El Rakhawy M: Levonorgestrel-releasing intrauterine system vs oral progestins for non-atypical endometrial hyperplasia: a systematic review and metaanalysis of randomized trials. Am J Obstet Gynecol 213:469-78, 2015
14. Kim MK, Seong SJ, Kim JW, et al: Management of Endometrial Hyperplasia With a Levonorgestrel-Releasing Intrauterine System: A Korean Gynecologic-Oncology Group Study. Int J Gynecol Cancer 26:711-5, 2016
15. Chandra V, Kim JJ, Benbrook DM, et al: Therapeutic options for management of endometrial hyperplasia. J Gynecol Oncol 27:e8, 2016
16. Chumsri S, Howes T, Bao T, et al: Aromatase, aromatase inhibitors, and breast cancer. J Steroid Biochem Mol Biol 125:13-22, 2011

17. Ghosh D, Griswold J, Erman M, et al: Structural basis for androgen specificity and oestrogen synthesis in human aromatase. Nature 457:219-23, 2009

18. Sobral AF, Amaral C, Correia-da-Silva G, et al: Unravelling exemestane: From biology to clinical prospects. J Steroid Biochem Mol Biol, 2016

19. Hong Y, Yu B, Sherman M, et al: Molecular basis for the aromatization reaction and exemestane-mediated irreversible inhibition of human aromatase. Mol Endocrinol 21:401-14, 2007

20. Kamdem LK, Flockhart DA, Desta Z: In vitro cytochrome P450-mediated metabolism of exemestane. Drug Metab Dispos 39:98-105, 2011

21. Paridaens R, Thomas J, Wildiers J, et al: Safety, activity and estrogen inhibition by exemestane in postmenopausal women with advanced breast cancer: a phase I study. Anticancer Drugs 9:675-83, 1998

22. Evans TR, Di Salle E, Ornati G, et al: Phase I and endocrine study of exemestane (FCE 24304), a new aromatase inhibitor, in postmenopausal women. Cancer Res 52:5933-9, 1992

23. Lonning PE, Eikesdal HP: Aromatase inhibition 2013: clinical state of the art and questions that remain to be solved. Endocr Relat Cancer 20:R183-201, 2013

24. Johannessen DC, Engan T, Di Salle E, et al: Endocrine and clinical effects of exemestane (PNU 155971), a novel steroidal aromatase inhibitor, in postmenopausal breast cancer patients: a phase I study. Clin Cancer Res 3:1101-8, 1997

25. Fontein DB, Charehbili A, Nortier JW, et al: Efficacy of six month neoadjuvant endocrine therapy in postmenopausal, hormone receptor-positive breast cancer patients--a phase II trial. Eur J Cancer 50:2190-200, 2014

26. Goss PE, Ingle JN, Ales-Martinez JE, et al: Exemestane for breast-cancer prevention in postmenopausal women. N Engl J Med 364:2381-91, 2011

27. Li HZ, Chen XN, Qiao J: Letrozole as primary therapy for endometrial hyperplasia in young women. Int J Gynaecol Obstet 100:10-2, 2008

28. Barker LC, Brand IR, Crawford SM: Sustained effect of the aromatase inhibitors anastrozole and letrozole on endometrial thickness in patients with endometrial hyperplasia and endometrial carcinoma. Curr Med Res Opin 25:1105-9, 2009

29. Burnett AF, Bahador A, Amezcua C: Anastrozole, an aromatase inhibitor, and medroxyprogesterone acetate therapy in premenopausal obese women with endometrial cancer: a report of two cases successfully treated without hysterectomy. Gynecol Oncol 94:832-4, 2004

30. Flannery CA, Saleh FL, Choe GH, et al: Differential Expression of IR-A, IR-B and IGF-1R in Endometrial Physiology and Distinct Signature in Adenocarcinoma. J Clin Endocrinol Metab 101:2883-91, 2016

31. Pavelic J, Radakovic B, Pavelic K: Insulin-like growth factor 2 and its receptors (IGF 1R and IGF 2R/mannose 6-phosphate) in endometrial adenocarcinoma. Gynecol Oncol 105:727-35, 2007

32. Mutter GL: Endometrial intraepithelial neoplasia (EIN): will it bring order to chaos? The Endometrial Collaborative Group. Gynecol Oncol 76:287-90, 2000

33. Cancer Genome Atlas Research N, Kandoth C, Schultz N, et al: Integrated genomic characterization of endometrial carcinoma. Nature 497:67-73, 2013

