Aspirin for Prevention of Venous Thromboembolism Among Ovarian Cancer Patients Receiving Neoadjuvant Chemotherapy

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A Supportive Care-Drug Intervention Study

Aspirin for Prevention of Venous Thromboembolism Among Ovarian Cancer Patients Receiving Neoadjuvant Chemotherapy

A phase IV, single-arm, single-center, pilot study among women with advanced epithelial ovarian cancer

DUKE CANCER INSTITUTE

A National Cancer Institute-designated Comprehensive Cancer Center

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2 LIST OF ABBREVIATIONS

Use this list as a starting point for abbreviations used in your protocol.

AE	Adverse event
ASA	Aspirin
EOC	Epithelial ovarian cancer
NACT	Neoadjuvant chemotherapy
VTE	Venous thromboembolism

3 PROTOCOL SYNOPSIS AND RESEARCH SUMMARY

3.1 Purpose

This is a pilot study to determine the efficacy and safety of low dose aspirin for the prevention of venous thromboembolism (VTE) among women with advanced ovarian cancer receiving NACT.

Primary Objectives:

1. To determine the efficacy of low dose aspirin for the reduction of VTE among women receiving NACT for advanced ovarian cancer.
2. To determine the safety of low dose aspirin for the reduction of VTE among women receiving NACT for advanced ovarian cancer.
3. To determine medication adherence with the use of low dose aspirin for the reduction of VTE among women receiving NACT for advanced ovarian cancer.

Hypotheses

1. Hypothesis-testing
2. Use of daily low dose aspirin will reduce the incidence of VTE among women with advanced ovarian cancer receiving NACT.
3. Use of daily low dose aspirin for VTE prophylaxis among women with advanced ovarian cancer receiving NACT will be safe with high medication adherence rates.

3.2 Background and Significance

VTE is a known potential complication of malignancy and is particularly common among women with epithelial ovarian cancer (EOC).[1,2] In addition to having active cancer, women with EOC are predisposed to other well-established risk factors for VTE, including impaired mobility, increasing age, and advanced disease.[3] The risk of VTE is even greater among patients with clear cell histology, thrombocytosis, high grade tumors, and co-morbid cardiovascular risk factors (e.g., obesity, hypertension, diabetes).[4-7] In a recent study at our institution, we found that women with advanced ovarian cancer receiving NACT are at high risk for VTE with an incidence of nearly 8%.[8]

Importantly, the occurrence of VTE among patients with EOC is associated with increased morbidity, decreased survival, and increased healthcare costs.[9-11] Timely interval debulking surgery and the ability to achieve of optimal surgical debulking also remain critical components of care for advanced EOC. In the aforementioned study, we observed that the average time from start of NACT to interval debulking surgery was longer for patients who experienced a VTE during NACT as compared to those who had not; these patients were also less likely to have their disease optimally debulked at the time of interval surgery. The high incidence of VTE during NACT reported in our study as well as the associated morbidity contributes to a growing body of evidence suggesting that thromboprophylaxis during NACT is warranted.

According to the current guidelines from the American Society of Clinical Oncology, thromboprophylaxis with either apixaban, rivaroxaban, or low molecular weight heparin (LMWH) is recommended for high risk ambulatory cancer patients (defined as a Khorana score greater than or equal to 2) receiving systemic chemotherapy. Patients with a primary gynecologic malignancy receive one point in the Khorana score at baseline, and the majority of ovarian cancer patients would meet criteria for an additional point. High risk Khorana scores defined as 3 or greater have a 6.7-7.1% risk of VTE which is similar to the incidence defined in the previously described study of patients receiving NACT for advanced EOC. These patients are therefore considered high risk for adverse thromboembolic events when initiating systemic chemotherapy.

Considering the above recommended agents, our recent institutional data (unpublished) demonstrated that apixaban is not a cost-effective strategy among women with ovarian cancer receiving NACT specifically, and insurance coverage of apixaban and other direct oral anticoagulants is not yet well established. A query of medical oncologists affiliated with the Duke Cancer Institute revealed that the majority of providers are generally not initiating direct oral anticoagulants despite the above guidelines. LMWH, another alternative injectable agent, is expensive and poorly tolerated by patients for prolonged periods of time due to its route of administration.

Low dose aspirin, in contrast, is an oral agent and performed better than apixaban in our cost effectiveness analyses even when potential bleeding rates were upwardly adjusted. It is also already used off-label for a broad range of clinical indications, including as an acceptable alternative for thromboprophylaxis among patients with multiple myeloma receiving antiangiogenesis agents with chemotherapy and/or dexamethasone as well as for postoperative prophylaxis after select orthopedic procedures. We therefore hypothesized that low dose aspirin would be a safe and effective method of thromboprophylaxis for women with advanced ovarian cancer receiving NACT.

The above ASCO guidelines were subsequently endorsed by the Society for Gynecologic Oncology in January 2021. Thus initiation of thromboprophylaxis with apixaban, rivaroxaban, or LMWH is recommended for high risk ambulatory gynecologic cancer patients receiving chemotherapy with a Khorana score ≥ 2. Interim analysis of the initial 10 recruited patients demonstrated 3 VTE events. The division of Gynecologic Oncology at Duke subsequently endorsed the new guidelines. However, patients receiving NACT with a KS equal to 1 may also be at risk of a VTE given the high incidence previously documented, and although not candidates for DOAC therapy, may potentially benefit from initiation of low dose aspirin

References listed in Section 15

3.3 Design and Procedure

Subjects with advanced EOC (including primaries of ovarian, Mullerian, fallopian tube, or peritoneal origin) will be screened for eligibility at Duke Gynecology Oncology clinic visits prior to initiation of NACT. Selection criteria are detailed in a subsequent section. Once determined eligible, a provider will approach the patient and inquire about interest in participating in the study. If the patient desires to receive more information, clinical research personnel will discuss the study with patient and obtain informed consent if all selection criteria are met (detailed in a subsequent section). If the research team is unable to meet with a patient face to face but the patient is interested in participating, the same process will be facilitated via telephone once secure identifiers are met. If the patient consents, they will then be considered an enrolled study subject. Electronic consent will be performed in REDcap. Following enrollment, basic demographic information for each patient will be recorded in a secure REDCap database. Specific demographic data and security concerns are further outlined in a later section.

Patients will be enrolled and will receive aspirin at the Macon Pond location. All study activities will be performed by the study coordinators, so we do not anticipate needing assistance from the Duke Raleigh study team.

The primary selection criterion is a Khorana score of 1; additional criteria are detailed in a subsequent section. The Khorana score will be calculated according to the following parameters in closest proximity to the first cycle of chemotherapy: 1 point for gynecologic cancer, 1 point for BMI ≥35, 1 point for Hgb <10 or use of red blood cell growth factors, 1 point for leukocyte count > 11,000, and 1 point for platelets ≥350,000. Patients therefore have a baseline Khorana score of 1 and are ineligible if any additional Khorana score parameters are met. Prior to the April 2021 amendment, Khorana score was not a part of the inclusion criteria. Any existing patient with a Khorana score of more than 1 who is receiving study drug at the time the amendment is approved will be contacted by the study PI to discuss switching to a DOAC. The patient will have the option to remain on study and complete their aspirin regimen or come off study and begin a

DOAC instead. Any existing patients with a Khorana score of more than 1 who have already completed their aspirin regimen and are considered "on follow up" will remain on study.

