CITY OF HOPE MEDICAL CENTER
1500 E. DUARTE ROAD
DUARTE, CA 91010

DEPARTMENT OF SURGERY/DIVISION OF GYNECOLOGIC ONCOLOGY

TITLE: Open-Label Randomized Phase II Trial of Megestrol Acetate with or without Pterostilbene in Patients with Endometrial Cancer Scheduled for Hysterectomy

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SITE: Uterus
STAGE (If applicable): Any
MODALITY: Hormonal Therapy vs Hormonal Therapy with Antioxidant
TYPE: Phase II

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Clinical Trial Protocol

Open-Label Randomized Phase II Trial of Megestrol Acetate with or without Pterostilbene in Patients with Endometrial Cancer Scheduled for Hysterectomy

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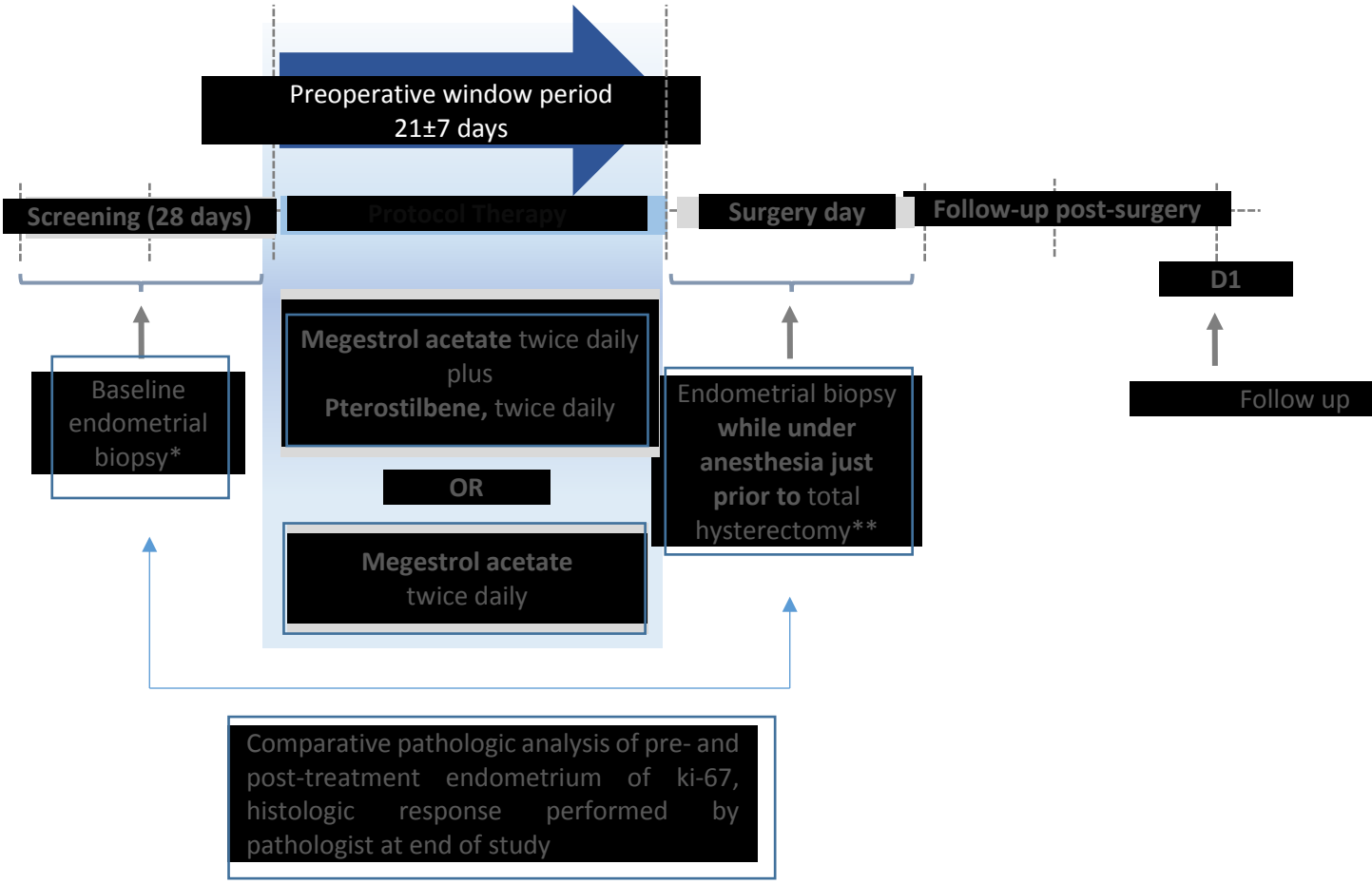
EXPERIMENTAL DESIGN SCHEMA

Endometrial cancer patients scheduled for hysterectomy and about to enter preoperative window period

Phase 2 (randomized 2-arm) = 36 evaluable participants (18 per arm)



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1.0 OBJECTIVES

This is an open-label Phase II randomized controlled trial of neoadjuvant therapy during the preoperative window period with megestrol acetate (MA) ± pterostilbene (PTE) in patients with endometrial cancer (EC) or endometrial complex atypical hyperplasia who are scheduled to undergo total hysterectomy. The study will compare the effect of MA plus PTE versus MA alone on tumor proliferation and histologic response during the preoperative window.

1.1 Primary Objective

- Determine the effect of MA plus PTE versus MA alone on tumor proliferation (Ki-67) during the preoperative window in patients with EC or endometrial complex atypical hyperplasia who are scheduled for hysterectomy. We will compare the treatment-associated change in tumor Ki-67 proliferation index between the two treatment arms (MA plus PTE versus MA alone) using endometrial tumor samples obtained before and after treatment.

1.2 Exploratory Objectives

- Determine the effect of MA plus PTE versus MA alone on histologic response during the preoperative window in patients with EC or endometrial complex atypical hyperplasia who are scheduled for hysterectomy. We will compare the treatment-associated change in markers of histologic response, growth, and apoptosis between the two treatment arms (MA plus PTE versus MA alone) using endometrial tumor samples obtained before and after treatment.
- Explore biological characteristics of tumors to determine potential biomarkers which could select for treatment eligibility in future studies.

2.0 BACKGROUND

2.1 Introduction/Rationale for Development

Endometrial cancer (EC) is the fourth most common cancer among U.S. women, with over 60,000 new diagnoses and 10,000 deaths per year in the U.S [1]. Unfortunately, its incidence and mortality have risen over the past decade. While early stage EC is frequently curable, up to a third of all endometrial cancer patients present with regional or distant metastases, with associated 5-year survival rates of 69% and 17%, respectively. Moreover, recurrent metastatic endometrial cancer is an incurable malignancy with an anticipated median overall survival (OS) of less than 15 months with currently available therapies [2, 3]. The most active chemotherapy agents in endometrial cancer are cisplatin/carboplatin, taxanes, and adriamycin [2, 4]. Limited options exist for women with recurrent endometrial cancer after platinum-based systemic therapy. Recent trials have shown that selected biologic targeted agents have modest to moderate activity in this setting (particularly bevacizumab and mTor/PI3K inhibitors) [5-8].

Unopposed estrogen signaling has been implicated as a driver both in the etiology and in the progression of type I EC, and progestins play an important role in the management of ER+/PR+ endometrial tumors [9]. Progestins induce cellular differentiation and remain the most active hormonal intervention for EC. The observed response rates of progestins in metastatic and recurrent EC patients ranges from 17% to 33%, with median progression free survival (PFS) of 3-4 months and OS of 11-13 months [10-12]. As progestins are generally well tolerated, there is **interest in optimizing their use** by designing **rational combinations** to exploit synergy with other pathway inhibitors and by identifying **select populations** likely

to benefit. Specifically, the comorbid patient population that is affected by recurrent EC would benefit from an agent with low toxicity profiles. We have therefore explored the therapeutic effects of **natural antioxidants** such as **pterostilbene (PTE)**, which possesses significant anti-tumor activity in numerous solid tumors [13-16]. Pterostilbene may represent a low-cost, low-toxicity addition or alternative to progestin therapy in metastatic and recurrent EC.

2.2 Phytochemicals and Cancer

Phytochemicals are chemical compounds produced by plants and include polyphenols, taxol analogues, and vinca alkaloids, the latter two of which are well-established chemotherapies in solid tumors, including ovarian cancer. Natural polyphenols are organic chemicals that contain phenol units in their structures. These include resveratrol, curcumin, pterostilbene, genistein, and quercetin. These compounds have also shown antitumor activity. To date, clinical trials testing polyphenols in cancer have included curcumin, EGCG (epigallocatechin gallate), genistein, and resveratrol. Evidence supports the advancement of EGCG into phase III trials in prostate cancer and cervical dysplasia. Current Phase III trials of curcumin in combination with gemcitabine and celebrex for colon cancer and pancreatic cancer are in development based on promising Phase I and II results. [17] Thus, there is growing evidence for the rationale of natural polyphenols in the treatment of solid malignancies.

2.3 Biological Rationale: Pterostilbene and Megestrol Acetate

Most natural polyphenols are subject to rapid in vivo metabolism. Therefore, polyphenols with superior pharmacokinetic profiles that also possess *in viv*o antitumor effects are attractive agents in cancer therapy. Pterostilbene (trans-3,5-dimethoxy-4-hydroxystilbene) is a naturally derived non-flavenoid polyphenol with a structure similar to resveratrol. It is the primary antioxidant in blueberries and a natural dietary supplement. Comparative pharmacokinetic studies in rats comparing PTE with resveratrol demonstrated markedly higher peak serum concentration and AUC values, as well as a several-fold higher oral bioavailability in PTE compared to resveratrol. [18] Moreover, the plasma levels of PTE metabolites were also greater than those of resveratrol, leading to a superior pharmacokinetic profile following equimolar dose administration.