34. Erickson BK, Kinde I, Dobbin ZC, et al: Detection of somatic TP53 mutations in tampons of

patients with high-grade serous ovarian cancer. Obstet Gynecol 124:881-5, 2014

35. Andersen JD, Boylan KL, Xue FS, et al: Identification of candidate biomarkers in ovarian cancer serum by depletion of highly abundant proteins and differential in-gel electrophoresis. Electrophoresis 31:599-610, 2010

36. Boylan KL, Andersen JD, Anderson LB, et al: Quantitative proteomic analysis by iTRAQ(R) for the identification of candidate biomarkers in ovarian cancer serum. Proteome Sci 8:31, 2010

37. Kooren JA, Rhodus NL, Tang C, et al: Evaluating the potential of a novel oral lesion exudate collection method coupled with mass spectrometry-based proteomics for oral cancer biomarker discovery. Clin Proteomics 8:13, 2011

38. de Jong EP, van Riper SK, Koopmeiners JS, et al: Sample collection and handling considerations for peptidomic studies in whole saliva; implications for biomarker discovery. Clin Chim Acta 412:2284-8, 2011

39. Bandhakavi S, Van Riper SK, Tawfik PN, et al: Hexapeptide libraries for enhanced protein PTM identification and relative abundance profiling in whole human saliva. J Proteome Res 10:1052-61, 2011

40. Attarha S, Andersson S, Mints M, et al: Individualised proteome profiling of human endometrial tumours improves detection of new prognostic markers. Br J Cancer 109:704-13, 2013

41. Mokhtar NM, Ramzi NH, Yin-Ling W, et al: Laser capture microdissection with genome-wide expression profiling displayed gene expression signatures in endometrioid endometrial cancer. Cancer Invest 30:156-64, 2012

42. Werner HM, Salvesen HB: Current status of molecular biomarkers in endometrial cancer. Curr Oncol Rep 16:403, 2014

43. Zaino RJ, Kauderer J, Trimble CL, et al: Reproducibility of the diagnosis of atypical endometrial hyperplasia: a Gynecologic Oncology Group study. Cancer 106:804-11, 2006

44. Smith L, Leiserowitz, G., Xing, G. and Bishop, J. : Short-term Femara (letrozole) treatment and suppression of Ki-67 expression in postmenopausal endometrial carcinoma. . Open Journal of Obstetrics and Gynecology 3:347-351, 2013

45. Eisen MB, Spellman PT, Brown PO, et al: Cluster analysis and display of genome-wide expression patterns. Proc Natl Acad Sci U S A 95:14863-8, 1998

46. Muir WM, Rosa GJ, Pittendrigh BR, et al: A mixture model approach for the analysis of small exploratory microarray experiments. Comput Stat Data Anal 53:1566-1576, 2009

47. Nafisi H, Ghorab Z, Ismill N, et al: Immunophenotypic Analysis in Early Mullerian Serous Carcinogenesis. Int J Gynecol Pathol 34:424-36, 2015

48. Helpman L, Kupets R, Covens A, et al: Assessment of endometrial sampling as a predictor of final surgical pathology in endometrial cancer. Br J Cancer 110:609-15, 2014

49. Nofech-Mozes S, Ismiil N, Dube V, et al: Interobserver agreement for endometrial cancer characteristics evaluated on biopsy material. Obstet Gynecol Int 2012:414086, 2012

50. Goss PE, Ingle JN, Ales-Martinez JE, Cheung AM, Chlebowski RT, Wactawski-Wende J, McTiernan A, Robbins J, Johnson KC, Martin LW, Winquist E, Sarto GE, Garber JE, Fabian CJ, Pujol P, Maunsell E, Farmer P, Gelmon KA, Tu D, Richardson H, NCIC CTG MAP.3 Study Investigators. Exemestane for breast-cancer prevention in postmenopausal women. N Engl J Med

2011;364:2381–91.

