Academic and Community Cancer Research United (ACCRU)

**A Phase III, Randomized, Open label Study Evaluating the Safety of Apixaban in Subjects with Cancer Related Venous thromboembolism**

***For any comminications regarding this protocol, please contact the person indicated on the Protocol Resource Page. This is a stand-alone document found on the ACCRU web site (www.ACCRU.org)***

ACCRU Study Chairs: Robert D. McBane, M.D.
Mayo Clinic
200 First Street SW
Rochester, MN 55905
507/284-4565
Mcbane.robert@mayo.edu

Charles L. Loprinzi, M.D.
Mayo Clinic
200 First Street SW
Rochester, MN 55905
507/284-4565
cloprinzi@mayo.edu

Co-Chair: [redacted]

Statistician: [redacted]

**Drug Availability**

**Drug Company Supplied:** Apixaban (Eliquis®) IND Exempt;
Dalteparin (Fragmin®) (commercial supply)

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

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

| Document History | (effective date) |
|---|---|
| Pre-activation ACCRU | September 11, 2015 |
| Activation | November 20, 2015 |
| Amendment 1 | December 10, 2015 |
| Amendment 2 | April 22, 2016 |
| Amendment 3 | December 01, 2017 |

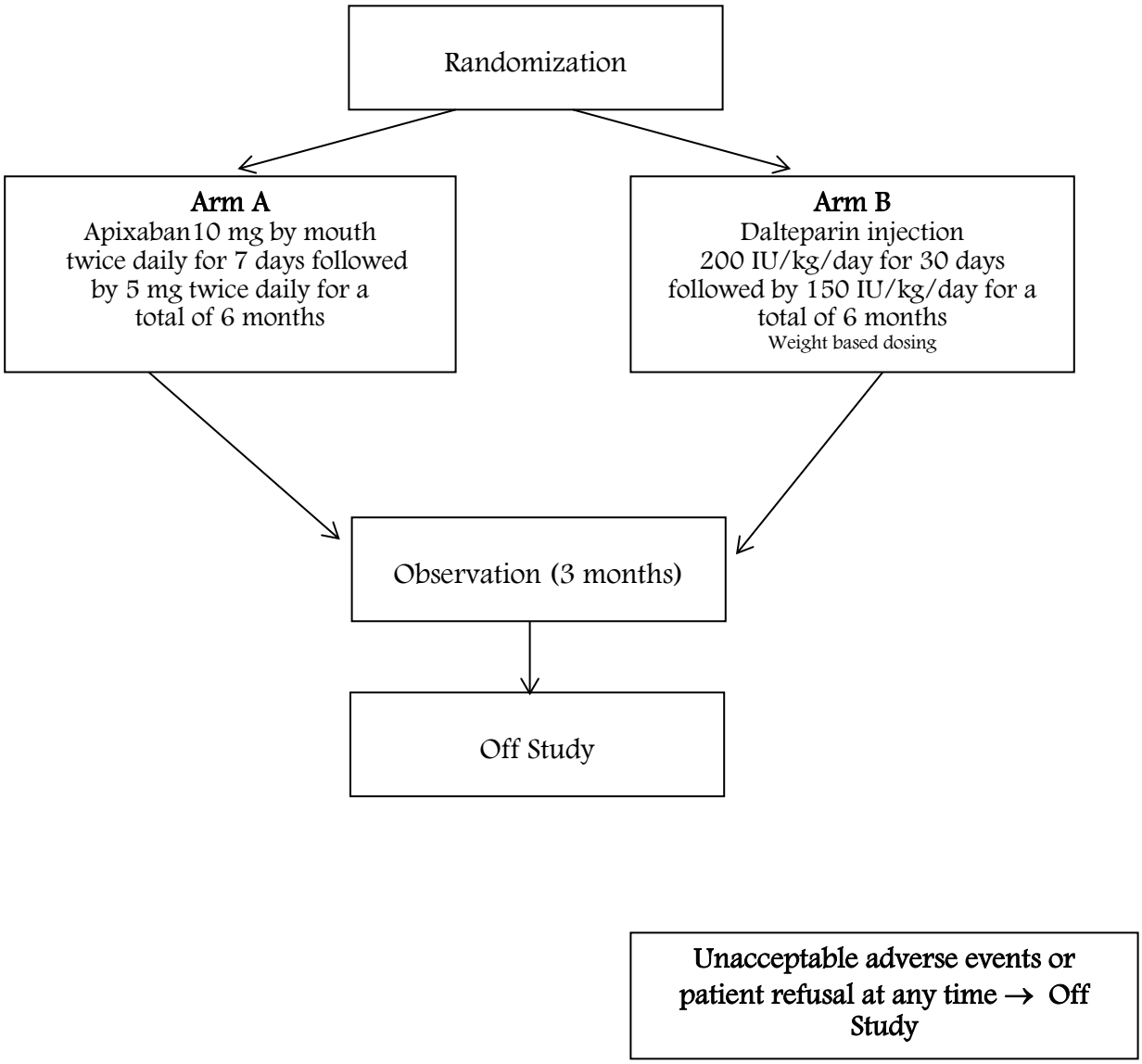
This trial will be conducted in compliance with the protocol, GCP and the applicable regulatory requirement(s). (ICH E6 section 6.2.5)