Once enrolled in the study, subjects will receive a 30-day supply of low dose aspirin from a study team member and will be instructed to start taking one 81 mg tablet daily starting the first day of their first neoadjuvant chemotherapy cycle. Subjects may also be consented after the first day of their first cycle so long as they are taking the aspirin by the end of the day of their second cycle.Patients who are already on low dose aspirin for another indication will still be eligible for the study but will be instructed to take the study drug such that adherence can be monitored. These patients will continue their prior regimen following completion of NACT. Participants will be instructed to complete medication adherence diaries and AE symptom questionnaires. At each subsequent clinic visit for consideration of an additional NACT cycle, a member of the research team will review medication adherence diaries and AE symptom questionnaires and administer the Voils DOSE-Nonadherence measure survey. If symptoms are concerning for a potential AE, the research team personnel will inquire further and discuss with the PI. Please see subsequent sections related to AE monitoring and reporting. No additional components of history and physical exam will be completed outside standard of care performed by the patient's provider prior to initiation of an additional cycle of NACT. Different patients may undergo different numbers of NACT cycles, and thus the 30-day supply of aspirin will be refilled by a member of the research team when the decision is made to proceed with an additional cycle.

Participants who experience clinically significant adverse drug events such as bleeding or medication intolerance will be withdrawn from the study. Subjects with significant chemotherapy-induced thrombocytopenia (platelet count less than 50,000) will be instructed to stop taking daily aspirin for 1 week until platelet counts normalize. If a subject withdraws from the study voluntarily, there will be no further follow up. If a participant is censored due to development of a VTE or clinically significant AE, the research team will continue to collect clinical data until the end of the predetermined follow up period.

3.4 Selection of Subjects

Subjects receiving NACT for advanced EOC (including primaries of ovarian, Mullerian, fallopian tube, or peritoneal origin) will be recruited from the Duke Gynecology Oncology clinics and will be screened for eligibility by a member of the research team. Sarasota Memorial Health Care System has been added as an additional site for this study and will also recruit patients. Inclusion and exclusion criteria are detailed in a subsequent section.

3.5 Duration of study

Participants will be included in the study from the time of enrollment through the day of their interval debulking surgery or completion of neoadjuvant chemotherapy (for those who will not undergo surgery). The duration of the study will vary depending on the number of cycles participants undergo, but approximately 6 months from enrollment to completion, including follow up.

3.6 Data Analysis and Statistical Considerations

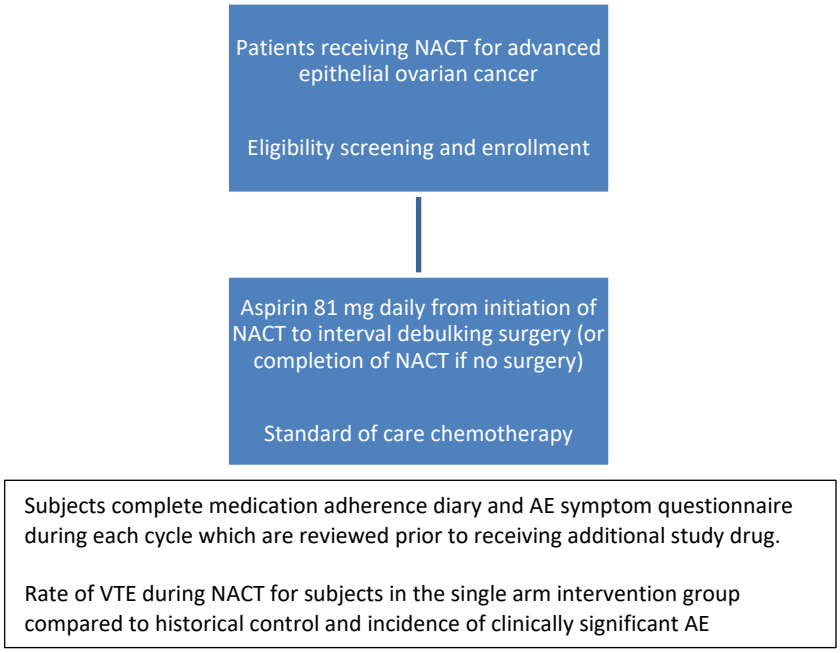
Project Statistician: Gloria Broadwater, MS

The goal for initiating accrual into this study will be September 1st, 2020. Patients will continue to be enrolled through December 30th, 2021. Subjects will be followed through the primary NACT treatment course until interval debulking surgery, with an estimated duration of 6-9 months following enrollment depending on the number of

NACT cycles the individual undergoes. The primary efficacy outcome of this study is rate of VTE among the study cohort during NACT. The primary safety outcome is the incidence of clinically significant adverse drug events. Data from medication adherence diaries and AE symptom questionnaires will be reviewed and entered into the REDCap database. An intention-to-treat analysis will be performed. Subjects withdrawn due to medication intolerance or adverse drug events will be censored, and the research team will continue to collect clinical data for the predetermined follow up period.

We will calculate the incidence of VTE during the study period defined above (enrollment to interval debulking surgery or 1 week after completion of the primary neoadjuvant chemotherapy course if debulking surgery is deferred) and estimate a 95% exact binomial confidence interval. Since this is a pilot study, the incidence of venous thromboembolism in the study population will be compared to a historical control from a previous research study of the incidence of venous thromboembolism among women receiving neoadjuvant chemotherapy for advanced ovarian cancer in which the majority of patients were from Duke. A drop greater than 20% (from approximately 8% to 6.4%) in the rate of venous thromboembolism would be considered clinically meaningful. We will also monitor for adverse safety events related to low dose aspirin use, including major or minor bleeding events, gastrointestinal complications, and medication intolerance (side effects or adverse reaction). Further detail regarding AE monitoring and reporting is outlined in a later section. Finally, we will calculate medication adherence and correlation with patient-reported measures in Voils DOSE-Nonadherence measure quesitonnaires.

4 STUDY SCHEMA



5 BACKGROUND AND SIGNIFICANCE

5.1 Study Condition

In a recent study at our institution, we found that women with advanced ovarian cancer (including primaries of ovarian, Mullerian, fallopian tube, or peritoneal origin) receiving neoadjuvant chemotherapy (NACT) are at high risk for VTE with an incidence of nearly 8%.[8]

Importantly, the occurrence of VTE among patients with EOC is associated with increased morbidity, decreased survival, and increased healthcare costs.[9-11] Timely interval debulking surgery and the ability to achieve of optimal surgical debulking also remain critical components of care for advanced EOC. In the aforementioned study, we observed that the average time from start of NACT to interval debulking surgery was longer for patients who experienced a VTE during NACT as compared to those who had not; these patients were also less likely to have their disease optimally debulked at the time of interval surgery. The high incidence of VTE during NACT reported in our study as well as the associated morbidity contributes to a growing body of evidence suggesting that thromboprophylaxis during NACT is warranted; there is currently no standard of care alternative for thromboprophylaxis during NACT.