The anti-tumor effects of PTE have been demonstrated in numerous solid tumors, including breast, prostate, and stomach cancer. Pterostilbene exerts its anticarcinogenic effect through induction of apoptosis and inhibition of cell proliferation, and these effects have been extensively observed *in vitro* and are supported by tumor models *in vivo*. Additionally, PTE inhibits oxidative stress and inflammatory enzymes. [19]

Endometrial cancer is a hormonally responsive neoplasm, and progestational therapies such as MA play an important role in the treatment of estrogen receptor positive (ER+) ECs, with a 20-30% response rate in metasta tic EC patients. Similarly, endometrial hyperplasia represents a precursor of endometrial cancer, and medical therapy consists of progestins. As progestins are generally well tolerated, there is interest in optimizing their use by designing rational combinations to exploit synergy with other pathway inhibitors and by identifying select populations likely to benefit. Specifically, the comorbid patient population that is affected by recurrent and metastatic EC would benefit from therapies with low toxicity profiles. We have therefore explored the synergistic combinations of the PTE with MA.

Preclinical studies by our group demonstrate antiproliferative effects of PTE and MA in EC cells [20]. Pterostilbene markedly reduced viability in two EC cell lines, and an additive effect was observed when PTE was used in combination with MA. Moreover, this combination exerted significant effects on cell survival and cell cycle regulation by markedly increasing cleavage of caspase 3 and greatly reducing expression of cell survival proteins bcl-2 and bcl-xl as well as cell cycle regulators cyclin D1, cycling B1 and

CDK4. *In vivo*, **the combination of PTE and MA produced additive effects to significantly suppress tumor growth in a xenograft mouse model** of EC.

2.4 Clinical Experience: Pterostilbene

To date, the safety of PTE in humans has been evaluated in a single trial as monotherapy in patients with hyperlipidemia. A randomized, double-blind, placebo-controlled trial (n=80) of PTE 100 mg to 250 mg daily for 6-8 weeks [21, 22] concluded that PTE is safe for use in humans with a MTD of up to 250 mg daily. Mild increases in LDL were observed in subjects treated with PTE regardless of dose, with attenuation of the increase in patients who were already on lipid-lowering medications; in contrast, no changes to HDL, triglycerides, or overall atherosclerotic cardiovascular disease score were observed regardless of dose.

2.5 Clinical Experience: Megestrol Acetate

Progestins induce cellular differentiation and remain the most active hormonal intervention for EC. The observed response rates of progestins such as megestrol acetate in metastatic and recurrent EC patients ranges from 17% to 33%, the median PFS was 3-4 months and OS was 11-13 months. [10-12]

2.6 Clinical Experience: Pterostilbene with Megestrol Acetate

To date, no prior clinical studies have investigated the safety or efficacy of the combination of MA and PTE.

2.7 Overview and Rationale of Study Design

This is a Phase II randomized controlled trial of neoadjuvant therapy during the preoperative window period with MA ± PTE in patients with EC who are scheduled to undergo total hysterectomy. The study will compare the effect of MA plus PTE versus MA alone on tumor proliferation and histologic response during the preoperative window.

The endpoints were chosen based on a previous neoadjuvant phase 0 study, GOG 211 [23], where 75 women with endometrioid EC were administered a daily dose of medroxyprogesterone acetate (MPA) for three weeks, followed by total hysterectomy. Preoperative endometrial biopsies and post-MPA hysterectomy specimens were compared to evaluate for a subjective histologic response and effect on growth and apoptosis.

Of 59 women who received progestins, 64% histologic response was noted following 21 days of daily MPA, with 2% resulting in a complete histologic response. Subjective histologic response as evaluated by a single pathologist was defined as decreased nuclear grade, mitotic figures, nucleoli, and gland cellularity, and increased eosinophilic cytoplasm, secretion, and squamous metaplasia. Secondary endpoints in this study included Ki-67, Bcl-2, Casp3, ER, PR, and PR-beta expression. The primary endpoint of the proposed trial was chosen based on data from GOG 211, where a 34.8% reduction in Ki-67 was reported following two weeks of treatment. Histologically confirmed EC or endometrial complex atypical hyperplasia patients who are scheduled for total hysterectomy and about to initiate the preoperative window period will be eligible for the trial. Participants must be naïve to prior chemotherapy EC. Since endometrial hyperplasia and endometrial cancer represent a continuum of disease progression, a risk of occult endometrial cancer of up to 42% exists in patients with diagnoses of endometrial complex atypical, as preoperative endometrial sampling can miss occult endometrial cancer. Therefore, patients with endometrial complex atypical hyperplasia are included in this study.

The approximate date of scheduled surgery (± 7 days) will define the duration of the preoperative window period and therefore, protocol therapy. Treatment will last 3 weeks ± 7 days, depending on planned surgery date. MA will be given 80 mg twice daily, with or without PTE, which will be given orally 100 mg twice daily. The dosing and schedule is consistent with prior clinical experience. [23, 24] Participants will end treatment the day before the scheduled surgery.

Serial endometrial samples will be collected (see **Section 8.0**). We plan to examine histologic and immunohistochemical measures of growth and apoptosis, including Ki-67, gland cellularity, nuclear grade, nucleoli, metaplasia, secretion, Bcl-2, and Casp3 to evaluate the effectiveness of MA plus PTE versus MA alone. Furthermore, we will identify biological characteristics of tumors (e.g. ER and progesterone receptor [PR] status, MMR status, PI3K mutational status, etc) that may correlate with histologic response to treatment.

3.0 ELIGIBILITY CRITERIA

Participants **must meet all of the following criteria** on screening examination to be eligible to participate in the study:

3.1 Inclusion Criteria

Informed Consent and Willingness to Participate

1. Documented informed consent of the participant and/or legally authorized representative.
2. Willing to undergo an intraoperative biopsy/or standard of care tissue collection during surgery, following completion of treatment with MA ± PTE.
3. Age ≥ 18 years.
4. ECOG performance status of 0-2 (**Appendix A**).
5. Histologically confirmed EC or complex atypical hyperplasia of the endometrium.
6. Candidate for a total hysterectomy with or without bilateral salpingo-oophorectomy.
7. About to initiate preoperative window period, with planned hysterectomy scheduled.
8. Platelets ≥ 100, 000/mm3
9. NOTE: Platelet transfusions are not permitted within 14 days of platelet assessment unless cytopenia is secondary to disease involvement.
10. Total bilirubin ≤ 1.5 X ULN
11. AST ≤ 1.5 x ULN
12. ALT ≤ 1.5 x ULN
13. Creatinine clearance of ≥ 60 mL/min per 24 hour urine test or the Cockcroft-Gault formula or

$$\text{CrCl (mL/min)} = \frac{(140\text{-age}) \times \text{actual body weight (kg)}}{72 \times \text{serum creatinine (mg/dL)}} \times 0.85 \text{ for females}$$

Or

$$\text{CrCl (mL/min)} = \frac{(140\text{-age}) \times \text{actual body weight (kg)}}{0.8136 \times \text{serum creatinine (umol/L)}} \times 0.85 \text{ for females}$$

14. **Women of childbearing potential**: negative urine or serum pregnancy test in premenopausal women. Postmenopausal women do not need to undergo a pregnancy test. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.

3.2 Exclusion Criteria

Prior and concomitant therapies

1. Pterostilbene supplements within 30 days prior to Day 1 of protocol therapy.
2. Any of the following phytochemical-based supplements within 30 days prior to Day 1 of protocol therapy: resveratrol, genistein, and quercetin.
3. Chemotherapy for EC.

Other Illnesses and Conditions

1. Allergic reaction/hypersensitivity to similar agents, excipients
2. Unstable cardiac disease as defined by one of the following:
    a. Cardiac events such as myocardial infarction (MI) within the past 6 months.
    b. NYHA (New York Heart Association) heart failure class III-IV (**Appendix B**).
    c. Uncontrolled atrial fibrillation or hypertensive emergency/urgency (defined as systolic blood pressure ≥180 mmHg and/or diastolic blood pressure ≥120 mmHg).
3. Active or history of recent thromboembolism or stroke, within the past 6 months.
4. Cushing's syndrome
5. Acute infection requiring systemic (intravenous) treatment
6. Known history of HIV infection
7. Known active Hepatitis B or C infection
8. Inability to swallow tablets/capsules
9. Any other condition that would, in the Investigator's judgment, contraindicate the patient's participation in the clinical study due to safety concerns or compliance with clinical study procedures, e.g., infection/inflammation, intestinal obstruction, unable to swallow medication, social/ psychological issues, etc.

Noncompliance

1. Prospective participants who, in the opinion of the investigator, may not be able to comply with all study procedures (including compliance issues related to feasibility/logistics).

3.3 Women and Minorities

The study is open to anyone regardless of race or ethnicity. Efforts will be made to extend the accrual to a representative population. If differences in outcome that correlate to racial or ethnic identity are noted, accrual may be expanded or additional studies may be performed to investigate those differences more fully.

4.0 PARTICIPANT ENROLLMENT

4.1 Pre-Enrollment Informed Consent and Screening Procedures

Diagnostic or laboratory studies performed exclusively to determine eligibility will be done only after obtaining written informed consent. Studies or procedures that are performed for clinical indications (not exclusively to determine study eligibility) may be used for baseline values and/or to determine pre-eligibility, even if the studies were done before informed consent was obtained. The informed consent process is to be fully documented (see **Section 16.4**), and the prospective participant must receive a copy of the signed informed consent document. Screening procedures are listed in **Section 9.0**.