ACCRU version date: April 22, 2016

**Index**



**Schema**




Cycle = 30 days
Observation = 3 months
Note that 'cycle' information is a data management tool to facilitate remote data entry.

| | |
|---|---|
| Generic name: Apixaban<br>Brand name(s): Eliquis®<br>ACCRU Abbreviation: APIXABAN<br>Availability: Biologics, Inc. | Generic name: Dalteparin<br>Brand name(s): Fragmin®<br>ACCRU Abbreviation: DALTEPARIN<br>Availability: Biologics, Inc. |

ACCRU version date: April 22, 2016

## 1.0 Background

### 1.1 Treatment

The association between cancer and venous-thromboembolism (VTE) is strong and well established (1-4). Active cancer with and without chemotherapy increases the risk of VTE by 5 to 6 fold (5). Furthermore, active cancer accounts for about 20% of the VTE burden occurring in a community (6). VTE is the second most common cause of death among patients with cancer (7). Indeed, cancer patients with VTE have a 2-fold or greater increase in mortality compared with cancer patients without VTE, even after adjusting for stage (8,9). Nearly half of the patients with cancer associated VTE have distant metastasis at the time of VTE diagnosis (8). The incidence of cancer in patients with recurrent idiopathic VTE is higher than in patients with secondary VTE (3).
The management of patients with active cancer can be particularly challenging given their increased propensity for both VTE recurrence as well as major bleeding (10-15). Patients with cancer pose a special challenge because of an increased risk of thrombosis due to cancer-specific prothrombotic activity, hormonal therapy, angiogenesis inhibitors and radiotherapy, and the presence of chronic indwelling central venous catheters (10,14,16). At the same time, cancer patients are at increased risk of major bleeding due to chemotherapy-related hepatic dysfunction, kidney injury, thrombocytopenia, and tumor friability (15,16).

There have been four important treatment trials of cancer associated VTE (17-22). The CLOT trial randomized 672 patients with active cancer and acute VTE to receive either low molecular weight heparin (LMWH) (Dalteparin 200 IU/kg/day for 1 month followed by 150 IU/kg/day for 5 months) or adjusted dose warfarin (18). At the end of the six-month study period, recurrent thromboembolism was 17% in the oral-anticoagulant group and 9% in the dalteparin group (hazard ratio, 0.48; P=0.002). There was no significant difference between groups in the rate of major bleeding (dalteparin 6% vs. warfarin 4%). Overall mortality rates did not differ between treatment arms. Substudy analysis of the CLOT trial however revealed improved survival in cancer patients without metastasis receiving dalteparin compared to warfarin (19). For patients with metastatic disease, there was no difference in survival by treatment allocation. In a separate study, 146 cancer patients with active VTE were randomized to receive enoxaparin (1.5mg/kg/day) or warfarin for 3 months (20). During the 3-month treatment period, patients assigned to receive warfarin experienced more major hemorrhage or recurrent thromboembolism (21.1%) compared to enoxaparin (10.5%) however this did not reach statistical significance (P = .09). Using a time to major event (recurrent VTE or major bleed) analysis, enoxaparin was however more effective than warfarin (p=0.04). The ONCENOX investigators compared enoxaparin (enoxaparin 1.0 mg/kg every 12 hours for 5 days, followed by 1.0 mg/kg daily or 1.5 mg/kg daily for 175 days) to warfarin in 122 adults with active malignancy (21). Enoxaparin treatment was feasible, generally well tolerated, and effective for a 180-day period in the secondary prevention of venous thromboembolic events in patients with active malignancy. There were no significant differences in major and minor bleeding rates between treatment groups. The LITE investigators compared once daily subcutaneous tinzaparin to warfarin in 200 adult cancer patients with acute VTE (22). At 12 months, warfarin treated patients had greater recurrent venous thromboembolism (16% versus 7%) compared to those receiving LMWH (P=.044; risk ratio=0.44; absolute difference -9.0; 95% CI -21.7 to -0.7). Major bleeding rates did not differ between the two groups.