5.2 Study Drug

Aspirin is a nonsteroidal anti-inflammatory drug (NSAID) that irreversibly inhibits cyclooxygenase-1 and 2. This activity results in a reduction in platelet aggregation (antiplatelet), which is the rationale for use as an agent for thromboprophylaxis among high risk patients.

5.2.1. Pre-clinical experience of study drug

Aspirin is approved by the Food and Drug Administration (FDA).

5.2.2. Clinical experience

Aspirin is approved by the FDA use as an antipyretic, anti-inflammatory, and analgesic medication. It is also an approved antiplatelet agent following certain revascularization procedures (cardiac stent placement, e.g.) and to reduce the risk of ischemic stroke or myocardial infarction. Aspirin also has several off-label uses, including for primary prevention of atherosclerotic cardiovascular disease, preeclampsia prevention, and for thromboprophylaxis; the latter provided the foundation for the study concept. Specifically, aspirin was found to be noninferior to other forms of anticoagulation for postoperative thromboprophylaxis following total hip and total knee replacement.[12] Aspirin is also an approved alternative agent for thromboprophylaxis among low risk patients with multiple myeloma receiving thalidomide-based chemotherapy and/or dexamethasone.[13] As an oral agent, aspirin may be a more favorable option for patients with the potential for greater medication adherence. Importantly, unpublished data from our institution demonstrated that aspirin is a more cost-effective option for VTE prophylaxis when compared with apixaban, an alternative oral agent.

Since aspirin is already widely used for a variety of indications, the risks and side effects are well-established. Data regarding bleeding events in the setting of limited duration low dose aspirin use for thromboprophylaxis are reassuring. In a retrospective study of low dose aspirin use for postoperative VTE prevention following total hip arthroplasty, the 90-day bleeding rate was 0.52%.[14] Similarly, a systematic review of low dose aspirin thromboprophylaxis after total hip and knee replacements reported no significant difference in cumulative adverse events between low dose aspirin and other anticoagulants; the event rate for major bleeding among patients receiving aspirin was 0.5% with a significant reduction in the incidence of bruising.[12]

References in Section 15

5.3 Study Purpose/Rationale

As previously described, the incidence of VTE during NACT among women with advanced ovarian cancer is nearly 8%. Venous thromboembolic events are associated with increased morbidity, cost, and possibly a longer time to interval debulking surgery, which is a critical component of treatment for advanced ovarian cancer. Reducing the incidence of venous thromboembolism would therefore have a positive impact both on individual patients and on the healthcare system at large.

At present, our institution does not utilize any thromboprophylaxis during NACT for advanced ovarian cancer (including primaries of ovarian, Mullerian, fallopian tube, or peritoneal origin). According to the current guidelines from the American Society of Clinical Oncology, thromboprophylaxis with either apixaban, rivaroxaban, or low molecular weight heparin (LMWH) is recommended for high risk ambulatory cancer patients (defined as a Khorana score greater than or equal to 2) receiving systemic chemotherapy. Patients with a primary gynecologic malignancy receive one point in the Khorana score at baseline, and the majority of ovarian cancer patients would meet criteria for an additional point. High risk Khorana scores defined as 3 or greater have a 6.7-7.1% risk of VTE which is similar to the incidence defined in the previously described study of patients receiving NACT for advanced EOC. These patients are therefore considered high risk for adverse thromboembolic events when initiating systemic chemotherapy.

Considering the above recommended agents, our recent institutional data (unpublished) demonstrated that apixaban is not a cost-effective strategy among women with ovarian cancer receiving NACT specifically, and insurance coverage of apixaban and other direct oral anticoagulants is not yet well established. In addition, a query of medical oncologists affiliated with the Duke Cancer Institute revealed that the majority of providers are generally not initiating direct oral anticoagulants despite the above guidelines. LMWH, another alternative injectable agent, is also expensive and poorly tolerated by patients for prolonged periods of time due to its route of administration. Low dose aspirin, in contrast, is an oral agent and performed better than apixaban in our cost effectiveness analyses even when potential bleeding rates were upwardly adjusted. In addition, low dose aspirin is already used off-label as an acceptable alternative for thromboprophylaxis among low risk patients with multiple myeloma receiving antiangiogenesis agents with chemotherapy and/or dexamethasone as well as for postoperative prophylaxis after some orthopedic procedures. As previously mentioned, there is no alternative agent routinely used for prevention of VTE among women with ovarian cancer receiving NACT.

The above ASCO guidelines were subsequently endorsed by the Society for Gynecologic Oncology in January 2021. Thus initiation of thromboprophylaxis with apixaban, rivaroxaban, or LMWH is recommended for high risk ambulatory gynecologic cancer patients receiving chemotherapy with a Khorana score ≥ 2. Interim analysis of the initial 10 recruited patients demonstrated 3 VTE events. The division of Gynecologic Oncology at Duke subsequently endorsed the new guidelines. However, patients receiving NACT with a KS equal to 1 may also be at risk of a VTE given the high incidence previously documented, and although not candidates for DOAC therapy, may potentially benefit from initiation of low dose aspirin.

6 OBJECTIVES AND ENDPOINTS

	Objective	Endpoint	Analysis
Primary	To determine the efficacy of low dose aspirin for the reduction of venous thromboembolism among women receiving neoadjuvant chemotherapy for advanced ovarian cancer.	Incidence of venous thromboembolism during neoadjuvant chemotherapy.	See Section 13.4
Other Primary	To determine safety and medication adherence with the use of low dose aspirin for the reduction of venous thromboembolism among women receiving neoadjuvant chemotherapy for advanced ovarian cancer.	Incidence of clinically significant adverse drug events. Rate of medication nonadherence.	See Section 13.4

7 INVESTIGATIONAL PLAN

7.1 Study Design

This is a single-arm, single-center, interventional pilot study to determine the efficacy and safety of low dose aspirin for the prevention of VTE among women receiving NACT for advanced ovarian cancer when compared with a historical control.

Eligible participants will be recruited from patients with advanced epithelial ovarian cancer (including primaries of ovarian, Mullerian, fallopian tube, or peritoneal origin) who are initiating NACT at the Duke Gynecology Oncology clinics at the Duke Cancer Center and Macon Pond location (Duke Women's Cancer Care Raleigh) or Sarasota Memorial Healthcare System. A provider will approach the patient and inquire about interest in participating in the study. If the patient desires to receive more information, clinical research personnel will discuss the study with the patient and obtain informed consent if all selection criteria are met (detailed in a prior section). If the patient consents, they will then be considered an enrolled study subject. Electronic consent will be performed in REDcap. Following enrollment in the study, basic demographic information for each patient will be recorded in a secure REDCap database. The initial medical history and physical examination will be conducted per standard of care by the patient's provider at the clinic visit. Patients will be enrolled and will receive aspirin at the Macon Pond location. All study activities will be performed by the study coordinators, so we do not anticipate needing assistance from the Duke Raleigh study team.