4.2 Participant Enrollment

Eligible participants will be registered on the study through the Clinical Trials Office at City of Hope. CTO staff are **available between the hours of 8:00 a.m. and 5:00 p.m. PST, Monday through Friday (except holidays).**

Phone: (626) 256-4673 ext. 83015

E-mail: rtinsley@coh.org

4.3 Slot Verification and Reservation

Designated study staff should call the CTO to verify current slot availability, and to reserve a slot for a specific prospective subject. Slots can only be held for a limited time.

4.4 Registration Process

To register a participant, the subsequent procedure is to be followed.

The data manager/coordinator/research nurse complete the following:

- Completed Eligibility Criteria List (**Section 3.0** of the protocol)
- Source documentation to support eligibility criteria**
- Signed informed consent document
- Signed HIPAA authorization form (if separate from the informed consent document)
- Signed subject's Bill of Rights

** Provide copies of source documentation only if not readily available as a finalized record in a COH Electronic Health Record (EHR).

1. Once eligibility has been confirmed, CTO staff will register the participant by: assigning a subject accession number, registering the subject on study centrally into the COH clinical trials management system for non-COH participants, and enter the subject into the eCRF system.

4.5 Screen Failures and Registered Participants who do not begin Study Treatment

Issues that would cause treatment delays should be discussed with the Principal Investigator.

5.0 TREATMENT PROGRAM

5.1 Treatment Program Overview

This is a randomized Phase II trial of neoadjuvant MA ± PTE during the preoperative window period for patients with endometrioid EC or endometrial complex atypical hyperplasia who are scheduled to undergo total hysterectomy.

For a detailed tabular view of the treatment, monitoring and follow-up schedule, see the Study Calendar (**Section 9.0**).

5.2 Duration of Treatment and Day Count

Day 1 is defined by the administration of MA ± PTE.

The approximate date of scheduled surgery will define the duration of the preoperative window period and therefore, protocol therapy. Study treatment will last 3 weeks (+/- 7 days), depending on the timing of surgery. Protocol therapy will end the day before the scheduled surgery.

5.3 Agent Administration

5.3.1 Pterostilbene

When *combined* with MA, the morning PTE dose will be taken first on Day 1.

Participants will be instructed to take PTE 100 mg twice daily at approximately 12 hours apart with a glass of water. The capsules should not be opened, broken or chewed. The capsules should be swallowed whole.

If a participant misses a dose and > 4 hours have passed since the scheduled dose time, the missed dose will be skipped and will not be made up.

If a PTE dose is vomited wait until the next scheduled dose; any vomited doses should not be made up.

Participants will be given a drug diary to document each dose of PTE that is taken or missed.

PTE-related AEs are outlined in **Section 6.1**.

5.3.2 Megestrol acetate

When *combined* with PTE, the morning MA dose will be taken after PTE on Day 1.

When taken alone (without PTE), the morning MA dose will be taken first on Day 1.

Participants will be instructed to take MA 80 mg twice daily at approximately 12 hours apart with a glass of water. The tablets should not be opened, broken or chewed. The tablets should be swallowed whole.

If a participant misses a dose and > 4 hours have passed since the scheduled dose time, the missed dose will be skipped and will not be made up.

If a MA dose is vomited wait until the next scheduled dose; any vomited doses should not be made up.

Participants will be given a drug diary to document each dose of MA that is taken or missed.

MA-related AEs are outlined in **Section 6.2**.

5.4 Assessments and Special Monitoring

Section 9.0 summarizes the trial procedures to be performed. It may be necessary to perform study procedures at unscheduled time points if deemed clinically necessary by the investigator.

5.5 Duration of Therapy and Criteria for Removal from Protocol Therapy

Participants will receive protocol therapy until one of the below criteria are met:

Completed protocol therapy during planned preoperative window period (3 weeks +/- 7 days), until the day before surgery.

Participant is deemed intolerant to protocol therapy because of toxicity, despite dose modification/ delay.

Note: If one agent is discontinued due to toxicity, then all therapies will be discontinued.

General or specific changes in the patient's condition which render the patient unacceptable for further treatment in the judgment of the investigator.

Withdrawal of consent for further protocol therapy (See **Section 16.5**).

When participant completes protocol therapy (or if participant meet criteria for removal from protocol therapy) the participant will proceed to surgery as scheduled (**Section 5.6**).

Documentation of the reason for discontinuing protocol therapy and the date effective should be made in the medical record and appropriate eCRF. The COH DCC and the Study PI should be promptly notified of the change in participant status.

In the case of a surgery delay, patients may stop the protocol therapy up to 14 days prior to surgery.

5.6 Surgery

Participants who end the window period will proceed to standard of care total hysterectomy, with or without bilateral salpingo-oophorectomy. Route of surgery (e.g. open versus robotic laparoscopic versus laparoscopic versus vaginal hysterectomy) will be up to the discretion of the treating surgeon. Staging procedures (pelvic and/or para-aortic lymphadenectomies and/or omentectomy) will be at the discretion of the treating surgeon. Note: The procedure can be performed at an institution outside of COH, and tissue will be collected as per standard of care. Blocks or slides of the endometrial tumor from the hysterectomy specimen will then be requested following surgery by the research team.

Post-surgery, participants will enter follow-up (**Section 5.7**).

Assessment time points and windows are detailed in **Section 9.0**.

5.7 Follow-Up

All participants will enter post-surgery follow-up. This is comprised of post-surgery visit at: 6 weeks (± 14 days).

Note: Any reportable adverse events (AEs) occurring during follow-up should be followed until stabilization or resolution for all reportable AEs (per the agreement of the Study PI).

Assessment time points and windows are detailed in **Section 9.0**.

5.8 Duration of Study Participation

Study participation may conclude when any of the following occur:

Completion of study activities (treatment, pre-surgery activities and follow-up).

Withdrawal of consent (See **Section 16.5**).

Participant is lost to follow-up. All attempts to contact the participant must be documented.

At the discretion of the investigator for safety, behavioral, study termination or administrative reasons.

Documentation of the reason for discontinuing study participation and the date effective should be made in the medical record and appropriate eCRF. The COH DCC should be promptly notified of the change in participant status.

5.9 Supportive Care, Prohibited and Concomitant Therapies/Medications

Participants must be instructed not to take any additional medications (including over-the-counter products) during the trial without prior consultation with the investigator.

If concomitant therapy must be added or changed, including over-the-counter medications or alternative therapies, the reason and name of the agent/therapy should be recorded in the eCRF and documented in the EHR.

5.9.1 Prohibited therapies

The following medications are **prohibited** during the 30-day preoperative window period.

Other investigational therapy.

Other anti-cancer therapy.

5.9.2 Supportive care

With the exception of prohibited therapies (see **Section 5.9**), participants should receive prophylactic or supportive care as clinically indicated per institutional policies.

6.0 ANTICIPATED TOXICITIES

6.1 Pterostilbene

The following expected AEs are based on n=60 treated with PTE [23]. Asterisk (*) denotes ≥ 10% and no asterisk denotes 1-10%:

Metabolism and Nutrition	Increased appetite
Musculoskeletal and Connective Tissue	Muscle pain

6.2 Megestrol Acetate

Per the 2017 package insert the expected toxicities for megestrol acetate are as follows (* signifies > 10%; no asterisk signifies 1-10% and † signifies < 1%):

Cardiac	Heart failure
Gastrointestinal	Nausea, vomiting
General Disorders and Administration Site	Malaise, asthenia, lethargy, sweating
Investigations	Increased weight*, high blood glucose
Metabolism and Nutrition	Glucose intolerance

Neoplasms benign, Malignant and unspecified (incl cysts and polyps)	Tumor flare reaction
Nervous system	Carpal tunnel syndrome
Psychiatric	Mood changes
Reproductive system and Breast disorders	Breakthrough menstrual bleeding, hot flashes
Respiratory, Thoracic and Mediastinal	Dyspnea
Skin and Subcutaneous Tissue	Alopecia, rash
Vascular	Hypertension, thromboembolic events, fatal thromboembolic events†

7.0 AGENT INFORMATION

7.1 Pterostilbene

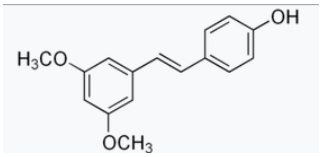
Pterostilbene is not FDA approved for any indication.

7.1.1 Other names

3',5'-dimethoxy-4E-stilbenol, 3',5'-dimethoxy-resveratrol

7.1.2 Description and molecular weight

Pterostilbene is a naturally occurring analogue of resveratrol. It is found in several types of blueberries and unripe Pinor noir grapes.

Structural formula:	
Empirical formula:	$C_{16}H_{16}O_3$
Molecular weight:	256.301
Chemical Name:	4-[(E)-2-(3,5-Dimethoxyphenyl)ethenyl]phenol

7.1.3 Mechanism of action

Preliminary studies suggest PTE has anti-tumor activities [25, 26].

7.1.4 Human toxicity

See **Section 6.1** for details.

7.1.5 Formulation

Oral capsule formulation supplement will be used for this trial.

7.1.6 Storage, handling

Follow package instructions.

7.1.7 Dose and administration

See **Section 5.3**.

7.1.8 Supplier

Pterostilbene is commercially available and will be purchased from Elysium Health.

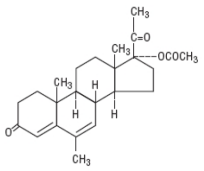
7.2 Megestrol Acetate

Please refer to the package insert for a detailed description. Megestrol acetate has been FDA approved for indicated for the palliative treatment of advanced carcinoma of the breast or endometrium (i.e., recurrent, inoperable, or metastatic disease).