Based on these four treatment trials in cancer patients, guideline recommendations for patients with VTE in the setting of an active malignancy include extended anticoagulation with LMWH as the preferred anticoagulant regardless of the bleeding risk (17). Anticoagulants are continued until there is no evidence of active malignancy defined as any evidence of cancer on cross-sectional imaging or any cancer related treatment (surgery, radiation, or chemotherapy) within the past 6 months. Chronic LMWH therapy however has several disadvantages. First, LMWH is given either once or twice daily by subcutaneous injections which may be painful and cause considerable local ecchymoses and hematomas. Second, the cost of LMWH may be prohibitive. For individuals without insurance, this can be more than $100 USD daily. Because this treatment is often given for months on end, health-care costs for medications alone can be thousands of dollars. Third, thrombocytopenia associated with the cancer or cancer treatments limit its use and raise clinical concerns regarding possible heparin induced thrombocytopenia. Fourth, there is neither a specific nor effective proven antidote should the patient develop bleeding complications. Fifth, renal failure which can be common with cancer or cancer related treatment limits the use of this medication. For these combined reasons, an alternative anticoagulation therapy for patients with cancer associated VTE would be extremely attractive.

## 1.2 Investigational Agent

Apixaban (Eliquis) is an oral direct factor Xa inhibitor which impairs coagulation by inhibiting the conversion of prothrombin to thrombin. It does not require antithrombin for antithrombotic activity and inhibits both free and clot-bound FXa. Apixaban has a half-life of about 12 hours and thus is dosed twice-daily. Bioavailability is approximately 50% after oral dosing with maximum concentrations at 4 hours post ingestion. The pharmacokinetics are linear and plasma protein binding in humans is high at approximately 87% with a volume of distribution of approximately 21 liters. Apixaban is metabolized in the liver mainly via the CYP3A4 pathway. Renal excretion accounts for about 27% of total clearance. Approximately 25% of the drug is eliminated in the urine and feces. This drug is not dialyzable due to its high plasma protein binding. ("The dialysis clearance of apixaban is approximately 18 mL/min resulting in a 14% decrease in exposure due to hemodialysis compared to off-dialysis period.") Apixaban is currently FDA approved for the treatment of DVT and PE, and for the reduction in the risk of recurrent DVT and PE following initial therapy, for the prophylaxis of deep vein thrombosis (DVT), which may lead to pulmonary embolism (PE), in patients who have undergone hip or knee replacement surgery and reducing the risk of stroke/systemic embolism in the setting of non-valvular atrial fibrillation.

## 1.3 Clinical Data to Date

The AMPLIFY investigators randomized 5395 patients with acute VTE to either apixaban (10 mg twice daily for 7 days followed by 5 mg twice daily for 6 months) or enoxaparin/warfarin (23). The primary efficacy outcome, recurrent symptomatic VTE or death related to VTE, occurred in 2.3% in the apixaban group compared to 2.7% in the conventional-therapy group. From an efficacy standpoint, apixaban was therefore deemed non-inferior to standard anticoagulant therapy. Both major bleeding and the composite of major plus non-major yet clinically relevant bleeding were significantly lower for patients receiving apixaban. The Amplify Extend investigators randomized 2482 patients with VTE who had recently completed 6 – 12 months of anticoagulation to

receive one of two doses of apixaban (5 mg twice daily or 2.5 mg twice daily) or placebo for an additional 12 months. Both apixaban doses reduced recurrent VTE without increasing major bleeding compared to placebo (24).

Despite these trial results, apixaban is not currently recommended for cancer related VTE treatment or prevention for several reasons. First, there are limited data supporting the use of apixaban in cancer patients with no trials specifically designed to evaluate its utility in cancer patients. In the AMPLIFY trial, only 2.65% (143 patients) had underlying cancer as a risk factor with only 66 patients with active cancer in the apixaban arm. In order to gain guideline endorsement, apixaban must be assessed in a randomized controlled trial compared to the current gold standard anticoagulation standard for cancer patients. The current standard of care for these patients is LMWH, and specifically dalteparin. Moreover the comparator in AMPLIFY was warfarin which is not guideline endorsed therapy in this setting. Second, opinion leaders in the field often recommend against the use of factor Xa inhibitors in cancer patients with VTE (personal communication). Third, many of our patients are concerned about starting a novel anticoagulant for cancer associated VTE treatment in the absence of data (personal experience). Irrespective of this knowledge limitation, the hypothesis supporting the use of apixaban in cancer related VTE remains quite attractive.