The primary selection criterion is a Khorana score of 1; additional criteria are detailed in a subsequent section. The Khorana score will be calculated according to the following parameters in closest proximity to the first cycle of chemotherapy: 1 point for gynecologic cancer, 1 point for BMI ≥35, 1 point for Hgb <10 or use of red blood cell growth factors, 1 point for leukocyte count > 11,000, and 1 point for platelets ≥350,000. Patients therefore have a baseline Khorana score of 1 and are ineligible if any additional Khorana score parameters are met. Prior to the April 2021 amendment, Khorana score was not a part of the inclusion criteria. Any existing patient with a Khorana score of more than 1 who is receiving study drug at the time the amendment is approved will be contacted by the study PI to discuss switching to a DOAC. The patient will have the option to remain on study and complete their aspirin regimen or come off study and begin a DOAC instead. Any existing patients with a Khorana score of more than 1 who have already completed their aspirin regimen and are considered "on follow up" will remain on study.

An estimated 120 patients will receive neoadjuvant chemotherapy for advanced ovarian cancer at Duke Gynecology Oncology clinics for the designated study recruitment period of 09/01/2020 to 12/30/2021 with an estimated 50% accrual rate for a total of 60 enrolled patients. Sarasota Memorial Health Care System has been added as an additional site and plans to recruit an additional 60 subjects.

Once enrolled in the study, subjects will receive a 30-day supply of low dose aspirin from the research team and will be instructed to start taking one 81 mg tablet daily starting the first day of their first NACT cycle. Subjects may also be consented after the first day of their first cycle so long as they are taking the aspirin by the end of the day of their second cycle. Subjects will continue taking aspirin until the day of their interval debulking surgery. Patients who are already on low dose aspirin for another indication will still be eligible for the study but will be instructed to take the study drug such that adherence can be monitored. These patients will continue their prior regimen following completion of NACT. Patients will be instructed to complete medication adherence diaries and AE symptom questionnaires. At each subsequent clinic visit for consideration of an additional NACT cycle, a member of the research team will review medication adherence diaries and AE symptom questionnaires. Patients will also be instructed to complete Voils DOSE-Nonadherence measures at each visit. If symptoms are concerning for a potential AE, the research team personnel will inquire further and discuss with the PI. Please see subsequent sections related to AE monitoring and reporting. No additional components of history and physical exam will be completed outside standard of

care performed by the patient's provider prior to initiation of an additional cycle of NACT. Different patients may receive different numbers of cycles, and thus the 30-day supply of aspirin will be re-filled when the decision is made to proceed with an additional cycle.

This study will not impact standard of care treatment. The incidence of VTE will be calculated from the study population and compared with a historical control from a similar population cohort. The incidence of adverse drug events will also be monitored and reported as detailed in a subsequent section.

3.1.1. Dose Modification

Not applicable

3.1.2. Safety Considerations

Aspirin is a well-established medication used routinely in a variety of clinical contexts. It is FDA-approved for use as an antipyretic, anti-inflammatory, and analgesic medication as well as for use following certain revascularization procedures (cardiac stent placement, e.g.). Low dose aspirin also has several off-label uses, including for primary prevention of atherosclerotic disease, preeclampsia prevention, and for thromboprophylaxis. Specifically, aspirin was found to be noninferior to other forms of anticoagulation for postoperative thromboprophylaxis following total hip and total knee replacement.[12] Aspirin is also approved for thromboprophylaxis among low risk patients with multiple myeloma receiving thalidomide-based chemotherapy and/or dexamethasone.[13]

Since aspirin is already widely used among many different patient populations, the risks and side effects are well-established and primarily include medication intolerance, gastrointestinal complications, and adverse bleeding events. Data regarding bleeding events in the setting of limited duration low dose aspirin use for thromboprophylaxis are reassuring. In a retrospective study of low dose aspirin use for postoperative VTE prevention following total hip arthroplasty, the 90-day bleeding rate was 0.52%.[14] Similarly, a systematic review of low dose aspirin thromboprophylaxis after total hip and knee replacements reported no significant difference in cumulative adverse events between low dose aspirin and other anticoagulants; the event rate for major bleeding among patients receiving aspirin was 0.5% with a significant reduction in the incidence of bruising.[12]

Patients receiving chemotherapy are already closely monitored in the outpatient setting with history, physical examination, and lab evaluations prior to every NACT cycle. At each subsequent clinic visit for consideration of an additional NACT cycle, a member of the research team will review medication adherence diaries and AE symptom questionnaires. If symptoms are concerning for a potential AE, the research team personnel will inquire further and discuss with the PI. Please see subsequent sections related to AE monitoring and reporting. No additional components of history and physical exam will be completed outside standard of care performed by the patient's provider prior to initiation of an additional cycle of NACT. Different patients may receive different numbers of cycles, and thus the 30-day supply of aspirin will be re-filled when the decision is made to proceed with an additional cycle.

Any patient with medication intolerance or clinically significant bleeding will be withdrawn from the study to minimize harm. Patients who experience chemotherapy-related thrombocytopenia with platelet count less than 50,000 will be monitored and asked to hold aspirin prophylaxis for 1 week until platelet counts normalize. A designated member of the research team will perform a cumulative review of

adverse events every 3 months and determine if adverse event rates are greater than expected in this patient population.

Performing a pilot study to determine the efficacy and safety of low dose aspirin for thromboprophylaxis when compared with a historical control will help delineate the feasibility of larger studies in the future. This approach mitigates risk while also exploring the potential benefits for patients and the healthcare system overall.

3.1.3. Missed Doses

Subjects will be asked to complete a medication adherence diary, but study analysis will occur in an intention-to-treat fashion. Thus there will be no consequences or alternative regimens for missed doses.

3.1.4. Concomitant Medications/Therapies

Patients who are already on anticoagulation or an alternative (non-aspirin) antiplatelet agent for a specific indication (e.g., cardiac stent) will be excluded from this study. Subjects will be encouraged to disclose any other medications or supplements to their primary provider to be reviewed for interactions with the study drug. Standard of care chemotherapy will not be altered in any way by this investigation. If subjects are already on low dose aspirin for an alternative indication, they will still be eligible for the study but will be instructed to take the study drug such that adherence can be monitored.

3.1.5. Study Drug Blinding

Not applicable

3.1.6. Randomization

Not applicable.

7.2 Rationale for Selection of Dose, Regimen, and Treatment Duration

As previously described, aspirin is approved by the Food and Drug Administration for use as an antipyretic, anti-inflammatory, analgesic, and antiplatelet medication. It is also used off-label for postoperative thromboprophylaxis following total hip and total knee replacement and for thromboprophylaxis among low risk patients with multiple myeloma receiving thalidomide-based chemotherapy and/or dexamethasone. The dosing, regimen, and treatment duration were established in accordance with the guidelines for the aforementioned off-label uses to achieve an appropriate balance between safety and efficacy. In our study specifically, subjects will be instructed to take 81 mg aspirin daily from the initiation of chemotherapy to the time of their interval debulking surgery, which encompasses the duration of the primary NACT treatment course.