7.2.1 Other names

Megace

7.2.2 Description and molecular weight

Structural formula:	
Empirical formula:	$C_{24}H_{32}O_4$
Molecular weight:	384.51
Chemical Name:	17 α-acetyloxy-6-methylpregna-4,6-diene-3,20-dione

7.2.3 Mechanism of action

The precise mechanism by which MA produces its anti-tumor effects against endometrial carcinoma is unknown at the present time. Possible mechanisms may be via inhibition of pituitary gonadotrophin production and via local tumor effect.

7.2.4 Human toxicity

See **Section 6.2** for details.

7.2.5 Pharmacokinetics

Absorption:	Tablet- Time to peak concentration, 1 h to 3 h (mean 2.2 h)
Half-life elimination	13 h to 104.9 h (mean 34.2 h)
Metabolism:	Hepatic (to free steroids and glucuronide conjugates)
Excretion:	Urine (57% to 78%; 5% to 8% as metabolites); feces (8% to 30%) within 10 days

7.2.6 Formulation

Tablet formulation will be used for this trial.

7.2.7 Storage

Per package insert.

7.2.8 Dose and administration

See **Section 5.3**.

7.2.9 Supplier

Megestrol acetate is commercially available.

8.0 CORRELATIVE/ SPECIAL STUDIES

8.1 Correlative Tumor Tissue

An overview of collection, processing, and analysis details are shown below.

Table 1: Tumor Tissue Studies Overview

Tissue requirements	Timepoints of Collection	Receiving Lab	Downstream Analysis
Endometrial tumor obtained via endometrial pipelle (biopsy) or as endometrial curettings.	• Baseline (prior to therapy) • Day of surgery	Pathology department →COH Pathology Core	See **Section 8.1.3**.

Baseline endometrial biopsy –An office endometrial biopsy will be performed at COH Duarte unless the block or slides from a previous endometrial biopsy or curettings is available, which confirms diagnosis of endometrial cancer. These slides/blocks may be obtained post-informed consent. FFPE block of tissue or slides may be obtained at COH or outside institution

Day of surgery- an endometrial biopsy will be performed in the operating room while under anesthesia immediately before the hysterectomy if feasible. Alternatively, if the surgery is performed at a hospital other than COH, then the blocks or slides from the endometrial tumor from the hysterectomy will be requested and received by COH postoperatively.

8.1.1 Collection details

1. Prior to therapy initiation and following consent, the patient will undergo an office endometrial biopsy (see procedure description below) unless the block or slides from prior endometrial biopsy or curettings is available.
2. On day of surgery, following adequate anesthesia, perform endometrial sampling with an endometrial pipelle (see procedure description below), if feasible.

Endometrial biopsy procedure (optional):

Under sterile conditions, a standard endometrial biopsy will be used, which is a flexible polypropylene suction cannula with an outer diameter of approximately 3.1 mm.

- Introduce the pipelle into the intrauterine cavity.
- Perform three successive passes.

8.1.2 Labeling of samples if collected outside of Standard of Care

For collection at COH, samples will labeled with the protocol ID, subject ID, date and time point of collection (per **Table 1**). If surgery is performed outside of COH, standard of care pathological collection will occur, and blocks or slides will be requested post-operatively by the research team.

8.1.3 Immunohistochemistry and pathology details

We will evaluate the correlation between expression of ER and PR in baseline specimen and hysterectomy specimens. ER and PR expression will be quantified by IHC based on intensity of staining (0 to 3+) and percentage of cells staining (0 to 100%). A modified H score will be calculated as the product of intensity X percentage of cells staining. We will examine the effects of PTE and MA on selected histologic and immunohistochemical measures of growth and apoptosis, including gland cellularity, nuclear grade, nucleoli, metaplasia, secretion, Ki-67, Bcl-2, and Casp3, to evaluate the mechanism of action of PTE and MA. These histologic and immunohistochemical measures were selected based on previously published results. [20, 24]. Exploratory endpoints include PTEN expression, presence of PI3K mutation, β-catenin mutation, MMR deficiency, and cyclin D1 correlation with histologic response. We will test the correlation between prognostic factors for endometrial cancer that are measured at baseline with histologic response. PTEN expression and MMR deficiency will be assessed by IHC as positive or negative. Presence of PI3K mutation and β-catenin mutations will be assessed by PCR as present or absent.

8.1.4 Genomic analyses

Paired tumor/normal whole exome sequencing (WES) and whole transcriptome sequencing (RNAseq) will be performed according to standard protocol methods using Illumina instruments. Endometrial tumor samples before and after protocol treatment will be collected in routine fashion for FFPE collection. Additionally, for normal germline analysis, two 4 mL EDTA blood tubes (purple top) will be collected. We will perform analyses of germline and somatic genomic landscapes, as well as gene expression phenotypes before and after treatment including assessment of driver mutations, mutation signatures, tumor mutation burden, immune signatures.

9.0 **STUDY CALENDAR**

Protocol Activities All procedures may increase in frequency if clinically indicated.	**Screening** [a]	**Preoperative Window Period** **Protocol Therapy (MA ± PTE)** [b] **Day 1**	**Pre-op** [d]	**Surgery** [e]	**Follow-Up Post-surgery** **6 weeks** [f]
Informed Consent[g]	X				
Eligibility	X				
Registration	X				
Medical History [h]	X				

Height	X				
Physical Exam	X	X [c]	X		X
Vital Signs [i]	X	X [c]	X		X
ECOG Status (**Appx. A**)	X	X [c]	X		X
Con-med review [j]	X	X [c]	X		X
AE assessment [k]		X	X		X
CBC w/diff, plt	X	X [c]	X		X
Serum chemistry [l]	X	X [c]	X		X
Lipid panel [m]	X	X [c]	X		X
Research blood collection [p]	X				
MA		Twice daily, oral 80 mg			
If receiving combination therapy: PTE		Twice daily, oral 100 mg			
MA drug diary		----------X----------	X		
If receiving combination therapy: PTE drug diary [n]		----------X----------	X		
Endometrial biopsy	X [o]			X [o]	
Scheduled total hysterectomy				X	

a. Screening evaluations to occur within 30 days prior to start of protocol therapy at COH.

b. Protocol therapy with PTE ± MA is planned for the duration of the preoperative window period. The date of scheduled surgery will define the duration of the preoperative window period and therefore, protocol therapy. In the absence of delay in planned surgery, treatment will last 3 weeks (+/- 7 days). Day 1 is defined as the day of PTE initiation during the preoperative window period. In the case of surgery delay, patients may stop the treatment regimen up to 14 days prior to surgery. If the surgery date is moved up, patients may undergo protocol therapy for less than 3 weeks. **It is not a deviation if the standard of care surgery falls outside the specified window**.

c. Only perform **if NOT** performed within 7 calendar days prior to D1.

d. *For participants who end the preoperative window period (i.e. protocol therapy)*, pre-op activities to be performed **within 7 days** prior to the scheduled surgery at COH or other institution.

e. Surgery defined as standard of care total hysterectomy with or without bilateral salpingo-oophorectomy, with or without staging. Surgery may be performed either at COH or at an outside institution,.

f. *Standard of care clinic visits and safety follow-up* to occur post-surgery at **(i)** 6 weeks (± 14 days). **It is not a deviation if the standard of care visit falls outside the specified window**. Follow up visits will take place at a COH clinic site, which includes community clinic sites. Expedited reporting will occur during this period. Safety follow-up may be extended until resolution/ stabilization of reportable AEs.

g. *Informed consent* process to be fully documented (see **Section 16.4**). Informed consent must occur prior to any research only screening procedures.

h. *Medical history* to include a review of treatment history, any ongoing medical conditions and medical history pertaining to eligibility on study and involvement during study.

i. *Vital signs*: Weight, heart rate, blood pressure, respiration rate, and temperature.

j. Concurrent medications and reason for administration to be documented in EHR and reported in the eCRFs from within 28 prior to protocol therapy up to the 6-week post-surgery visit. A medical review of the EHR may be performed if there are any reportable AEs occurring beyond the 6-week post-surgery visit. See **Section 5.9** for concomitant therapy restrictions and guidelines.

k. Adverse events (AEs) will be assessed using CTCAE v.4.0 and documented from Day 1 of protocol therapy until the 6-week post-surgery visit, at the defined study visits and at standard of care visits. Reportable AEs should be followed until resolution/stabilization of the event.

l. *Serum chemistry to include*: Albumin, Total Bilirubin, Total Calcium, Bicarbonate, Chloride, Creatinine, Glucose, Alkaline Phosphatase, Potassium, Total Protein, Sodium, ALT, AST, and BUN.

m. *Lipid panel* to include, Low-density lipoprotein (LDL), triglycerides, total cholesterol, High-density lipoprotein (HDL). May use lipid panel results from up to 6 months prior to treatment start as baseline labs. Laboratory studies may be drawn at laboratories outside of COH.

n. *Drug diary* for each study agent will be given to the participant and will be reviewed for adherence. See **Appendix C** (PTE) and **Appendix D** (MA). Drug bottles and drug diaries may be collected by the research nurse or investigator, or may be shipped to the study team.

o. *Endometrial biopsy* at screening time point does not need to be performed if the block is readily available for histologic analysis from a previous endometrial biopsy. The endometrial biopsy at time of hysterectomy is optional.

p. If not collected at baseline, it may be collected at any time during or after treatment.

10.0 ENDPOINT DEFINITIONS

10.1 Primary Endpoints

The **primary endpoint** is the tumor Ki-67 proliferation index, measured pre- and post-treatment in each treatment arm.