Beyond apixaban, other factor Xa inhibitors have proven efficacy in VTE treatment. For example, rivaroxaban, an oral direct factor Xa inhibitor, has a time to peak concentration of 2-4 hours with an elimination half-life of 7-11 hours. The EINSTEIN DVT trial randomized 3449 patients with symptomatic DVT to oral rivaroxaban alone (15 mg twice daily for 3 weeks, followed by 20 mg once daily) or enoxaparin followed by warfarin (or acenocoumarol) (25). The EINSTEIN-PE investigators randomized 4832 patients with acute PE to either rivaroxaban or enoxaparin/warfarin (26). In both trials, rivaroxaban was initiated without parenteral anticoagulant bridging or monitoring and was non-inferior to enoxaparin/warfarin for safety and efficacy. After completing the initial treatment phase, 1196 patients were re-randomized to either continued rivaroxaban 20 mg daily or placebo (20). Continued rivaroxaban reduced recurrent thrombotic events compared to placebo (1.3% vs. 7.1%) yet with similar bleeding rates (0.7% vs. 0%). In the Einstein trials, 321 patients with active cancer were randomized to rivaroxaban therapy. The interpretations of these data are limited whereby we have no data on the types of cancer, presence of metastasis and type of chemotherapy used. Moreover, like AMPLIFY, the comparator in these trials was warfarin and not LMWH as endorsed by the guidelines.

Either factor Xa inhibitors may therefore be chosen for a cancer related VTE therapy trial compared to LMWH. Apixaban however is a contender for first line therapy for several reasons. First, the twice daily dosing of apixaban, although maybe less convenient, may improve efficacy and safety. The peak levels are anticipated to be lower than once daily dosing thus decreasing potential bleeding (32). The trough levels are anticipated to be higher thus improving efficacy with continued presence of drug relative to once daily dosing. Second, the multiple routes of elimination are attractive particularly in these patients who may intermittently suffer renal or hepatic toxicities related to the underlying disease and cancer treatment. Third, apixaban has been shown to have extremely low rates of major bleeding. This is particularly attractive in cancer patients who are at increased risk of bleeding with thrombocytopenia, coagulopathy, tissue friability and cancer related invasive procedures.

1.4 Dose Rationale and Risk/Benefits

The AMPLIFY investigators compared apixaban (10 mg twice daily for 7 days followed by 5 mg twice daily for 6 months) to enoxaparin/warfarin in 5395 patients with acute VTE (23). At the 6 month follow up, recurrent VTE occurred in 2.3% in the apixaban group compared to 2.7% in the enoxaparin/warfarin group meeting the criteria for noninferiority (relative risk 0.84 (95% CI 0.60-1.18; p<0.001). Similar outcomes were noted regardless of whether the initial event was a DVT or PE. Major bleeding occurred in 0.6% of the apixaban compared to 1.8% of the conventional-therapy group. The difference in major bleeding was superior for apixaban (relative risk 0.31 (95% CI, 0.17-0.55; P<0.001). The AMPLIFY-Extend investigators then compared prolonged treatment with apixaban (2.5 mg or 5 mg, twice daily) with placebo in 2486 patients who had just completed 6 – 12 months of anticoagulation treatment for an acute VTE (24). Recurrent VTE or death from VTE was significantly lower in those patients assigned to either 2.5 mg (1.7%) or 5 mg (1.7%) twice daily apixaban compared to placebo (8.8%). Major bleeding rates were similarly low for apixaban 2.5 mg (0.2%), apixaban 5 mg (0.1%) and placebo (0.5%). Based on these data from the AMPLIFY trials, apixaban 10 mg twice daily for 7 days followed by 5 mg twice daily will be the prescribed dose for this trial.

The CLOT trial randomized 672 patients with active cancer and acute venous thromboembolism to receive either LMWH (dalteparin 200 IU/kg/day for 1 month followed by 150 IU/kg/day for 5 months) or adjusted dose warfarin (18). At the end of the six-month study period, recurrent thromboembolism was 17% in the oral-anticoagulant group and 9% in the dalteparin group (hazard ratio, 0.48; P=0.002). There was no significant difference between groups in the rate of major bleeding (dalteparin 6% vs. warfarin 4%). Therefore, based on the CLOT trial, and the Fragmin USPI recommended dosing, dalteparin 200 IU/kg/day for 1 month followed by 150 IU/kg/day will be the comparator drug and dosing schedule prescribed.

1.5 General Design

This is a multicenter, randomized, open-label, superiority trial for safety. Participating centers will be from the Academic and Community Cancer Research United (ACCRU) research consortium. This research consortium is comprised of more than 80 leading academic institutions and community oncology practices in the United States and Canada. The goal of this consortium is to collaborate with industry partners to develop and conduct clinical trials in cancer research.