7.3 Rationale for Correlative Studies

Not applicable.

7.4 Definition of Evaluable Subjects, On Study, and End of Study

Evaluable subjects are participants who are enrolled in the study, given the study drug (aspirin) and receiving NACT until interval debulking surgery.

On study participants are those who are receiving aspirin or who are censored due to VTE or AE but for whom clinical data is still being collected.

End of study is defined as one year from the investigation start date.

7.5 Early Study Termination

This study can be terminated at any time for any reason by the PI-sponsor. If this occurs, all subjects on study should be notified as soon as possible. Additional procedures and/or follow up should occur in accordance with Section 10.6, which describes procedures and process for prematurely withdrawn patients.

8 STUDY DRUG

8.1 Names, Classification, and Mechanism of Action

Aspirin is a nonsteroidal anti-inflammatory drug (NSAID) that irreversibly inhibits cyclooxygenase-1 and 2. This activity results in a reduction in platelet aggregation (antiplatelet).

8.2 Packaging and Labeling

Medication will be packaged by the Duke Pharmacy Stockroom. The study team will place a 30-day supply of aspirin in labeled, childproof medication vials provided by the Duke bulk pharmacy. Label information will include: patient name, date of birth, medical record numbers, medication dose, and instructions.

8.3 Supply, Receipt, and Storage

Aspirin will be purchased from the Duke Pharmacy Stockroom and placed in labeled, childproof vials for participant distribution. Trained key personnel will maintain responsibility for study drug storage, inventory and distribution. Study drug (ASA) will be securely stored in locked Duke GYN-ONC Office, White Zone, in a locked cabinet with key in custody of GYN ONC CRC.

8.4 Dispensing and Preparation

Study personnel will dispense study drug in Duke GYN ONC Clinics, outpatient settings. If, for some reason, the patient does not receive the drug in person, the same dispensing protocol will be followed but the drug will instead be mailed to the subject's home. The research team will confirm receipt of the study drug.

8.5 Compliance and Accountability

Subjects will complete medication adherence diaries and AE symptom questionnaires that will be reviewed by the research team at subsequent clinic visits (prior to initiation of each cycle of chemotherapy) and will be input into the REDCap database CRF.

8.6 Disposal and Destruction

The study team will destroy unused study drug at the end of the study.

9 SUBJECT ELIGIBILITY

9.1 Inclusion Criteria

- Khorana score = 1
- Over age 18
- English-speaking female patients
- Able to consent
- Recruited from the Duke Gynecology Oncology clinics or Sarasota Memorial Healthcare System
- Receiving neoadjuvant chemotherapy for advanced epithelial ovarian cancer (including primaries of ovarian, Mullerian, fallopian tube, or peritoneal origin)

9.2 Exclusion Criteria

- Allergy or intolerance to study medication
- Indication for a specific form of non-aspirin antiplatelet (i.e. cardiac stent)
- Already on alternative form of anticoagulation
- Active bleeding
- High risk for active bleeding (i.e. recent intracranial bleed or gastrointestinal bleed, known brain metastases)
- Thrombocytopenia (platelet count < 50,000)
- Unable to complete medication adherence diary
- Unable to take oral medications

10 TRIAL PROCEDURES AND ASSESSMENTS

Eligible participants will be recruited from patients with advanced epithelial ovarian cancer (including primaries of ovarian, Mullerian, fallopian tube, or peritoneal origin) who are initiating NACT at the Duke Gynecology Oncology clinics at the Duke Cancer Center and Macon Pond location (Duke Women's Cancer Care Raleigh) or at Sarasota Memorial Healthcare System. A provider will approach the patient and inquire about interest in participating in the study. If the patient desires to receive more information, clinical research personnel will discuss the study with the patient and obtain informed consent if all selection criteria are met (detailed in a prior section). If the patient consents, they will then be considered an enrolled study subject. Electronic consent will be performed in REDcap. Following enrollment in the study, basic demographic information for each patient will be recorded in a secure REDCap database. The initial medical history and physical examination will be conducted per standard of care by the patient's provider at the clinic visit.

Patients will be enrolled and will receive aspirin at the Macon Pond location. All study activities will be performed by the study coordinators, so we do not anticipate needing assistance from the Duke Raleigh study team.

An estimated 120 patients will receive neoadjuvant chemotherapy for advanced ovarian cancer at Duke Gynecology Oncology clinics for the designated study recruitment period of 09/01/2020 to 12/30/2021 with an estimated 50% accrual rate for a total of 60 enrolled patients. Sarasota Memorial Health Care System has been added as an additional site and plans to recruit an additional 60 subjects.

Once enrolled in the study, subjects will receive a 30-day supply of low dose aspirin from the research team and will be instructed to start taking one 81 mg tablet daily starting the first day of their first NACT cycle. Subjects may also be consented after the first day of their first cycle so long as they are taking the aspirin by the end of the day of their second cycle. Subjects will continue taking aspirin until the day of their interval debulking surgery unless previously on low dose aspirin for an alternative indication, in which case they will continue as directed by the prescribing physician. Patients will be instructed to complete medication adherence diaries and AE symptom questionnaires. At each subsequent clinic visit for consideration of an additional NACT cycle, a member of the research team will review medication adherence diaries and AE symptom questionnaires. If symptoms are concerning for a potential AE, the research team personnel will inquire further and discuss with the PI. Please see subsequent sections related to AE monitoring and reporting. No additional components of history and physical exam will be completed outside standard of care performed by the patient's provider prior to initiation of an additional cycle of NACT. Different patients may receive different numbers of cycles, and thus the 30-day supply of aspirin will be re-filled when the decision is made to proceed with an additional cycle.

This study will not impact standard of care treatment. The incidence of venous thromboembolism will be calculated from the study population and compared with a historical control. The incidence of adverse drug events will also be monitored and reported as detailed in a subsequent section.

Subjects will be followed as described above from the initiation of NACT and enrollment through interval debulking surgery unless they withdraw. There will be no additional monitoring in this follow up period with the exception of standard of care evaluation and documentation of the primary outcomes, including adverse drug events.

An outline of the trial procedures and assessments is detailed below:

	Treatment initiation						End of Study

Phase	Screening	Cycle 1	Cycle 2	Cycle 3	Cycle 4	Cycle 5	Cycle 6	Follow-up (interval debulking surgery or completion of NACT)
Obtain Informed Consent	X							
Vital Signs	X	X	X	X	X	X	X	X
Height	X	X						
Weight, BP, Pulse	X	X	X	X	X	X	X	X
Laboratory Assessments (per standard of care)	X	X	X	X	X	X	X	X
Adverse Events		X	X	X	X	X	X	X
Medication Adherence Diary		X	X	X	X	X	X	X
Voils DOSE-Nonadherence measure		X	X	X	X	X	X	X
Provision of additional 30-day supply of study drug		X	X	X	X	X	X	

10.1 Screening Examination

Not applicable

10.2 Treatment Period

Subjects will be instructed to take one 81 mg tablet aspirin daily per study protocol from the time of initiation of NACT through the day of their interval debulking surgery.