10.2 Exploratory Endpoints

The **exploratory endpoints** are:

1. Measurements of histologic response, tumor growth, and apoptosis measured pre- and post-treatment in each treatment arm including:
    - Response: gland cellularity, nuclear grade, nucleoli, metaplasia, eosinophilic cytoplasm, secretion
    - Growth: Bcl-2
    - Apoptosis: Casp3
2. Biological characteristics of tumors measured pre- and post-treatment in each treatment arm including:
    - ER status
    - PR status
    - MMR status
    - PI3K mutational status
3. **Genomic analyses**
    - Germline and somatic genomic landscapes of endometrial tumor pre- and post-treatment in each arm
    - Gene expression phenotypes before and after treatment:
        - driver mutations
        - mutation signatures
        - tumor mutation burden
        - immune signatures

11.0 STATISTICAL CONSIDERATIONS

11.1 Study Design

This is an open-label randomized Phase II study to compare the efficacy of neoadjuvant MA plus PTE versus MA alone among EC patients undergoing scheduled total hysterectomy. The primary measure of efficacy will be treatment-associated change in tumor Ki-67 proliferation index. The primary endpoint of the proposed trial was chosen based on data from GOG-211 [24], where a 34.8% reduction in Ki-67 was reported following two weeks of MPA treatment.

11.2 The planned sample size is 18 evaluable participants per treatment arm. With 18 evaluable subjects per arm and using a 1-sided t test at $p<0.05$, the trial will provide 90% power to detect a difference in efficacy, favoring MA plus PTE, of at least 10% (with standard deviation 10%) in the mean reduction in Ki67. For example, the trial will be able to differentiate between a 40% and a 30% mean reduction in Ki67 per arm. Thus, the trial will study 2x18=36 evaluable subjects. Little dropout is anticipated due to tolerability issues or inconvenient protocol. Randomized allocation will be 1:1, allocated within strata of diagnosis and menopausal status.

11.3 Definitions, Evaluable Participants and Participant Replacement

***Evaluable for toxicity*:** All patients who receive at least one dose of protocol therapy will be evaluable for toxicity.

Evaluable for efficacy: Subjects who receive at least 10 days of study treatment and who provide pre- and post-treatment tissue samples will be evaluable for the efficacy endpoint, Ki67.

Non-evaluable subjects who receive at least 1 dose of study treatment will be included in the Toxicity analysis but will be replaced for the Efficacy (Ki67) analysis.

11.4 Sample Size, Accrual Rate, Study Duration

***Total accrual*:** 36 evaluable participants will be treated. The study will accrue a maximum of 45 participants, assuming up to 20% are non-evaluable.

Accrual rate and study duration: Assuming 1-2 patients are enrolled each month, accrual is expected to be completed in 66 months. Duration of study per participant will be approximately 14 weeks, including 4 weeks of screening, up to 3 weeks of treatment, and 6 weeks of post-surgery follow-up. Thus, the study is expected to be completed in 60 months.

11.5 Statistical Analysis Plan

Patient demographics and clinical characteristics at baseline will be summarized using descriptive statistics.

All patients evaluable for toxicity will be included in the toxicity analysis. Observed toxicities will be summarized by type (organ affected or laboratory determination), severity, time of onset, duration, probable association with the study treatment, and reversibility or outcome.

The primary analysis of efficacy will compare treatment-associated change in Ki-67 proliferation index between the 2 study arms, using a 1-sided test with significance at $p<0.05$. Using a generalized estimating

equation to take into account the repeated assessment of subjects (pre and post treatment), analysis will use a generalized linear regression model of Ki-67 index. Adjustment for potential confounding factors will be made as appropriate.

12.0 DATA HANDLING, DATA MANAGEMENT, RECORD KEEPING

12.1 Source Documents

Source documents are original documents, data, and records (e.g., medical records, pharmacy dispensing records, recorded data from automated instruments, laboratory data) that are relevant to the clinical trial. The investigator or their designee will prepare and maintain adequate and accurate source documents. These documents are designed to record all observations and other pertinent data for each patient enrolled in this clinical trial. Source documents must be adequate to reconstruct all data transcribed onto the case report forms.

12.2 Data Capture Methods and Management

Data for this trial will be collected using City of Hope's electronic capture system that is compliant with 21 CFR Part 11. Study personnel will enter data from source documents corresponding to a subject's visit into the protocol-specific electronic Case Report Form (eCRF).

12.3 Case Report Forms/Data Submission Schedule

Study personnel will enter data from source documents corresponding to a subject's visit into the protocol-specific electronic Case Report Form (eCRF) when the information corresponding to that visit is available.

The investigator is responsible for all information collected on subjects enrolled in this study. All data collected during the course of this study must be reviewed and verified for completeness and accuracy by the investigator. All case report forms must be completed by designated study personnel. The completed case report forms must be reviewed, signed and dated by the Investigator or designee in a timely fashion.

All data will be collected using electronic data collection, stored as indicated in **Section 12.2**, and will be submitted according to the timelines indicated in **Table 2**.

Table 2: Data Submission Schedule

Form	Submission Timeline
Eligibility Checklist	Complete prior to registration
On Study Forms	Within 14 calendar days of registration.
Baseline Assessment Forms	Within 14 calendar days of registration.
Treatment Forms	Within 10 calendar days of treatment administration.
Adverse Event Report Forms	**Window period**: Within 7 calendar days of AE assessment/notification. **Post-window period**: Within 10 calendar days of AE assessment/notification.
Response Assessment Forms	Within 10 calendar days of the response assessment.
Other Assessment Forms (concomitant medications)	Within 10 calendar days of the assessment.
Off Treatment/Off Study Forms	Within 10 calendar days of end of treatment/study.
Follow up/Survival Forms	Within 14 calendar days of the follow up activity.

12.4 Regulatory Records

The investigator will maintain regulatory records, including updating records in accordance with Good Clinical Practice guidelines and FDA regulations.

13.0 ADVERSE EVENTS AND UNANTICIPATED PROBLEMS

13.1 Definitions

13.1.1 Adverse Event (AE)

An adverse event is any untoward medical experience or change of an existing condition that occurs during or after treatment, whether or not it is considered to be related to the protocol intervention.

13.1.2 Serious Adverse Event (SAE)

A serious adverse event is any expected or unexpected adverse events that result in any of the following outcomes:

- Death
- Is life-threatening experience (places the subject at immediate risk of death from the event as it occurred)
- Unplanned hospitalization (equal to or greater than 24 hours) or prolongation of existing hospitalization
- A persistent or significant disability/incapacity
- A congenital anomaly/birth defect
- Secondary malignancy*
- Any other adverse event that, based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the outcomes listed above (examples of such events include allergic bronchospasm requiring intensive treatment in the emergency room or at home, blood dyscrasias of convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse).

*Modified from 21 CFR 312.32

13.1.3 Unanticipated Problems Involving Risks to Subjects or Others

An unanticipated problem is any incident, experience, or outcome that **meets all three** of the following criteria:

1. Unexpected (in terms of nature, severity, or frequency) given the following: a) the research procedures described in the protocol-related documents such as the IRB approved research protocol, informed consent document or Investigator Brochure (IB); and b) the characteristics of the subject population being studied; **AND**
2. Related or possibly related to participation in the research (possibly related means there is a reasonable possibility that the incident, experience, or outcomes may have been caused by the drugs, devices or procedures involved in the research); **AND**
3. Suggests that the research places subjects or others at greater risk of harm (including physical, psychological, economic, or social harm) than previously known or recognized.

13.2 Assessment of Adverse Events

The site Investigator will be responsible for determining the event name, assessing the severity (i.e. grade), expectedness, and attribution of all adverse events.

13.2.1 Assessment of Adverse Event Name and Grade

Adverse events will be characterized using the descriptions and grading scales found in the most recent version of the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE). The determination of severity for all other events not listed in the CTCAE should be made by the investigator based on medical judgment and the severity categories of Grade 1 to 5 as defined below:

- Grade 1 (mild) – An event that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
- Grade 2 (moderate) – An event that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the subject.
- Grade 3 (severe) – An event that requires intensive therapeutic intervention. The event interrupts usual activities of daily living, or significantly affects the clinical status of the subject.
- Grade 4 (life threatening) – An event, and/or its immediate sequelae, that is associated with an imminent risk of death or with physical or mental disabilities that affect or limit the ability of the subject to perform activities of daily living (eating, ambulation, toileting, etc).
- Grade 5 (fatal) – Death (loss of life) as a result of an event.

13.2.2 Assessment of Attribution

The following definitions will be used to determine the causality (attribution) of the event to the study agent or study procedure.

- **Unrelated –** The event is clearly related to other factors such as the participant's clinical state, other therapeutic interventions, or concomitant medications administered to the participant.
- **Unlikely –** The event is doubtfully related to the investigational agent(s). The event was most likely related to other factors such as the participant's clinical state, other therapeutic interventions, or concomitant drugs.
- **Possible –** The event follows a reasonable temporal sequence from the time of drug administration, but could have been produced by other factors such as the participant's clinical state, other therapeutic interventions, or concomitant drugs.
- **Probable –** The event follows a reasonable temporal sequence from the time of drug administration, and follows a known response pattern to the study drug. The event cannot be reasonably explained by other factors such as the participant's clinical state, therapeutic interventions, or concomitant drugs.
- **Definite –** The event follows a reasonable temporal sequence from the time of drug administration, follows a known response pattern to the study drug, cannot be reasonably explained by other factors such as the participant's condition, therapeutic interventions, or

concomitant drugs, AND occurs immediately following study drug administration, improves upon stopping the drug, or reappears on re-exposure.