Subjects will be screened at both outpatient clinic visit appointments and during hospitalizations using direct referrals or by twice daily automated screening of vascular radiology ultrasound and computed tomography reports. Interested qualified subjects will be consented and offered participation in this trial. Pre-randomization anticoagulation treatment is allowed up to a maximum of 7 days. After randomization, patients allocated to apixaban will receive 10 mg twice daily for 7 days, followed by 5 mg twice daily. Patients allocated to the comparator will receive dalteparin 200 IU/kg/day for 1 month followed by 150 IU/kg/day. Allocation to treatment will be done centrally. Once consent has been obtained baseline values will be established and subjects will begin treatment and follow-up for 6 months.

The principal safety outcome is major bleeding. All episodes of major bleeding and deaths will be evaluated by a central, blinded, independent adjudication committee. Adjudication results will be the basis for the final analyses. An independent data and safety monitoring board (DSMB) will monitor the patients' safety and give recommendations to the executive committee.

## 2.0 Goals

### 2.1 Primary

2.11 The primary safety endpoint will include: any episode of major bleeding including fatal bleeding. The following criteria will be used to confirm and categorize a bleeding episode:

- Major bleeding is defined as overt bleeding plus a hemoglobin decrease of ≥ 2 g/dL or transfusion of ≥ 2 units of packed red blood cells, or intracranial, intraspinal/epidural, intraocular, retroperitoneal, pericardial, intra-articular, intramuscular with compartment syndrome or fatal bleeding. Intracranial hemorrhage includes intracerebral (hemorrhagic stroke), subarachnoid, and subdural bleeds.

- Clinically relevant non-major bleeding is defined as overt bleeding not meeting the criteria for major bleeding but associated with medical intervention, an unscheduled contact with a member of the health care team, or temporary cessation of study treatment.

- Minor bleeding is defined as overt bleeding that did not meet criteria for major bleeding or clinically relevant non-major bleeding.

### 2.2 Secondary

2.21 The secondary efficacy endpoint of this study will be VTE recurrence including DVT, PE, fatal PE, or arterial thromboembolism. The following criteria will be used to confirm and categorize a VTE recurrence:

- Suspected (recurrent) DVT: The original DVT must be confirmed by duplex ultrasonography, venography, CT, or MRI. A recurrent DVT must be distinguished from the original thrombus by comparing serial imaging modalities. In order to be classified as a recurrent event, there must be new filling defects evident on the second study not appreciated on the original images or an interval study clearly showing thrombus resolution.

- Suspected (recurrent) PE: The original PE must be confirmed by CT, MR, conventional pulmonary angiography, or VQ perfusion imaging. A recurrent PE must be distinguished from the original thrombus by comparing serial imaging modalities. In order to be classified as a recurrent event, there must be new filling defects evident on the second study not appreciated on the original images or an interval study clearly showing thrombus resolution.

- Fatal PE: PE based on objective diagnostic testing, autopsy, or death which

cannot be attributed to a documented cause and for which PE/DVT cannot be ruled out (unexplained death).

- Incidental VTE recurrence: Due to the nature of cancer surveillance related imaging, it is anticipated that recurrent venous thrombosis or thrombus propagation may be identified. In order to be classified as an event, the thrombus in question must be distinguished from the original thrombus by comparing serial imaging modalities. In order to be classified as a recurrent event, there must be new filling defects evident on the second study not appreciated on the original images or an interval study clearly showing thrombus resolution.

- Arterial thromboembolism: Myocardial infarction (MI), stroke, transient ischemic attack (TIA), or peripheral arterial embolism.

2.22 The secondary safety endpoint will include the combined endpoints of any episode of major bleeding including fatal bleeding or any episode of clinically relevant non-major bleeding.

## 3.0 Patient Eligibility

3.1 Inclusion Criteria

3.11 Age ≥18 years.

3.12 Confirmed acute lower extremity or upper extremity (jugular, innominate, subclavian, axillary, brachial) DVT, PE, splanchnic (hepatic, portal, splenic, mesenteric, renal, gonadal), or cerebral vein thrombosis.

3.13 Active cancer defined as metastatic disease and/or any evidence of cancer on cross-sectional or PET imaging, cancer related surgery, chemotherapy or radiation therapy within the past 6 months. Note: non-melanoma skin cancer does not meet the cancer requirement.

3.14 Life expectancy ≥ 60 days.

3.15 ECOG Performance Status (PS) of 0, 1, or 2. (Form is available on the ACCRU web site https://www.accru.org/accru/forms/NonProtocolSpecificForms/index.html).