51. Alvogen Inc. Exemestane tablets, for oral use. Full prescribing information. Rev. 10/2016..
52. PMID 25656898 Dienstmann R, Jang IS, Bot B, Friend S, Guinney J. Database of genomic biomarkers for cancer drugs and clinical targetability in solid tumors. Cancer Discov. 2015 Feb;5(2):118-23.
53. PMID 27684579 Ainscough BJ, Griffith M, Coffman AC, Wagner AH, Kunisaki J, Choudhary MN, McMichael JF, Fulton RS, Wilson RK, Griffith OL, Mardis ER. DoCM: a database of curated mutations in cancer. Nat Methods. 2016;13(10):806-7.
54. PMID 26643039 Yang R, Nelson AC, Henzler C, Thyagarajan B, Silverstein KA. ScanIndel: a hybrid framework for indel detection via gapped alignment, split reads and de novo assembly. Genome Med. 2015 Dec 7;7:127.
55. Pmid 23303603 Kinde I, Bettegowda C, Wang Y, Wu J, Agrawal N, Shih IeM, Kurman R, Dao F, Levine DA, Giuntoli R, Roden R, Eshleman JR, Carvalho JP, Marie SK, Papadopoulos N, Kinzler KW, Vogelstein B, Diaz LA Jr. Evaluation of DNA from the Papanicolaou test to detect ovarian and endometrial cancers. Sci Transl Med. 2013 Jan 9;5(167).
56. Scholten AN, Smit VT, Beerman H, van Putten WL et al. Prognostic Significance and Interobserver Variability of Histologic Grading Systems for Endometrial Carcinoma. Cancer. 2004;100:764-72.
57. Alkushi A, Abdul-Rahman Z, Lim P, Schulzer M et al. Description of a Novel System for Grading of Endometrial Carcinoma and Comparison with Existing Grading Systems. Am J Surg Pathol 2005;29:295-304.
58. Nofech-Mozes S, Ghorab Z, Ismiil N et al. Endometrial Endometrioid Adenocarcinoma A Pathologic Analysis of 827 consecutive cases. Am J Clin Pathol. 2008; 129: 110-114.
59. Piulats JM, Guerra E, Gil-Martin M, Roman-Canal B et al. Molecular approaches for classifying endometrial carcinoma. Gynecologic Oncology. Vol 145:1. April 2017, pages 200-207.

APPENDIX A
Performance Status Criteria

ECOG Performance Status Scale

Grade	Descriptions
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (*e.g.*, light housework, office work).
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

APPENDIX B
Telephone Consent

Hello, my name is _____ (name of person screening) and I am from the _____ (insert institution name).

☐ (For clinic patients)
I am calling from Dr. _____ office whom you are visiting for a surgical consult. He / She wanted me to reach out to you and talk about a research study that you may qualify for. Would you be interested in learning about this study?

If No: Thank you so much for your time.
If Yes: This phone call may take up to 15-20mins. Is this a good time to talk to you about the study?

☐ (For self-referrals through NCT's website)
I am calling regarding your enquiry for the research study being conducted at our site. I will be providing a short description of the study and will answer any questions you may have. This phone call may take up to 15-20mins. Is this a good time to talk to you about the study?

If No: Is there a better time to speak to you about this research study? (Get time and best phone number to reach them). If they aren't interested in being called again, thank them and disconnect phone contact. Assure them that their information will be destroyed.
If Yes: Continue with the script

Participation in this call and participation in the study is voluntary and you can stop at any time without any consequences to any on-going care.
Before I talk about the study, can you tell me a little bit about what you know about your diagnosis and why you are coming in so I can direct my conversation accordingly?

Hysterectomy is currently the treatment for uterine cancer (or pre-cancer). To find a less invasive treatment option, researchers are contacting patients who are being scheduled for hysterectomy to take an oral medication until the day of their surgery. Researchers will then study the effects of the medication on the tissue samples collected during the study to understand if the medication has any effect on the uterine cells and thickness of the lining. The results of this study may lead to future research with this medication to possibly prevent or treat uterine cancers.

The medication that is given for this study is called exemestane, which you will take orally, once a day for 3 to 6 weeks prior to your surgery, depending on when your surgery is scheduled. Exemestane is FDA approved medication primarily used in patients with breast cancer. It is an anti-estrogen drug that reduces the levels of the female hormone estrogen. Researchers believe that the changes you have in your cervix/uterus are also to be related to estrogen. They want to find out if taking this medication has similar effect on uterine cells as it has on breast cells.

For this research study, we will be collecting tissue samples of your uterus before and after the treatment with exemestane. If you decide to participate, at your pre-operative visit we will be conducting an endometrial biopsy to obtain this tissue sample. Several tests will be done on the samples to see if changes can be detected. Part of the study also involves studying samples obtained from a vaginal tampon, which we will ask you to place 8-12 hours before your clinic visit.