13.2.3 Assessment of Expectedness

The following definitions will be used to determine the expectedness of the event:

- **Unexpected** – An adverse event is unexpected if it is not listed in the investigator's brochure and/or package insert; is not listed at the specificity or severity that has been observed; is not consistent with the risk information described in the protocol and/or consent; is not an expected natural progression of any underlying disease, disorder, condition, or predisposed risk factor of the research participant experiencing the adverse event. *Modified from 21 CFR 312.32 (a)
- **Expected –** An adverse event is expected if it does not meet the criteria for an unexpected event, OR is an expected natural progression of any underlying disease, disorder, condition, or predisposed risk factor of the research participant experiencing the adverse event.

13.3 Reporting of Adverse Events

13.3.1 Routine Reporting of Non-Serious Adverse Events

Routine AE recording will occur via data entry into the study eCRF. Recording of adverse events will begin once the patient is consented and will continue until the post-op follow up appointment. Adverse events will be monitored by the Protocol Management Team (PMT). Adverse events that do not meet the criteria of serious OR are not unanticipated problems do not require expedited reporting. AEs reported through expedited processes (i.e. reported to the IRB, DSMC, FDA, etc.) must also be reported in routine study data submissions.

13.3.2 Expediting Reporting Requirements of SAEs and UPs

Adverse events that meet the criteria of serious OR are unanticipated problems will be reported according to the approved City of Hope's Institutional policy via the AE/UP reporting form in iRIS. Reportable serious adverse events must be followed until the event is resolved, stabilized, or determined to be irreversible by the investigator. Follow-up SAE reports must be submitted for all events that require expedited reporting when the status of the event changes and until the resolution or stabilization of the event.

14.0 PROTOCOL DEVIATIONS AND SINGLE SUBJECT EXCEPTIONS

It is understood that deviations from the protocol should be avoided, except when necessary to eliminate an immediate hazard to a research participant. Brief interruptions and delays may occasionally be required because of travel delays, airport closures, inclement weather, family responsibilities, security alerts, government holidays, and so forth. Delays can also extend to complications of disease or unrelated medical illnesses not related to disease progression. The PI has the discretion to deviate from the protocol when necessary so long as such a deviation does not threaten patient safety or protocol scientific integrity. As a result of deviations, corrective actions are to be developed by the study staff and implemented promptly.

14.1 Definitions

14.1.1 Deviation

A deviation is a divergence from a specific element of a protocol that occurred without prior IRB approval. Investigators may deviate from the protocol to eliminate immediate hazard(s) for the protection, safety, and well-being of the study subjects without prior IRB approval. Examples include, but are not limited to: a) dose adjustments based on excessive patient weight; b) alteration in treatment schedule due to non-availability of the research participant for treatment; and c) laboratory test results which are slightly outside the protocol requirements but at levels that do not affect participant safety.

14.1.2 Single Subject Exceptions (SSE)

An SSE is a planned deviation, meaning that it involves circumstances in which the specific procedures called for in a protocol are not in the best interests of a specific patient. It is a deviation that is anticipated and receives **prior** approval by the Principal Investigator and the COH IRB.

14.2 Reporting of Deviations and SSEs

14.2.1 Reporting Deviations

For any deviation, the Investigator will notify the COH DSMC and IRB within 5 calendar days of its occurrence via iRIS in accordance with the Clinical Research Protocol Deviation policy.

14.2.2 Reporting Single Subject Exceptions

The SSE must be submitted as a "Single Subject Exception Amendment Request" via iRIS in accordance with IRB guidelines and the Clinical Research Protocol Deviation policy. An IRB approved SSE does not need to be submitted as a deviation to the DSMC.

In addition, if contractually obligated, the sponsor must also approve the deviation.

15.0 STUDY OVERSIGHT, QUALITY ASSURANCE, AND DATA & SAFETY MONITORING

15.1 All Investigator Responsibilities

An investigator is responsible for ensuring that an investigation is conducted according to the signed investigator statement, the investigational plan, and applicable regulations; for protecting the rights, safety, and welfare of subjects under the investigator's care; and for the control of drugs under investigation.

All Investigators agree to:

- Conduct the study in accordance with the protocol and only make changes after notifying the Sponsor (or designee), except when necessary to protect the safety, rights or welfare of subjects.
- Personally conduct or supervise the study (or investigation).
- Ensure that the requirements relating to obtaining informed consent and IRB review and approval meet federal guidelines, as stated in § 21 CFR, parts 50 and 56.

- Report to the Sponsor or designee any AEs that occur in the course of the study, in accordance with §21 CFR 312.64.
- Ensure that all associates, colleagues and employees assisting in the conduct of the study are informed about their obligations in meeting the above commitments.
- Maintain adequate and accurate records in accordance with §21 CFR 312.62 and to make those records available for inspection with the Sponsor (or designee).
- Ensure that an IRB that complies with the requirements of §21 CFR part 56 will be responsible for initial and continuing review and approval of the clinical study.
- Promptly report to the IRB and the Sponsor all changes in the research activity and all unanticipated problems involving risks to subjects or others (to include amendments and IND safety reports).
- Seek IRB and Sponsor approval before any changes are made in the research study, except when necessary to eliminate hazards to the patients/subjects.
- Comply with all other requirements regarding the obligations of clinical investigators and all other pertinent requirements listed in § 21 CFR part 312.

15.2 Study Principal Investigator Responsibilities

The Study Principal Investigator is responsible for the conduct of the clinical trial, including overseeing that sponsor responsibilities as defined in § 21 CFR 312. Subpart D are executed in accordance with federal regulations.

15.3 Protocol Management Team (PMT)

The Protocol Management Team (PMT), minimally consisting of the study PI, collaborating investigators, research nurse, clinical research associate/coordinator, and the study biostatistician, is responsible for ongoing monitoring of the data and safety of this study, including implementation of the stopping rules for safety/toxicity.

The PMT is recommended to meet (in person or via teleconference) at least monthly to review study status. This review will include, but not be limited to, reportable AEs and UPs, and an update of the ongoing study summary that describes study progress in terms of the study schema. The meeting will be a forum to discuss study related issues including accrual, SAE/AEs experienced, study response, deviations/violations and study management issues. The appropriateness of further subject enrollment and the specific intervention for subsequent subject enrollment are addressed. It is recommended that minutes of these discussions be taken to document the date of these meetings, attendees and the issues that were discussed (in a general format).

15.4 Monitoring

Clinical site monitoring is conducted to ensure that the rights of human subjects are protected, that the study is implemented in accordance with the protocol and regulatory requirements, and that the quality and integrity of study data and data collection methods are maintained. Monitoring for this study will be performed by the City of Hope Office of Clinical Trials Auditing and Monitoring (OCTAM).

The Investigator will permit the study monitors and appropriate regulatory authorities direct access to the study data and to the corresponding source data and documents to verify the accuracy of this data. The Investigator will allocate adequate time for such monitoring activities. The Investigator will also ensure that the monitor or other compliance or quality assurance reviewer is given access to all the above noted study-related documents and study related facilities (e.g. pharmacy, diagnostic laboratory, etc.), and has adequate space to conduct the monitoring visit.

Details of clinical site monitoring are documented in the OCTAM SOP. This document specifies the frequency of monitoring, monitoring procedures, the level of clinical site monitoring activities (e.g., the percentage of subject data to be reviewed), and the distribution of monitoring reports. Staff from OCTAM will conduct monitoring activities and provide reports of the findings and associated action items in accordance with the details described in the SOP. Documentation of monitoring activities and findings will be provided to the study team, and the COH DSMC.

15.5 Quality Assurance

The City of Hope Clinical Research Information Support will provide support for this multi-center trial as detailed in the COH DCC Operations Plan provided as a supplement to this document.

15.6 City of Hope Data and Safety Monitoring Committee

This is a risk level 3 study as defined in the City of Hope Institutional Data and Safety Monitoring Plan. This determination was made because the study does not involve a COH held IND.

The DSMC is a multidisciplinary committee charged with overseeing the monitoring of safety of participants in clinical trials, and the conduct, progress, validity, and integrity of the data for all clinical trials that are sponsored by City of Hope. The committee is composed of clinical specialists with experience in oncology and who have no direct relationship with the study. The committee reviews the progress and safety of all active research protocols that are not monitored by another safety and data monitoring committee or board.

The Study Principal Investigator is required to submit periodic status reports (the PMT report) according to the guidelines outlined in the City of Hope Institutional Data and Safety Monitoring Plan. The PMT report will be submitted to the COH DSMC semi-annually from the date of activation.

The COH Data and Safety Monitoring Committee (DSMC) will review and monitor toxicity and accrual data from this trial. The DSMC will review up-to-date participant accrual; summary of all adverse events captured via routine and expedited reporting; a summary of deviations; any response information; monitoring reports, and summary comments provided by the study team. Other information (e.g. scans, laboratory values) will be provided upon request. For Phase I studies, a Phase I Tracking Log will be utilized and reviewed by the DSMC to monitor data and safety for dose escalation. A review of outcome results (response, toxicity and adverse events) and factors external to the study (such as scientific or therapeutic developments) is discussed, and the Committee votes on the status of each study. Information that raises any questions about participant safety will be addressed with the Principal Investigator, statistician and study team.

16.0 **ETHICAL AND REGULATORY CONSIDERATIONS**

16.1 Ethical Standards

This study will be conducted in conformance with the principles set forth in The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research (US National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, April 18, 1979) and the Declaration of Helsinki.