10.3 End of Treatment

End of treatment is defined as the day of the subject's interval debulking surgery or, if the patient is not undergoing surgery, 1 week following the last cycle of NACT.

10.4 Follow-up Period

Patients will be followed from initiation of NACT through interval debulking surgery without any additional follow up period.

10.5 End of Study

End of study is defined as one year following initiation of study. We do not anticipate loss to follow up given the association between the study intervention and receipt of neoadjuvant chemotherapy. Participants will be censored at the time of VTE diagnosis or if aspirin is discontinued due to clinically significant AE. In the event

of censorship, data will continue to be collected by the study team until the predetermined follow up period is complete (interval debulking surgery or following completion of NACT, if no surgery).

10.6 Early Withdrawal of Subject(s)

6.6.1. Criteria for Early Withdrawal

Subjects may voluntarily withdraw from the study at any time. The PI may also withdraw a subject from the study at any time based on his/her discretion. Reasons for PI-initiated withdrawal may include, but is not limited to the following:

- Khorana score greater than 1
- Adverse events
- Abnormal laboratory values
- Abnormal test procedure results
- Protocol deviation
- Administrative issues
- Disease progression
- Pregnancy

6.6.2. Follow-up Requirements for Early Withdrawal

When subjects withdraw from the study, whether voluntarily or due to adverse drug events, they will continue to receive standard of care treatment at the discretion of their Gynecology Oncology provider and will continue to be followed accordingly. Since no other method of thromboprophylaxis is routinely implemented during NACT for ovarian cancer, subjects will not receive any other regimen. If subjects withdraw voluntarily, no additional follow up will be required. If subjects are withdrawn due to VTE occurrence of clinically significant AE, the study team will continue to collect clinical data until the predetermined follow up period is complete (interval debulking surgery or following completion of NACT, if no surgery).

6.6.3. Replacement of Early Withdrawal(s)

Subjects who prematurely withdraw from the study will not be replaced.

10.7 Study Assessments

6.7.1. Medical History

Medical history assessments will be conducted at the discretion of the provider per standard of care at clinic visits prior to the initiation of each cycle of chemotherapy. Questionnaires related to assessment of adverse drug events will be administered to subjects at these visits. If there is concern for AEs, a member of the research team will ask additional history to further delineate these events, but no additional medical history will be obtained outside of these requirements.

6.7.2. Physical Exam

Physical examination will be conducted at the discretion of the provider per standard of care at clinic visits prior to the initiation of each cycle of chemotherapy. No additional physical examination components will be required by the study team beyond what is routinely included in clinic visits.

6.7.3. Subject-Rated Measures at Clinic Visits and/or in Daily Diaries

Subjects will be asked to complete medication adherence diaries with each cycle of chemotherapy that will be evaluated by the research team. Data from these diaries will be added to the REDCap database. An example is included in the appendix section 16. Medication adherence diaries will also include a section in which subjects can detail symptoms or adverse events that may be related to use of the study drug. These will be reviewed by a member of the study team at each clinic visit and additional inquiries made, if applicable, when the subject is seen by a member of the study team. At each clinic visit, subjects will also complete the Voils DOSE-Nonadherence questionnaire to evaluate medication adherence.

11 SAFETY MONITORING AND REPORTING

The PI is responsible for the identification and documentation of adverse events and serious adverse events, as defined below. At each study visit, the PI or designee must assess, through non-suggestive inquiries of the subject or evaluation of study assessments, whether an AE or SAE has occurred.

11.1 Adverse Events

An adverse event (AE) is any untoward medical occurrence in a subject receiving study therapy and which does not necessarily have a causal relationship with this treatment. For this protocol, the definition of AE also includes worsening of any pre-existing medical condition. An AE can therefore be any unfavorable and unintended or worsening sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of study therapy, whether or not related to use of the study therapy. Abnormal laboratory findings without clinical significance (based on the PI's judgment) should not be recorded as AEs. But laboratory value changes that require therapy or adjustment in prior therapy are considered adverse events.

From the time the subject signs the informed consent form through the End of Study visit (as defined in Section 10.3), all AEs must be recorded in the subject medical record and adverse events case report form.

AEs will be assessed according to the CTCAE version 4.0. If CTCAE grading does not exist for an AE, the severity of the AE will be graded as mild (1), moderate (2), severe (3), life-threatening (4), or fatal (5).

Attribution of AEs will be indicated as follows:

- Definite: The AE is clearly related to the study therapy
- Probably: The AE is likely related to the study therapy
- Possible: The AE may be related to the study therapy
- Unlikely: The AE is doubtfully related to the study therapy
- Unrelated: The AE is clearly NOT related to the study therapy

7.1.1. AEs of Special Interest

Adverse events of special interest related to low dose aspirin use include:

- Major bleeding events (as defined by the International Society on Thrombosis and Hemostasis as fatal bleeding, symptomatic bleeding in a critical area or organ, or bleeding causing a decrease in hemoglobin of 2g/dL or more or leading to a transfusion of 2 or more units of blood)
- Minor bleeding events (all other clinically significant bleeding events not addressed by the above criteria)
- Medication intolerance (defined as intolerable medication side effects or adverse medication reaction)

7.1.2. Reporting of AEs

The study team, including PI, will be alerted in the event of an AE. AEs will be reported as required by the Institutional Review Board as described above.

11.2 Serious Adverse Events

An AE is considered "serious" if in the opinion of the investigator it is one of the following outcomes:

- Fatal
- Life-threatening

- Constitutes a congenital anomaly or birth defect
- A medically significant condition (defined as an event that compromises subject safety or may require medical or surgical intervention to prevent one of the three outcomes above).
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant incapacity or substantial disruption to conduct normal life functions.

7.2.1. Reporting of SAEs

The study team, including PI, will be alerted in the event of an serious AE. Serious AEs will be reported as required by the Institutional Review Board as described above.

11.3 Emergency Unblinding of Investigational Treatment

Not applicable

11.4 Other Reportable Information

Pregnancy tests are conducted as standard of care prior to initiation of chemotherapy for women of reproductive age. The research team will be notified in the event of pregnancy and the patient will be withdrawn from the study.

11.5 Special Warnings and Precautions

As above, pregnancy tests are conducted as standard of care prior to initiation of chemotherapy for women of reproductive age. The research team will be notified in the event of pregnancy and the patient will be withdrawn from the study.

11.6 Stopping Rules

Any patient with medication intolerance or clinically significant bleeding will be withdrawn from the study to minimize harm. In the event of chemotherapy-induced thrombocytopenia with platelet count less than 50,000, participants will be asked to hold aspirin for 1 week until platelet counts normalize.

11.7 Safety Oversight Committee (SOC)

Since this is a pilot phase IV study, the safety oversight committee is not applicable.

11.8 External Data and Safety Monitoring Board (DSMB)

No member of the research team, including the PI, has a potential conflict of interest with the conduct of this protocol.