If you decide to participate, we will meet with you at your pre-operative clinic visit and on the day of your surgery. No additional visits will be required. We will collect eligibility information including your medical history, diagnosis and lab tests during the visit. Your doctor will be collecting a research biopsy of your uterine lining (called endometrial tissue) and the tampon sample you inserted if you agreed to this portion of the study during this pre-operative visit for research. You will not be charged for this procedure and will be paid $150 as compensation for your efforts.

Your total duration of participation in this study will depend on when your surgery gets scheduled which may be about 6-9 weeks long. We will follow up after your surgery if any side-effects are ongoing. If this study sounds like something you might be interested in, we will mail you a copy of the consent form as well as a tampon kit with instructions for using the tampon the before your pre-operative clinic visit. You can change your decision to be in the study at any time and it will not affect the care you receive in any way.

What questions do you have? Note down the questions if any: _____
_____
_____

Would you be interested in participating in the study?
If No: If Patient DOES NOT agree: Thank her for the call and do not proceed further.
If Yes: Continue with script to obtain consent for tampon insertion.

If you choose to participate, would you be interested in participating in the tampon collection?
☐ **No**: If Patient DOES NOT agree: That is ok, you can still participate in the main study. You will be receiving a copy of the informed consent form that will be mailed to you, for you to read prior to coming for your pre-operative clinic visit. The informed consent form will be discussed at length on the day of the clinic visit and you will have the chance to discuss this and to ask more questions you may have. In addition, it is advised that you bring a family member or friend with you to all study visits including the pre-operative clinic visit.
☐ **Yes**: Please note that this will be documented as your verbal consent to provide you with the Tampon kit to insert the tampon prior to your visit. This is NOT considered a consent to participate in the full study I have described and you can change your mind and not participate in the tampon portion at any time. There are minimal risks in placing a tampon or having it removed during your exam. You will be receiving a copy of the informed consent form in the kit that will be mailed to you, for you to read prior to coming for your pre-operative clinic visit. The informed consent form will be discussed at length on the day of the clinic visit and you will have the chance to discuss this and to ask more questions you may have. In addition, it is advised that you bring a family member or friend with you to all study visits including the pre-operative clinic visit.

Document date and time of verbal consent given. Person screening must also sign and date this form.

Verbal consent given at _____am/pm on _____ (date).

Person obtaining verbal consent: _____ Date: _____

Obtain the following information from the participant or medical records:

Name: _____

Address (for mailing the kit): _____

Diagnosis: ☐ CAH/EIN; ☐ EC grade 1 ☐ EC grade 2 **Age:** _____

APPENDIX C

PILL DIARY

Dosing Instructions:	Take one (1) tablet by mouth daily (at approximately the same time each day) after a meal. Do not chew, cut or crush the tablets. Do not take on an empty stomach. If you miss a dose, take it with your next meal on the same day within 8 hours. Do not make up a dose by taking two doses in one day.
Important Reminders:	• It is very important that you notify the study staff prior to having any medical tests or scans so they can advise you on any changes you need to make in your study medication dosing. • Check with study staff before taking any new medications to be sure the medication is safe to take with your study medication. • Report any medications (prescription, over-the-counter, vitamin/mineral or herbal supplements) taken. You can keep track of periodic use of medications in the comments section of this Pill Diary.
Instructions for Completing the Pill Diary:	• Record the date and time, you take your dose each day and initial each entry. • In the Comments column: o List any side effects or symptoms noticed. o List any new medications taken and reason for taking. o If you missed a dose, indicate why. o Make a note if you've lost any pills o Include any additional information you would like to note.

DO NOT THROW AWAY YOUR PILL BOTTLE!

BRING IT ALONG WITH THIS PILL DIARY TO YOUR NEXT STUDY VISIT.

DAY	DATE	TIME	COMMENTS	INITIALS
1				
2				
3				
4				

5				
6				
7				
8				
9				
10				
11				
12				
13				
14				
15				
16				
17				
18				
19				
20				
21				
22				
23				
24				
25				
26				
27				
28				

29				
30				
31				
32				
33				
34				
35				
36				
37				
38				
39				
40				
41				
42				

Verification of review of Pill Diary	
I reviewed this Pill Diary with the participant	_____ __ __/__ __/__ __ __ __ (Reviewer's signature) (Date)
I verify that the information on this Pill Diary is correct.	_____ __ __/__ __/__ __ __ __ (Participant's signature) (Date)
Document discrepancies in number of capsules expected to be taken vs number actually taken in the visit notes.	