16.2 Regulatory Compliance

This study is to be conducted in compliance with the IRB approved protocol and according to the following considerations:

US Code of Federal Regulations (CFR) governing clinical study conduct

- Title 21 Part 11 – Electronic Records; Electronic Signatures
- Title 21 Part 50 – Protection of Human Subjects
- Title 21 Part 54 – Financial Disclosure by Clinical Investigators
- Title 21 Part 56 – Institutional Review Boards
- Title 21 Part 58 – Good Laboratory Practice for Nonclinical Laboratory Studies
- Title 21 Part 312 – Investigational New Drug Application
- Title 45 Part 46 – Protection of Human Subjects

US Federal legislation, including but not limited to

- Health Insurance Portability and Accountability Act of 1996
- Section 801 of the Food and Drug Administration Amendments Act (FDAAA 801)

Applicable state and local laws. For research occurring in California, this includes but is not limited to State of California Health and Safety Code, Title 17
Applicable NIH policies and procedures
Applicable institutional research policies and procedures

16.3 Institutional Review Board

An Institutional Review Board (IRB) that complies with the federal regulations at 45 CFR 46 and 21 CFR 50, 56 and State of California Health and Safety code, Title 17, must review and approve this protocol, informed consent form and any additional documents that the IRB may need to fulfill its responsibilities (Investigator's Brochure, information concerning patient recruitment, payment or compensation procedures, or other pertinent information) prior to initiation of the study. Revisions to approved documents will require review and approval by the IRB before the changes are implemented in the study. All institutional, NCI, Federal, and State of California regulations must be fulfilled.

The IRB's written unconditional approval of the study protocol and the informed consent document must be in the possession of the investigator before the study is initiated.

The IRB will be informed of serious unexpected, unanticipated adverse experiences, and unanticipated problems occurring during the study, and any additional adverse experiences in accordance with the standard operating procedures and policies of the IRB; new information that may affect adversely the safety of the patients of the conduct of the study; an annual update and/or request for re-approval; and when the study has been completed.

16.4 Informed Consent

The Principal Investigator or IRB approved named designee will explain the nature, duration, purpose of the study, potential risks, alternatives and potential benefits, and all other information contained in the informed consent document. In addition, they will review the experimental subject's bill of rights and the HIPAA research authorization form. Prospective participants will be informed that they may withdraw from the study at any time and for any reason without prejudice, including as applicable, their current or future care or employment at City of Hope or any relationship they have with City of Hope. Prospective participants will be afforded sufficient time to consider whether or not to participate in the research.

After the study has been fully explained, written informed consent will be obtained from either the prospective participant or his/her guardian or legal representative before study participation. The method of obtaining and documenting the informed consent and the contents of the consent must comply with the ICH-GCP and all applicable regulatory requirements.

A copy of the signed informed consent will be given to the participant or his/her legally authorized representative. The original signed consent must be maintained by the investigator and available for inspection by sponsor designated representatives, or regulatory authority at any time.

Informed consent is a process that is initiated prior to the individual agreeing to participate in the study and continues throughout study participation.

16.5 Participant Withdrawal

Participants may withdraw from the study at any time and for any reason without prejudice. The withdrawal must be documented per institutional policies. The COH DCC should be promptly notified of the change in participant status.

Participant withdrawal may consist of any of the following with regard to study procedures and data collection:

- Withdrawal from study treatment, but agreement to continue with chart review and laboratory follow-up.
- Withdrawal from study treatment and all active procedures, but agreement for chart review and survival follow-up.
- Withdrawal from study treatment, all active procedures, and any future data collection.

Participants who agreed to the collection of research tissue samples may withdraw consent to use their specimens, if they are not yet processed as detailed in the consent form. Once the PI is notified of this withdrawal of informed consent, the research specimens will not be used in any research. At that time, any of the existing specimens will be destroyed.

16.6 Participant Confidentiality

Participant confidentiality is strictly held in trust by the investigators, study staff, and the sponsor(s) and their agents. This confidentiality is extended to cover testing of biological samples in addition to any study information relating to participants.

This research will be conducted in compliance with federal and state requirements relating to protected health information (PHI), including the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). HIPAA regulations require a signed subject authorization informing the subject of the nature of the PHI to be collected, who will have access to that information and why, who will use or disclose that information, and the rights of a research participant to revoke their

authorization for use of their PHI. In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e. that the subject is alive) at the end of their scheduled study period.

Release of research results should preserve the privacy of medical information and must be carried out in accordance with Department of Health and Human Services Standards for Privacy of Individually Identifiable Health Information, 45 CFR 164.508. When results of this study are reported in medical journals or at meetings, identification of those taking part will not be disclosed and no identifiers will be used.

Medical records of subjects will be securely maintained in the strictest confidence, according to current legal requirements. Data will be entered, analyzed and stored in encrypted, password protected, secure computers that meet all HIPAA requirements. All data capture records, drug accountability records, study reports and communications will identify the patient by initials and the assigned patient number.

The investigator/institution will permit direct access to source data and documents by sponsor representatives, the FDA, and other applicable regulatory authorities. The access may consist of trial-related monitoring, including remote monitoring, audits, IRB/IEC reviews, and FDA/regulatory authority inspections. The patient's confidentiality will be maintained and will not be made publicly available to the extent permitted by the applicable laws and regulations.

Participant specimens with a limited data set will be provided to research laboratories. The specimens will be labeled with the study number, subject (accession) ID, date and time point of collection. The key to the code will be maintained in the COH clinical trials management system which is a secure environment.

16.7 Conflict of Interest

Any investigator who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must have the conflict reviewed by a properly constituted Conflict of Interest Committee with a Committee-sanctioned conflict management plan that has been reviewed and approved by the study Sponsor (City of Hope) prior to participation in this study. All City of Hope investigators will follow the City of Hope conflict of interest policy.

16.8 Financial Obligations, Compensation, and Reimbursement of Participants

Pterostilbene will be provided free of charge to participants.

Neither the research participant nor the insurance carrier will be responsible for the research procedures related to this study.

Megestrol acetate and standard of care drugs or procedures provided during the course of study participation will be the responsibility of the research participant and/or the insurance carrier. The participant will be responsible for all copayments, deductibles, and other costs of treatment and diagnostic procedures as set forth by the insurance carrier. The participant and/or the insurance carrier will be billed for the costs of treatment and diagnostic procedures in the same way as if the participant were not in a research study.

In the event of physical injury to a participant resulting from research procedures, appropriate medical treatment will be available at City of Hope to the injured participant. There are no plans for City of Hope to provide financial compensation in the event of physical injury to a participant.

The research participant will not receive reimbursement or payment for taking part in this study.

16.9 Publication/ Data Sharing

Neither the complete nor any part of the results of the study carried out under this protocol, nor any of the information provided by City of Hope for the purposes of performing the study, will be published or passed on to any third party without the written approval of the Study PI. Any investigator involved with this study is obligated to provide City of Hope with complete test results and all data derived from the study.

The publication or presentation of any study results shall comply with all applicable privacy laws, including, but not limited to, the Health Insurance Portability and Accountability Act of 1996.

In accordance with the U.S. Public Law 110-85 (Food and Drug Administration Amendments Act of 2007 or FDAAA), Title VIII, Section 801, this trial will be registered onto ClinicalTrials.gov. Results will be reported on ClinicalTrials.gov generally within 12 months after the completion date unless criteria to delay submission are met per the final rule.

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APPENDIX A: PERFORMANCE STATUS

ECOG Performance Scale [27]	
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: NEW YORK HEART ASSOCIATION CLASSIFICATION OF HEART FAILURE

Modified from Dolgin et al., 1994 [28]

NYHA Classification of Heart Failure	
Class I	No symptoms. Ordinary physical activity such as walking and climbing stairs does not cause fatigue or dyspnea.
Class II	Symptoms with ordinary physical activity. Walking or climbing stairs rapidly, walking uphill, walking or stair climbing after meals, in cold weather, in wind or when under emotional stress causes undue fatigue or dyspnea.
Class III	Symptoms with less than ordinary physical activity. Walking one to two blocks on the level and climbing more than one flight of stairs in normal conditions causes undue fatigue or dyspnea.
Class IV	Symptoms at rest. Inability to carry on any physical activity without fatigue or dyspnea.

APPENDIX C-1: PTEROSTILBENE DRUG DIARY INSTRUCTIONS (IF GETTING COMBINATION THERAPY)

Subject ID#:	Patient Initials (F, M, L):
Start date:	

Remember to bring this diary, all capsule bottles, and any unused capsules to each clinic visit.
Call your study doctor or nurse immediately if you are having any new or worsening side effects.

Study drug Instructions – When and How:

- Take pterostilbene about **every 12 hours** with water; once in the morning and once in the evening.
- Swallow capsules; do not chew them or crush them.
- Take pterostilbene at approximately the same time each day.
- Do not skip any doses.

What if I miss a scheduled dose?

- If **less than 4 hours** have passed from the scheduled time, then **take the missed dose** as soon as you remember.
- If more than 4 hours have passed from the scheduled time, then skip the missed dose. Wait for your next scheduled dose. Do not take extra medicine to make up the missed dose.

What if I vomit a dose?

- If you vomit your capsules, write this down in your drug diary.
- Wait until the next scheduled dose; do not take extra medicine to make up the vomited dose.

Additional Instructions:

- **Write down your side effects in this diary**.
- Your dose may be adjusted based on your side effects.
- Keep your study drug in the original container until you take it.
- Do NOT throw away empty study drug bottles or unused capsules.
- Bring this diary, all study drug bottles, and any unused capsules to each clinic visit.

Study Contact Information		
Study Doctor **Phone:** **Name:**	**Study Nurse** **Phone:** **Name:**	**Backup Study Nurse** **Phone:** **Name:**

APPENDIX C-2: PTEROSTILBENE DRUG DIARY (IF GETTING COMBINATION THERAPY)

Subject ID#:	Patient Initials (F, M, L):
Start date:	

Call your study doctor or nurse <u>immediately</u> if you are having any new or worsening side effects. *Your study doctor or nurse will tell you what to do.*

Write your side effects in this diary. Your dose may be adjusted based on your side effects.