12 QUALITY CONTROL AND QUALITY ASSURANCE

12.1 Monitoring

This clinical research study will be monitored both internally by the PI, and institutionally by the Duke Cancer Institute (DCI). In terms of internal review the PI will continuously monitor and tabulate adverse events. Appropriate reporting to the Duke University Medical Center IRB will be made. If an unexpected frequency of Grade III or IV events occur, depending on their nature, action appropriate to the nature and frequency of these adverse events will be taken. This may require a protocol amendment, dose de-escalation, or potentially closure of the study. The PI of this study will also continuously monitor the conduct, data, and safety of this study to ensure that:

- Interim analyses occur as scheduled;
- Stopping rules for toxicity and/or response are met;
- Risk/benefit ratio is not altered to the detriment of the subjects;
- Appropriate internal monitoring of AEs and outcomes is done;
- Over-accrual does not occur;
- Under-accrual is addressed with appropriate amendments or actions;
- Data are being appropriately collected in a reasonably timely manner.

DCI Protocol Review and Monitoring systems (PRMS) review of this protocol begins with an initial review by the Cancer Protocol Committee (CPC). CPC new protocol review focuses on scientific relevance, study design, adequacy of biostatistical input, protocol prioritization, feasibility of completing the study within a reasonable time frame and risk assessment of the trial. The PI will abide by CPC assessment of the level of risk, which will determine the intensity of subsequent DCI monitoring. CPC also conducts annual scientific progress reviews on protocols that are open to enrollment and focus on protocol prioritization, accrual and scientific progress. These reviews are conducted at the time of IRB annual renewals and documentation of all CPC reviews will be maintained in eIRB/iRIS systems.

A determination for the degree of monitoring conducted by the DCI monitoring team is made at the time of initial CPC approval to commensurate with the type and level of intervention, phase, endpoints, degree of risk, size and complexity of the protocol. A formal, independent monitoring will be conducted by the DCI monitoring team according to the risk level and monitoring plan assigned by the CPC until the study is closed to enrollment or subjects are no longer receiving study drug or other interventions that are more than minimal risk. Additional monitoring may be prompted by findings from monitoring visits, unexpected frequency of serious and/or unexpected toxicities, or other concerns. Monitoring visits may also be initiated upon request by DUHS and DCI Leadership, CPC, SOC, a sponsor, an investigator, or the IRB.

The DCI monitoring team reviews the adequacy of informed consent, enrollment of eligible patients, implementation of protocol-specified procedures and treatment, adequacy of data collection, and appropriateness of adverse event monitoring and reporting. The DCI monitoring team presents final monitoring reports to the DCI Safety Oversight Committee (SOC) highlighting safety concerns and unresolved issues. The SOC, at a convened meeting, assigns an overall rating of satisfactory, marginal, or unsatisfactory to reflect the overall quality of data, regulatory, consent, eligibility, study conduct and AE reporting. Corrective action plans (CAPs) are developed, implemented, and evaluated as indicated. The SOC will notify the sponsor-investigator and DUHS IRB when significant safety concerns are identified.

The SOC in concert with DCI monitoring team conducts data and safety monitoring for DUHS sponsor-investigator phase I and II, therapeutic interventional oncology studies that do not have an independent DSMB. These reviews occur at a minimum annually and more frequently for the high risk studies. The SOC safety reviews include review of safety data, enrollment status, stopping rules if applicable, accrual, toxicities,

reference literature, and interim analyses as provided by the sponsor-investigator. The SOC, at a convened meeting, assigns a rating of satisfactory when adequate accrual with lack of excessive toxicity is present.

12.2 Data Management and Processing

8.3.1. Case Report Forms (CRFs)

The electronic CRF in REDCap will be the primary data collection document for the study. The CRFs will be updated in a timely manner following acquisition of new source data. Only approved study staff as approved in Key Personnel are permitted to make entries, changes, or corrections in the CRF.

An audit trail will be maintained automatically by the electronic REDCap CRF management system. Designated personnel will complete user training, as required or appropriate per regulations.

8.3.2. Data Management Procedures and Data Verification

Designated personnel using the electronic CRF will have access based on their specific roles in the protocol. These are outlined in the REDCap system and all requests must be approved by the owners of the database (PI, coordinators). Only individuals specified as Key Personnel will be included.

Completeness of entered data will be checked automatically by the eCRF system, and users will be alerted to the presence of data inconsistencies. Additionally, the data manager and research team coordinators, Taylor Hayes and Julia Salinaro, will cross-reference the data to verify accuracy. Missing or implausible data will be highlighted for the PI requiring appropriate responses (i.e. confirmation of data, correction of data, completion or confirmation that data is not available, etc.).

The database will be reviewed and discussed prior to database closure, and will be closed only after resolution of all remaining queries. An audit trail will be kept of all subsequent changes to the data.

8.3.3. Study Closure

Following completion of the studies, the PI will be responsible for ensuring the following activities:

- Data clarification and/or resolution
- Accounting, reconciliation, and destruction/return of used and unused study drugs
- Review of site study records for completeness

13 STATISTICAL METHODS AND DATA ANALYSIS

All statistical analysis will be performed under the direction of the statistician designated in key personnel, Gloria Broadwater. Any data analysis carried out independently by the investigator must be approved by the statistician before publication or presentation.

13.1 Analysis Sets

The analysis set will include data from the study cohort for the duration of the defined study period. Considerations for data analysis are outlined below.

13.2 Patient Demographics and Other Baseline Characteristics

Baseline characteristics analyzed will include age, body mass index, CA-125 at diagnosis, Khorana score, ECOG performance score, and number of cycles of neoadjuvant chemotherapy.

13.3 Treatments

This is a single arm study with the intervention arm receiving 81 mg aspirin daily during the primary neoadjuvant chemotherapy treatment course.

13.4 Primary Objective

Refer to Section 6 for the primary objective and endpoint. In brief, the primary objectives of this study are to determine the efficacy and safety of low dose aspirin for the prevention of VTE among women receiving neoadjuvant chemotherapy for advanced ovarian cancer.

8.4.

8.7.1. Variable

The study variable is whether or not women receive aspirin thromboprophylaxis during neoadjuvant chemotherapy.

8.7.2. Statistical Hypothesis, Model, and Method of Analysis

The goal for initiating accrual into this study will be September 1st, 2020. Patients will continue to be enrolled through December 30th, 2021. Subjects will be followed through the primary NACT treatment course until interval debulking surgery, with an estimated duration of 6-9 months following enrollment depending on the number of NACT cycles the individual undergoes. The primary efficacy outcome of this study is rate of VTE among the study cohort during NACT. The primary safety outcome is the incidence of clinically significant adverse drug events. Data from medication adherence diaries and AE symptom questionnaires will be reviewed and entered into the REDCap database. An intention-to-treat analysis will be performed. Subjects withdrawn due to medication intolerance or adverse drug events will be censored, and the research team will continue to collect clinical data for the predetermined follow up period.