APPENDIX D

Tampon Insertion/Collection Instruction Sheet

When to use the Tampon:
If your appointment is in the morning, (7am-12pm), place this tampon the night before coming to clinic (up to 8-12 hours before you see the physician). If your appointment is in the afternoon (1pm-5pm), place this tampon first thing in the morning (preferably 8 hours before your appointment)

How to Insert a Tampon:

1. Wash your hands thoroughly with soap and water and then unwrap the tampon. The slim applicator tip should be rounded and strings should hang out the bottom of the Anti-Slip Grip Applicator. Gently pull on strings to make sure they are firmly attached. If you notice any flaws, do not use.

2. Get comfortable. Try sitting on the toilet with knees apart or standing with one foot on the toilet seat.

3. Gently insert the tampon applicator into your vagina: hold the Anti-Slip Grip applicator plunger using your thumb and middle finger. Place the applicator tip into your vagina at a 45˚ angle. Now, gently slide the smooth, tapered applicator all the way into your vagina until your fingers touch your body.

4. Push the tampon inside: push the plunger all the way into the barrel with your pointer finger. This will release the tampon. The plunger should now be inside the barrel. Still holding the Anti-slip grip applicator plunger, gently pull out the two-piece applicator. The tampon should now be comfortably inside you with the strings outside your body.

5. After you have inserted the tampon, place the used applicator back into the discreet wrapper and throw away. DO NOT FLUSH THE PLASTIC APPLICATOR.

6. Any discomfort? The tampon may not be far enough inside. If this happens, just remove the tampon and try again with a new one. You shouldn't feel any discomfort when the tampon is correctly in place.

7. **Removal:** The physician will remove it at your clinic visit. If the tampon falls out, or you feel that it needs to be removed, please dispose of the used tampon, place a new one in your vagina and make a note of when the tampon was replaced.

Time of Tampon insertion: _____ AM / PM	**Initial and Date: _____**

APPENDIX E

UWI2016-08-01 Pilot Study of Daily Exemestane in Women with Complex Atypical Hyperplasia of the Endometrium / Endometrial Intraepithelial Neoplasia or Low Grade Endometrial Cancer	PID#: __ __ __ __ __ __ __ Date: __ __/__ __/__ __ __ __

TOBACCO ASSESSMENT – BASELINE

Instructions:
When a number is requested in the response, please enter a whole number (i.e. "4") and not a range or fraction of a number.

Section A. Basic Cigarette Use Information

1. Have you smoked at least 100 cigarettes (5 packs = 100 cigarettes) in your entire life?

☐ Yes
☐ No → **Skip to Section B**
☐ Don't know/Not sure → **Skip to Section B**

2. How old were you when you first smoked a cigarette (even one or two puffs)?
_____ Years old

3. How old were you when you first began smoking cigarettes regularly?

_____ Years old
☐ Check here if you have never smoked cigarettes regularly.

4. How many total years have you smoked (or did you smoke) cigarettes? Do not count any time you may have stayed off cigarettes.

_____ Years (If you smoked less than one year, write "1.")

5. On average when you have smoked, about how many cigarettes do you (or did you) smoke a day? (A pack usually has 20 cigarettes in it).

_____ Number of cigarettes per day

6. Do you NOW smoke cigarettes?
☐ Everyday
☐ Some days
☐ Not at all → **Skip to question 8**

7. How soon after you wake up do you smoke your first cigarette?
☐ Within 30 minutes
☐ After 30 minutes

UWI2016-08-01 Pilot Study of Daily Exemestane in Women with Complex Atypical Hyperplasia of the Endometrium / Endometrial Intraepithelial Neoplasia or Low Grade Endometrial Cancer	PID#: __ __ __ __ __ __ __ Date: __ __/__ __/__ __ __ __

8. How long has it been since you last smoked a cigarette (even one or two puffs)?

First check which one of the following choices applies to you. Then, if applicable, write a number on the line for how many days, weeks, months, or years it has been since your last cigarette.