3.16 The following laboratory values obtained ≤30 days prior to randomization.
- Platelet count ≥50,000/$mm^3$
- Alanine aminotransferase (ALT) or Aspartate transaminase (AST) ≤3 x ULN
- INR ≤1.6 (if not taking anticoagulant therapy)
- Calculated creatinine clearance must be ≥30 ml/min using the Cockcroft-Gault formula below:

**Cockcroft-Gault Equation:**

**Creatinine clearance for males =** $\frac{\text{(140 - age)(weight in kg)}}{\text{(72)(serum creatinine in mg/dL)}}$

**Creatinine clearance for females =** $\frac{\text{(140 - age)(weight in kg)}}{\text{(72)(serum creatinine in mg/dL)}} \text{ *(0.85)}$

3.17 Negative serum or urine pregnancy test done ≤24 hours prior to randomization, for women of childbearing potential only.
Note: A Women of childbearing potential (WOCBP) is defined as any female who has experienced menarche and who has not undergone surgical sterilization (hysterectomy or bilateral oophorectomy) and is not postmenopausal. Menopause is defined as 12 months of amenorrhea in a woman over age 45 years in the absence of other biological or physiological causes.

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

3.19a Ability to provide informed written consent.

3.19b Willing to return to enrolling institution for follow-up (during the Active Monitoring Phase of the study).

3.2 Exclusion Criteria

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

- Pregnant women
- Nursing women
- Men or women of childbearing potential who are unwilling to employ adequate contraception
    - Note: Women of child bearing potential must agree to follow instructions for method(s) of contraception for the duration of treatment with study drug (s) plus 33 days after finishing the last dose.
    - Males who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception for the duration of treatment with study drug (s) plus 93 days after finishing the last dose.
    - Azoospermic males and WOCBP who are continuously not heterosexually active are exempt from contraceptive requirements. However they must still undergo pregnancy testing as described in this section.

Note: Investigators shall counsel WOCBP and male subjects who are sexually active with WOCBP on the importance of pregnancy prevention and the implications of an unexpected pregnancy Investigators shall advise WOCBP and male subjects who are sexually active with WOCBP on the use of highly effective methods of contraception. Highly effective methods of contraception have a failure rate of < 1% when used consistently and correctly.

At a minimum, subjects must agree to the use of one method of highly effective contraception as listed below:

**HIGHLY EFFECTIVE METHODS OF CONTRACEPTION**

- Male condoms with spermicide
- Hormonal methods of contraception including combined oral contraceptive pills, vaginal ring, injectables, implants and intrauterine devices (IUDs) such as Mirena® by WOCBP subject or male subject's WOCBP partner.
- Female partners of male subjects participating in the study may use hormone based contraceptives as one of the acceptable methods of contraception since they will not be receiving study drug
- IUDs, such as ParaGard®
- Tubal ligation
- Vasectomy.
- Complete Abstinence*

*Complete abstinence is defined as complete avoidance of heterosexual intercourse and is an acceptable form of contraception for all study drugs. Female subjects must continue to have pregnancy tests. Acceptable alternate methods of highly effective contraception must be discussed in the event that the subject chooses to forego complete abstinence.

3.22 Treatment with an anticoagulant for more than 7 days for the current blood clot, prior to randomization.

3.23 Active bleeding.

3.24 Severe hypersensitivity reaction to apixaban, dalteparin, heparin or pork products (e.g., anaphylactic reactions).

3.25 Use of the following CYP3A4 inducers: rifampin, rifabutin, carbamazepine, efavirenz, phenobarbital, phenytoin, fosphenytoin, primidone, and St. John's wort [see list in appendix II]).

3.26 Thienopyridine therapy (clopidogrel, prasugrel, or ticagrelor) that will be continued on study.

3.27 Severe liver disease (known cirrhosis Childs Pugh class B or C), or active hepatitis.

3.28 Use of a Factor Xa Inhibitor (e.g. apixaban, rivaroxiban, or edoxaban) ≤3 months prior to randomization.

3.29a Treatment of a thromboembolic event ≤6 months prior to randomization.

3.29b Documented venous thromboembolism while on therapeutic anticoagulation ("anticoagulation failure").

3.29c Mechanical heart valve.

3.29d Documented hemorrhagic tendencies.

3.29e Bacterial endocarditis.

3.29f History of heparin induced thrombocytopenia.