We will calculate the incidence of VTE during the study period defined above (enrollment to interval debulking surgery or 1 week after completion of the primary neoadjuvant chemotherapy course if debulking surgery is deferred) and estimate a 95% exact binomial confidence interval. Since this is a pilot study, the incidence of venous thromboembolism in the study population will be compared to a historical control from a previous research study

of the incidence of venous thromboembolism among women receiving neoadjuvant chemotherapy for advanced ovarian cancer in which the majority of patients were from Duke. A drop greater than 20% (from approximately 8% to 6.4%) in the rate of venous thromboembolism would be considered clinically meaningful. If the true VTE rate is 6.4%, the width of the 95% exact binomial confidence interval will be 0.098. We will also monitor for adverse safety events related to low dose aspirin use, including major or minor bleeding events, gastrointestinal complications, and medication intolerance (side effects or adverse reaction). Further detail regarding AE monitoring and reporting is outlined in a previous section.

8.7.3. Handling of missing values, censoring, and discontinuations

An intention-to-treat analysis will be performed for all enrolled subjects. Due to the small sample size, we will not impute missing data. If a participant is censored due to the occurrence of a VTE or a significant AE, the study team will continue to collect clinical data until the predetermined follow up period is complete.

13.5 Interim Analysis

As this is a pilot study, we do not intend to perform any interim analysis. However the study team, including the PI, will review cumulative adverse drug events every 3 months.

13.6 Sample Size Calculation

Sample size calculation is not applicable to this study. Since this is a pilot investigation, the incidence of venous thromboembolism in the study population will be compared to a historical control from a previous research study of the incidence of venous thromboembolism among women receiving neoadjuvant chemotherapy for advanced ovarian cancer in which the majority of patients were from Duke. A drop greater than 20% (from approximately 8% to 6.4%) in the rate of venous thromboembolism would be considered clinically meaningful.

14 ADMINISTRATIVE AND ETHICAL CONSIDERATIONS

14.1 Regulatory and Ethical Compliance

This protocol was designed and will be conducted and reported in accordance with the International Conference on Harmonization (ICH) Harmonized Tripartite Guidelines for Good Clinical Practice, the Declaration of Helsinki, and applicable federal, state, and local regulations.

14.2 DUHS Institutional Review Board and DCI Cancer Protocol Committee

The protocol, informed consent form, advertising material, and additional protocol-related documents must be submitted to the DUHS Institutional Review Board (IRB) and DCI Cancer Protocol Committee (CPC) for review. The study may be initiated only after the Principal Investigator has received written and dated approval from the CPC and IRB.

The Principal Investigator must submit and obtain approval from the IRB for all subsequent protocol amendments and changes to the informed consent form. The CPC should be informed about any protocol amendments that potentially affect research design or data analysis (i.e. amendments affecting subject population, inclusion/exclusion criteria, agent administration, statistical analysis, etc.).

The Principal Investigator must obtain protocol re-approval from the IRB within 1 year of the most recent IRB approval. The Principal Investigator must also obtain protocol re-approval from the CPC within 1 year of the most recent IRB approval, for as long as the protocol remains open to subject enrollment.

14.3 Informed Consent

The informed consent form must be written in a manner that is understandable to the subject population. Prior to its use, the informed consent form must be approved by the IRB.

The Principal Investigator or authorized key personnel will discuss with the potential subject the purpose of the research, methods, potential risks and benefits, subject concerns, and other study-related matters. This discussion will occur in a location that ensures subject privacy and in a manner that minimizes the possibility of coercion. Appropriate accommodations will be made available for potential subjects who cannot read or understand English or are visually impaired. Potential subjects will have the opportunity to contact the Principal investigator or authorized key personnel with questions, and will be given as much time as needed to make an informed decision about participation in the study.

Before conducting any study-specific procedures, the Principal Investigator must obtain written informed consent from the subject or a legally acceptable representative. The original informed consent form will be stored with the subject's study records, and a copy of the informed consent form will be provided to the subject. The Principal Investigator is responsible for asking the subject whether the subject wishes to notify his/her primary care physician about participation in the study. If the subject agrees to such notification, the Principal Investigator will inform the subject's primary care physician about the subject's participation in the clinical study.

14.4 Study Documentation

Study documentation includes but is not limited to source documents, case report forms (CRFs), monitoring logs, appointment schedules, study team correspondence with sponsors or regulatory bodies/committees, and regulatory documents that can be found in the DCI-mandated "Regulatory Binder", which includes but is not limited to signed protocol and amendments, approved and signed informed consent forms, FDA Form 1572, CAP and CLIA laboratory certifications, and clinical supplies receipts and distribution records.

Source documents are original records that contain source data, which is all information in original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source documents include but are not limited to hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories and at medico-technical departments involved in the clinical trial. When possible, the original record should be retained as the source document. However, a photocopy is acceptable provided that it is a clear, legible, and an exact duplication of the original document.

An electronic case report form (CRF) will be the primary data collection document for the study. The CRFs will be updated within two weeks of acquisition of new source data. Only study staff designated in Key Personnel and approved within the study REDCap database are permitted to make entries, changes, or corrections in the CRF. An audit trail will be maintained by the REDCap electronic CRF management system.

14.5 Privacy, Confidentiality, and Data Storage

The Principal Investigator will ensure that subject privacy and confidentiality of the subject's data will be maintained. Research Data Security Plans (RDSPs) will be approved by the appropriate institutional Site Based Research group.

To protect privacy, every reasonable effort will be made to prevent undue access to subjects during the course of the study. Prospective participants will be consented in an exam room where it is just the research staff, the patient and his family, if desired. For all future visits, interactions with research staff (study doctor and study coordinators) regarding research activities will take place in a private exam room. All research related

interactions with the participant will be conducted by qualified research staff who are directly involved in the conduct of the research study.

To protect confidentiality, subject files in paper format will be stored in secure cabinets under lock and key accessible only by the research staff. Subjects will be identified only by a unique study number and subject initials. Electronic records of subject data will be maintained using a dedicated database (REDCap) which is housed in the encrypted and password-protected laptop computers of study personnel. Access to electronic databases will be limited to (please specify). Subject data may be stored temporarily on encrypted and password-protected portable memory devices such as flash drives and external hard drives, but only when absolutely necessary. Data stored on portable memory devices will be de-identified. Subject data will be deleted from the portable memory device at the earliest opportunity. The security and viability of the IT infrastructure will be managed by the DCI and/or Duke Medicine.

Upon completion of the study, research records will be archived and handled per DUHS HRPP policy.

Subject names or identifiers will not be used in reports, presentations at scientific meetings, or publications in scientific journals.

14.6 Data and Safety Monitoring

For a more detailed description of the DSMP for this protocol, refer to Section 11 (Sections 11.7 and 11.8 in particular) along with section 12.

14.7 Protocol Amendments

All protocol amendments must be initiated by the Principal Investigator and approved by the IRB prior to implementation. IRB approval is not required for protocol changes that occur to protect the safety of a subject from an immediate hazard. However, the Principal Investigator must inform the IRB and all other applicable regulatory agencies of such action immediately.

14.8 Records Retention

The Principal Investigator will maintain study-related records for the longer of a period of:

- at least six years after study completion (Duke policy)

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16 APPENDICES

A sample medication adherence diary and AE symptom questionnaire are included as part of the Institutional Review Board application.