☐ I smoked a cigarette today (at least one puff)
☐ 1-7 days → Number of days since last cigarette _____
☐ Less than 1 month → Number of weeks since last cigarette _____
☐ Less than 1 year → Number of months since last cigarette _____
☐ More than 1 year → Number of years since last cigarette _____
☐ Don't know/Don't remember

Section B. Use of Other Forms of Tobacco

9. Have you ever used other forms of tobacco, not including cigarettes?

☐ Yes
☐ No → **Skip to Section C**

10. How often do you/did you use other forms of tobacco?

☐ Every day → Number of times per day _____
☐ Some days → Number of days _____ per ☐ Week ☐ Month ☐ Year

11. Which of the following products have you ever used regularly?
Check all that apply

☐ Cigarettes
☐ E-cigarettes or other electronic nicotine delivery system
☐ Traditional cigars, cigarillos or filtered cigars
☐ Pipes
☐ Waterpipe
☐ Hookah
☐ Clove cigarettes or kreteks
☐ Bidis
☐ Smokeless tobacco, like dip, chew, or snuff
☐ Snus
☐ Paan with tobacco, gutka, zarda, khaini
☐ Other, Please specify:_____

UWI2016-08-01 Pilot Study of Daily Exemestane in Women with Complex Atypical Hyperplasia of the Endometrium / Endometrial Intraepithelial Neoplasia or Low Grade Endometrial Cancer	PID#: __ __ __ __ __ __ __ Date: __ __/__ __/__ __ __ __

12. If you do not currently use other forms of tobacco, but did in the past, how long has it been since you last used other forms of tobacco regularly?

- ☐ Within the past month (0 to 1 month ago)
- ☐ Between 1 and 3 months (1 to 3 months ago)
- ☐ Between 3 and 6 months (3 to 6 months ago)
- ☐ Between 6 and 12 months (6 to 12 months ago)
- ☐ Between 1 and 5 years (1 to 5 years ago)
- ☐ Between 5 and 15 years (5 to 15 years ago)
- ☐ More than 15 years ago
- ☐ Don't know/Not sure
- ☐ Never used other forms of tobacco regularly

Section C. Second-Hand Smoke Exposure

13. Are you currently living with a smoker?

- ☐ Yes
- ☐ No

14. In the past 30 days, have you lived in a place where other people smoked cigarettes indoors?

- ☐ Yes
- ☐ No

15. In the past 30 days, have you worked in a place where other people smoked cigarettes indoors?

- ☐ Yes
- ☐ No

16. Thinking of all your childhood and adult years, have you ever lived in a place where other people smoked cigarettes indoors?

- ☐ Yes → In total, for about how many years? _____ If less than 1, write "1."
- ☐ No

UWI2016-08-01 Pilot Study of Daily Exemestane in Women with Complex Atypical Hyperplasia of the Endometrium / Endometrial Intraepithelial Neoplasia or Low Grade Endometrial Cancer	PID#: __ __ __ __ __ __ __ Date: __ __/__ __/__ __ __ __

17. Thinking of all the years you have worked, have you ever worked in a place where other people smoked cigarettes indoors?

☐ Yes → In total, for about how many years? _____ If less than 1, write "1."
☐ No

This assessment was completed by: ☐ Study Team Member ☐ Participant

Completed By: _____ Date __ __ / __ __ / __ __ __ __
(Signature of person completing) *(MM/DD/YYYY)*

Completed By: _____
(Printed name of person completing)

UWI2016-08-01 Pilot Study of Daily Exemestane in Women with Complex Atypical Hyperplasia of the Endometrium / Endometrial Intraepithelial Neoplasia or Low Grade Endometrial Cancer	PID#: __ __ __ __ __ __ __ Date: __ __/__ __/__ __ __ __

TOBACCO ASSESSMENT - FOLLOW-UP

Instructions:
When a number is requested in the response, please enter a whole number (i.e. "4") and not a range or fraction of a number.

1. Do you NOW smoke cigarettes?

☐ Everyday
☐ Some days
☐ Not at all → **Skip to Question 3.**
☐ Never Smoked → **Skip to Question 4.**

2. On average, when you smoked, about how many cigarettes do you (or did you) smoke a day? (A pack usually has 20 cigarettes in it).

_____ Number of cigarettes per day

3. How long has it been since you last smoked a cigarette (even one or two puffs)?

First check which one of the following choices applies to you. Then, if applicable, write a number on the line for how many days, weeks, months, or years it has been since your last cigarette.