3.29g Any of the following conditions:

- Intracranial bleeding ≤6 months prior to randomization
- Intraocular bleeding ≤6 months prior to randomization
- Gastrointestinal bleeding and/or endoscopically proven ulcer ≤6 months prior to randomization
- Head trauma or major trauma ≤1 month prior to randomization
- Neurosurgery ≤2 weeks prior to randomization
- Major surgery ≤1 week prior to randomization
- Overt major bleeding at the time of randomization
- Gross hematuria at the time of randomization

**4.0 Test Schedule**

| Tests and procedures | Active Monitoring Phase | | | |
|---|---|---|---|---|
| | ≤14_days prior to registration (baseline) | Every 30 days after the start of treatment (± 1 week) | End of treatment | Observation: 3 months after the completion of treatment (as defined per protocol) (± 1 week) |
| History and exam (including weight and bleeding assessment, see App. IV) | X | X[6] | | |
| ECOG PS | X | X | | |
| Height | X | | | |
| Adverse event assessment | X | X | | X |
| Hematology:<br>• CBC<br>• Platelets | X[1] | X | X[5] | |
| INR | X[1] | | | |
| Chemistry:<br>• SGOT (AST) or ALT<br>• Creatinine | X[1] | X | X[5] | |
| Selected concomitant meds (see CRF for this form) | X | X | | |
| US, CT, MRI, or VQ scan to confirm acute lower extremity or upper extremity DVT, PE or splanchnic vein thrombosis | X | | | |
| Pregnancy test[2] | X | | | |
| Patient Questionnaire Booklets[3] (App.VI, VII)<br>• Mayo Blood Thinner Questionnaire<br>• Bruising Question | X[4] | X | | |
| Patient Phone Call (including bleeding assessment, see App. IV and VIII) | | | X | X |

1. ≤30 days prior to registration.
2. For women of childbearing potential only. Must be done ≤24 hours prior to randomization.
3. Patient questionnaire booklets **must** be used; copies are not acceptable for this submission.
4. Must be completed after registration and prior to treatment.
5. If feasible.
6. If it is not feasible for the patient to return to the enrolling center for the physical examination, a detailed history will be obtained by phone using a structured interview (see Appendix X).

## 5.0 Stratification Factors

5.1 Cancer stage: Residual (intact primary or metastatic) vs. no residual (no evidence of disease).

5.2 Risk: High risk vs. lower risk using validated Khorana score (see appendix III).

## 6.0 Registration/Randomization Procedures

6.1 Registration Procedures

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

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

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

6.12 Documentation of IRB approval must be on file in the Registration Office before an investigator may register any patients.

In addition to submitting initial IRB approval documents, ongoing IRB approval documentation must be on file (no less than annually) at the Registration Office [redacted]. If the necessary documentation is not submitted in advance of attempting patient registration, the registration will not be accepted and the patient may not be enrolled in the protocol until the situation is resolved.

When the study has been permanently closed to patient enrollment, submission of annual IRB approvals to the Registration Office is no longer necessary.

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

- IRB approval at the registering institution
- Patient eligibility
- Existence of a signed consent form

- Existence of a signed authorization for use and disclosure of protected health information

6.14 Treatment cannot begin prior to registration and must begin ≤5 days after registration.

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

6.16 All required baseline symptoms (see Section 10.3) must be documented and graded.

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

6.18 Study drug is available on site.

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

6.2 Randomization Procedures

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

6.22 After the patient has been registered into the study, the values of the stratification factors will be recorded, and the patient will be assigned to one of the following treatment groups using the Pocock and Simon dynamic allocation procedure which balances the marginal distributions of the stratification factors between the treatment groups (Pocock-Simon).

- Apixaban
- Dalteparin

## 7.0 Protocol Treatment

7.1 Treatment Schedule - Use actual weight (Kg)

| Arm | Agent | Dose Level | Frequency | Route |
|---|---|---|---|---|
| **A** | Apixaban* | 10 mg | Twice daily days 1-7 | Oral |
| | | 5 mg | Twice daily days 8-180 | |
| **B** | Dalteparin* | 200 IU/kg/day | Once daily for days 1- 30 | Subcutaneous Injection** |
| | | 150 IU/kg/day | Once daily for days 31-180 | |

*If a dose of apixaban or dalteparin is not taken at the scheduled time, the dose should be taken as soon as possible on the same day and the prescribed dosing schedule should be resumed. The dose should not be doubled to make up for missed doses.

** The dosage will be calculated on the patient's current weight in kilograms, rounded to the nearest whole kilogram. The syringe dose will be chosen based on the weight adjusted calculation based on the table 7.11. The patient will be taught by on site nursing staff how to administer the medication, and also how to "waste" from each syringe such that the appropriate weight adjusted

dose is delivered.