Week 1					
				# of capsules to take: **AM: _____** **PM: _____**	
Cycle Day	**Week Day**	**Date**	**Time**	**# of capsules taken** *(Write down below)*	**Comments** *Write down missed/ vomited doses, side-effects (e.g. nausea, vomiting etc.)*
1			___:___AM		
			___:___PM		
2			___:___AM		
			___:___PM		
3			___:___AM		
			___:___PM		
4			___:___AM		
			___:___PM		
5			___:___AM		
			___:___PM		
6			___:___AM		
			___:___PM		
7			___:___AM		
			___:___PM		

Participant Signature *(please sign when submitting your diary)*	**Date:**
_____	____/_____/_____

Subject ID#:	Patient Initials (F, M, L):
Start date:	

Call your study doctor or nurse <u>immediately</u> if you are having any new or worsening side effects. *Your study doctor or nurse will tell you what to do.*

Write your side effects in this diary. Your dose may be adjusted based on your side effects.

Week 2					
				# of capsules to take: **AM: _____** **PM: _____**	
Cycle Day	**Week Day**	**Date**	**Time**	**# of capsules taken** *(Write down below)*	**Comments** *Write down missed/ vomited doses, side-effects (e.g. nausea, vomiting etc.)*
8			___:___AM		
			___:___PM		
9			___:___AM		
			___:___PM		
10			___:___AM		
			___:___PM		
11			___:___AM		
			___:___PM		
12			___:___AM		
			___:___PM		
13			___:___AM		
			___:___PM		
14			___:___AM		
			___:___PM		

Participant Signature (please sign when submitting your diary)	Date:
_____	____/_____/_____

Subject ID#:	Patient Initials (F, M, L):
Start date:	

Call your study doctor or nurse <u>immediately</u> if you are having any new or worsening side effects. *Your study doctor or nurse will tell you what to do.*

Write your side effects in this diary. Your dose may be adjusted based on your side effects.

Week 3					
				# of capsules to take: **AM: _____** **PM: _____**	
Cycle Day	**Week Day**	**Date**	**Time**	**# of capsules taken** *(Write down below)*	**Comments** *Write down missed/ vomited doses, side-effects (e.g. nausea, vomiting etc.)*
15			___:___AM		
			___:___PM		
16			___:___AM		
			___:___PM		
17			___:___AM		
			___:___PM		
18			___:___AM		
			___:___PM		
19			___:___AM		
			___:___PM		
20			___:___AM		
			___:___PM		
21			___:___AM		
			___:___PM		

Participant/ Caregiver Signature *(please sign when submitting your diary)*	**Date:**
_____	____/_____/_____

Subject ID#:	Patient Initials (F, M, L):
Start date:	

Call your study doctor or nurse <u>immediately</u> if you are having any new or worsening side effects. *Your study doctor or nurse will tell you what to do.*

Write your side effects in this diary. Your dose may be adjusted based on your side effects.

Week 4					
				# of capsules to take: **AM: _____** **PM: _____**	
Cycle Day	**Week Day**	**Date**	**Time**	**# of capsules taken** *(Write down below)*	**Comments** *Write down missed/ vomited doses, side-effects (e.g. nausea, vomiting etc.)*
22			___:___AM		
			___:___PM		
23			___:___AM		
			___:___PM		
24			___:___AM		
			___:___PM		
25			___:___AM		
			___:___PM		
26			___:___AM		
			___:___PM		
27			___:___AM		
			___:___PM		
28			___:___AM		
			___:___PM		

Participant/ Caregiver Signature *(please sign when submitting your diary)* _____	**Date:** ____/_____/_____

Study Team ONLY: # of Study Drug Bottles Returned: _____ # of capsules returned: _____

Compare with drug diary entries made by participant/guardian. If there is a discrepancy (in the # of bottles or the # of capsules returned), please reconcile (initials & date):_____

APPENDIX D-1: MEGESTROL ACETATE DRUG DIARY INSTRUCTIONS

Subject ID#:	Patient Initials (F, M, L):
Start date:	

Remember to bring this diary, all capsule bottles, and any unused tablets to each clinic visit.
Call your study doctor or nurse immediately if you are having any new or worsening side effects.

Study drug Instructions – When and How:

- Take megestrol acetate about **every 12 hours** with water; once in the morning and once in the evening.
- Swallow tablets; do not chew them or crush them.
- Take megestrol acetate at approximately the same time each day.
- Do not skip any doses.

What if I miss a scheduled dose?

- If **less than 4 hours** have passed from the scheduled time, then **take the missed dose** as soon as you remember.
- If more than 4 hours have passed from the scheduled time, then skip the missed dose. Wait for your next scheduled dose. Do not take extra medicine to make up the missed dose.

What if I vomit a dose?

- If you vomit your capsules, write this down in your drug diary.
- Wait until the next scheduled dose; do not take extra medicine to make up the vomited dose.

Additional Instructions:

- **Write down your side effects in this diary**.
- Your dose may be adjusted based on your side effects
- Keep your study drug in the original container until you take it.
- Do NOT throw away empty study drug bottles or unused tablets.
- Bring this diary, all study drug bottles, and any unused capsules to each clinic visit.

Study Contact Information		
Study Doctor **Phone:** **Name:**	**Study Nurse** **Phone:** **Name:**	**Backup Study Nurse** **Phone:** **Name:**

APPENDIX D-2: MEGESTROL ACETATE DRUG DIARY

Subject ID#:	Patient Initials (F, M, L):
Start date:	

Call your study doctor or nurse <u>immediately</u> if you are having any new or worsening side effects. *Your study doctor or nurse will tell you what to do.*

Write your side effects in this diary. Your dose may be adjusted based on your side effects.

Week 1					
				# of tablets to take: **AM: _____** **PM: _____**	
Cycle Day	**Week Day**	**Date**	**Time**	**# of tablets taken** *(Write down below)*	**Comments** *Write down missed/ vomited doses, side-effects (e.g. nausea, vomiting etc.)*
1			___:___AM		
			___:___PM		
2			___:___AM		
			___:___PM		
3			___:___AM		
			___:___PM		
4			___:___AM		
			___:___PM		
5			___:___AM		
			___:___PM		
6			___:___AM		
			___:___PM		
7			___:___AM		
			___:___PM		

Participant Signature *(please sign when submitting your diary)*	**Date:**
_____	____/_____/_____

Subject ID#:	Patient Initials (F, M, L):
Start date:	

Call your study doctor or nurse <u>immediately</u> if you are having any new or worsening side effects. *Your study doctor or nurse will tell you what to do.*

Write your side effects in this diary. Your dose may be adjusted based on your side effects.

Week 2					
				# of tablets to take: **AM: _____** **PM: _____**	
Cycle Day	**Week Day**	**Date**	**Time**	**# of tablets taken** *(Write down below)*	**Comments** *Write down missed/ vomited doses, side-effects (e.g. nausea, vomiting etc.)*
8			___:___AM		
			___:___PM		
9			___:___AM		
			___:___PM		
10			___:___AM		
			___:___PM		
11			___:___AM		
			___:___PM		
12			___:___AM		
			___:___PM		
13			___:___AM		
			___:___PM		
14			___:___AM		
			___:___PM		

Participant Signature (please sign when submitting your diary)	Date:
_____	____/_____/_____

Subject ID#:	Patient Initials (F, M, L):
Start date:	

Call your study doctor or nurse <u>immediately</u> if you are having any new or worsening side effects. *Your study doctor or nurse will tell you what to do.*

Write your side effects in this diary. Your dose may be adjusted based on your side effects.

Week 3					
				# of tablets to take: **AM: _____** **PM: _____**	
Cycle Day	**Week Day**	**Date**	**Time**	**# of tablets taken** *(Write down below)*	**Comments** *Write down missed/ vomited doses, side-effects (e.g. nausea, vomiting etc.)*
15			___:___AM		
			___:___PM		
16			___:___AM		
			___:___PM		
17			___:___AM		
			___:___PM		
18			___:___AM		
			___:___PM		
19			___:___AM		
			___:___PM		
20			___:___AM		
			___:___PM		
21			___:___AM		
			___:___PM		

Participant/ Caregiver Signature *(please sign when submitting your diary)*	**Date:**
_____	____/_____/_____

Subject ID#:	Patient Initials (F, M, L):
Start date:	

Call your study doctor or nurse <u>immediately</u> if you are having any new or worsening side effects. *Your study doctor or nurse will tell you what to do.*

Write your side effects in this diary. Your dose may be adjusted based on your side effects.

Week 4					
				# of tablets to take: **AM: _____** **PM: _____**	
Cycle Day	**Week Day**	**Date**	**Time**	**# of tablets taken** *(Write down below)*	**Comments** *Write down missed/ vomited doses, side-effects (e.g. nausea, vomiting etc.)*
22			___:___AM		
			___:___PM		
23			___:___AM		
			___:___PM		
24			___:___AM		
			___:___PM		
25			___:___AM		
			___:___PM		
26			___:___AM		
			___:___PM		
27			___:___AM		
			___:___PM		
28			___:___AM		
			___:___PM		

Participant/ Caregiver Signature *(please sign when submitting your diary)* _____	**Date:** ____/_____/_____

Study Team ONLY: # of Study Drug Bottles Returned: _____ # of tablets returned: _____

Compare with drug diary entries made by participant/guardian. If there is a discrepancy (in the # of bottles or the # of tablets returned), please reconcile (initials & date):_____