☐ I smoked a cigarette today (at least one puff)
☐ 1-7 days → Number of days since last cigarette _____
☐ Less than 1 month → Number of weeks since last cigarette _____
☐ Less than 1 year → Number of months since last cigarette _____
☐ More than 1 year → Number of years since last cigarette _____
☐ Don't know/Don't remember

4. Since your last visit, have you used other forms of tobacco, not including cigarettes?

☐ Yes
☐ No (**End)**

5. How often do you/did you use other forms of tobacco?
☐ Every day → Number of times per day _____
☐ Some days → Number of days _____ per ☐ Week ☐ Month ☐ Year

UWI2016-08-01 Pilot Study of Daily Exemestane in Women with Complex Atypical Hyperplasia of the Endometrium / Endometrial Intraepithelial Neoplasia or Low Grade Endometrial Cancer	PID#: __ __ __ __ __ __ __ Date: __ __/__ __/__ __ __ __

6. Since your last visit, which of the following products have you used? ***Check all that apply***

- ☐ Cigarettes
- ☐ E-cigarettes or other electronic nicotine delivery system
- ☐ Traditional cigars, cigarillos or filtered cigars
- ☐ Pipes
- ☐ Waterpipe
- ☐ Hookah
- ☐ Clove cigarettes or kreteks
- ☐ Bidis
- ☐ Smokeless tobacco, like dip, chew, or snuff
- ☐ Snus
- ☐ Paan with tobacco, gutka, zarda, khaini
- ☐ Other, Specify _____

7. If you do not currently use other forms of tobacco, but did in the past, how long has it been since you last used other forms of tobacco regularly?
   - ☐ Within the past month (0 to 1 month ago)
   - ☐ Between 1 and 3 months (1 to 3 months ago)
   - ☐ Between 3 and 6 months (3 to 6 months ago)
   - ☐ Between 6 and 12 months (6 to 12 months ago)
   - ☐ Between 1 and 5 years (1 to 5 years ago)
   - ☐ Between 5 and 15 years (5 to 15 years ago)
   - ☐ More than 15 years ago
   - ☐ Don't know/Not sure
   - ☐ Never used other forms of tobacco regularly

The following instructions pertain to questions 8 - 10. During each of the following time frames, please indicate whether you smoked cigarettes every day, some days, or not at all.

8. During study treatment

- ☐ Smoked every day
- ☐ Smoked some days
- ☐ Did not smoke at all
- ☐ Don't know/not sure
- ☐ Not applicable

UWI2016-08-01 Pilot Study of Daily Exemestane in Women with Complex Atypical Hyperplasia of the Endometrium / Endometrial Intraepithelial Neoplasia or Low Grade Endometrial Cancer	PID#: __ __ __ __ __ __ __ Date: __ __/__ __/__ __ __ __

9. After the end of study treatment

- ☐ Smoked every day
- ☐ Smoked some days
- ☐ Did not smoke at all
- ☐ Don't know/not sure
- ☐ Not applicable (I have not completed the study treatment)

10. Since your last visit to this clinic

- ☐ Smoked every day
- ☐ Smoked some days
- ☐ Did not smoke at all
- ☐ Don't know/not sure

This assessment was completed by: ☐ Study Team Member ☐ Participant

Completed By: _____ Date __ __ / __ __ / __ __ __ __
(Signature of person completing) *(MM/DD/YYYY)*

Completed By: _____
(Printed name of person completing)

UWI2016-08-01 Pilot Study of Daily Exemestane in Women with Complex Atypical Hyperplasia of the Endometrium / Endometrial Intraepithelial Neoplasia or Low Grade Endometrial Cancer	PID#: __ __ __ __ __ __ __ Date: __ __/__ __/__ __ __ __

ALCOHOL ASSESSMENT – BASELINE

Instructions:

For the following questions about drinking alcoholic beverages, a drink means a 12 oz. beer, a 5 oz. glass of wine, or one and a half ounces of liquor.

When a number is requested in the response, please enter a whole number (i.e. "4") and not a range or fraction of a number.

1. In your entire life, have you had at least 12 drinks of any kind of alcoholic beverage?

   ☐ Yes
   ☐ No **(End)**
   ☐ Refused **(End)**
   ☐ Don't know/Not sure

2. In the past 12 months, on average, how often did you drink any type of alcoholic beverage?
   _____ (Enter the number of days you drank based on the timeframe checked below. Enter 0 if you never drank and skip to Question 6.)

   ☐ Week
   ☐ Month
   ☐ Year
   ☐ Refused
   ☐ Don't know/Not sure

3. In the past 12 months, on those days that you drank alcoholic beverages, on average, how many drinks did you have per day?
   _____ (Enter the average number of drinks per day)

   ☐ Refused
   ☐ Don't know/Not sure

4. In the past 12 months, on how many days did you have 5 or more drinks of any alcoholic beverage?

   _____ (Enter the number of days you had 5 or more drinks, or enter 0 if none.)

   ☐ Refused
   ☐ Don't know/Not sure

UWI2016-08-01 Pilot Study of Daily Exemestane in Women with Complex Atypical Hyperplasia of the Endometrium / Endometrial Intraepithelial Neoplasia or Low Grade Endometrial Cancer	PID#: __ __ __ __ __ __ __ Date: __ __/__ __/__ __ __ __

5. Was there ever a time or times in your life when you drank 5 or more drinks of any kind of alcoholic beverage almost every day?

   ☐ Yes
   ☐ No
   ☐ Refused
   ☐ Don't know/Not sure

6. If you do not currently drink alcoholic beverages, but did in the past, how long has it been since you last drank regularly?

   ☐ Within the past month (0 to 1 month ago)
   ☐ Between 1 and 3 months (1 to 3 months ago)
   ☐ Between 3 and 6 months (3 to 6 months ago)
   ☐ Between 6 and 12 months (6 to 12 months ago)
   ☐ Between 1 and 5 years (1 to 5 years ago)
   ☐ Between 5 and 15 years (5 to 15 years ago)
   ☐ More than 15 years ago
   ☐ Don't know/Not sure
   ☐ Never drank regularly

7. At the heaviest point, either now or in the past, on the days when you drank, about how many drinks did you drink a day on the average?

   _____ (Enter the number of drinks a day)

   ☐ Refused
   ☐ Don't know/Not sure

8. How many years have you been drinking (or did drink) regularly?

   _____ years

   ☐ Refused
   ☐ Don't know/Not sure

UWI2016-08-01 Pilot Study of Daily Exemestane in Women with Complex Atypical Hyperplasia of the Endometrium / Endometrial Intraepithelial Neoplasia or Low Grade Endometrial Cancer	PID#: __ __ __ __ __ __ __ Date: __ __/__ __/__ __ __ __

9. At what age did you begin drinking regularly?

_____ years of age

☐ Refused
☐ Don't know/Not sure

10. What type(s) of alcohol do you drink? (Mark ALL that apply)

☐ Wine
☐ Liquor
☐ Beer
☐ Wine cooler

This assessment was completed by: ☐ Study Team Member ☐ Participant

Completed By: _____ Date __ __ / __ __ / __ __ __ __
(Signature of person completing) *(MM/DD/YYYY)*

Completed By: _____
(Printed name of person completing)

UWI2016-08-01 Pilot Study of Daily Exemestane in Women with Complex Atypical Hyperplasia of the Endometrium / Endometrial Intraepithelial Neoplasia or Low Grade Endometrial Cancer	PID#: __ __ __ __ __ __ __ Date: __ __/__ __/__ __ __ __

ALCOHOL ASSESSMENT - FOLLOW-UP

Instructions:
For the following questions about drinking alcoholic beverages, a drink means a 12 oz. beer, a 5 oz. glass of wine, or one and a half ounces of liquor.

When a number is requested in the response, please enter a whole number (i.e. "4") and not a range or fraction of a number.

1. During the past 30 days, did you drink any alcoholic beverages?

   ☐ Yes
   ☐ No **(End)**
   ☐ Refused **(End)**
   ☐ Don't know/Not sure

2. During the past 30 days, how many days per week or per month did you drink any alcoholic beverages, on the average?
   _____ (Enter number of days you drank based on the timeframe checked below. Enter 0 if you did not drink.)

   ☐ Week
   ☐ Month
   ☐ Refused
   ☐ Don't know/Not sure

3. On the days when you drank, on average, about how many drinks did you have?
   _____ (Enter the average number of drinks you had per day.)

   ☐ Refused
   ☐ Don't know/Not sure

4. In the past 30 days, on how many days did you have 5 or more drinks per day?
   _____(Enter the number of days you had 5 or more drinks, or enter 0 if none)

   ☐ Refused
   ☐ Do not know/Not sure

This assessment was completed by: ☐ Study Team Member ☐ Participant

Completed By: _____ Date __ __ / __ __ / __ __ __ __
(Signature of person completing) *(MM/DD/YYYY)*

Completed By: _____
(Printed name of person completing)