7.11

Month 1: 200 IU/kg SQ daily

| Body Weight (kg) | Dalteparin Dose (IU) once daily |
|---|---|
| ≤ 40 | 7,500 |
| 41-56 | 10,000 |
| 57-68 | 12,500 |
| 69-82 | 15,000 |
| 83-94 | 18,000 |
| 95-107 | 10,000 & 10,000 =20,000 |
| 108-120 | 18,000 & 5,000 = 23,000 |
| 121-133 | 15,000 & 10,000 = 25,000 |
| 134-147 | 18,000 & 10,000 = 28,000 |
| 148-160 | 15,000 & 15,000 = 30,000 |
| ≥161 | 200 IU/kg SQ daily |

Months 2-6: 150 IU/kg SQ daily

| Body Weight (kg) | Dalteparin Dose (IU) once daily |
|---|---|
| ≤ 40 | 5,000 |
| 41-57 | 7,500 |
| 58-77 | 10,000 |
| 78-92 | 12,500 |
| 93-110 | 15,000 |
| 111-130 | 18,000 |
| 131-141 | 10,000 & 10,000 = 20,000 |
| 142-160 | 18,000 & 5,000 = 23,000 |
| ≥161 | 150 IU/kg SQ daily |

7.12 **Dalteparin therapy is weight based dosing**. Monthly weights should be performed and communicated with the study coordinator. For patients experiencing more than 10% weight loss or gain, the dose of dalteparin will be adjusted to current body weight. Round according to table 7.11.

7.13 Scheduled visits should include a standardized assessment of the signs and symptoms of recurrent thromboembolism, bleeding episodes, and adverse reactions. Patients should be instructed to report to the clinic immediately (or call 911/go to the Emergency Room) if they had any bleeding, or symptoms of recurrent deep-vein thrombosis, pulmonary embolism, or both. Written patient education materials will be provided to each patient outlining signs and symptoms to watch for regarding VTE recurrences (appendix IX). All suspected episodes of recurrent thrombosis should be investigated with the use of objective

tests, according to pre-specified diagnostic algorithms.

7.2 Post protocol completion: Anticoagulation decision algorithm

7.21 Following the 6 months of protocol completion, a decision regarding anticoagulation continuation will be clinically determined. (31) Although cancer is associated with a high risk of recurrent venous thromboembolism, the rate of recurrence differs significantly by cancer type, stage of disease, and stage progression over time. For the following patient characteristics, we recommend continuing anticoagulation: patients with brain, lung, pancreatic, or ovarian cancer; myeloproliferative or myelodysplastic disorders; stage IV cancer; cancer stage progression; or leg paresis. Anticoagulation options could include: continued LMW heparin (dalteparin or enoxaparin), apixaban (or other oral novel direct factor inhibitors or warfarin.

For patients not meeting these specific criteria or if their presenting thrombus was limited to the calf (distal to and not including the popliteal vein), it is reasonable to discontinue anticoagulation therapy.

7.22 For surveillance purposes, participants will be contacted by telephone at 3 months post protocol completion to determine the incidence of thrombosis recurrence, major bleeding and clinically relevant non-major bleeding.

## 8.0 Dosage Modification Based on Adverse Events

8.1 Apixaban is cleared through several mechanisms including renal clearance, hepatic metabolism, and fecal excretion. Dalteparin is excreted through renal clearance. For both drugs, severe thrombocytopenia, liver and renal failure represents an increased bleeding risk. For these purposes, patients will require monthly assessment of complete blood counts (CBC), renal function (creatinine clearance calculation), and liver function (ALT). Each of these measures is clinically indicated for anticoagulation management.

Patients with calculated creatinine clearance ≤30 ml/min (using the Cockcroft-Gault formula) must discontinue treatment and go to observation. They may get alternative anticoagulation treatment per the attending physician judgment.

For patients who are receiving concomitant use of strong CYP3A4 and/or P-glycoprotein inhibitors (i.e. ketoconazole, itraconazole, ritonavir, or clarithromycin; see appendix II for a list of strong CYP3A4 inhibitors), the dose of apixaban will be reduced to 2.5 mg twice daily. Upon discontinuation of the strong CYP3A4 inhibitor, then the full dose of apixaban 5 mg twice daily should be instated/reinstated.

For patients receiving a strong CYP3A4 inducer (appendix II), alternative agents within the specific class of drug should be sought. If no good alternative agent within that class can be identified and the drug is required, the ACCRU Data Manager should be notified and the subject removed from the trial and go to observation.

For thrombocytopenia (> 50,000/microliter), no dose adjustment is necessary. For

thrombocytopenia (25,000-50,000/microliter), apixaban dose reduction to 2.5 mg twice daily is necessary. For thrombocytopenia (< 25,000/microliter), apixaban will be held

until platelet count recovers. Once the platelet count improves, the apixaban dose should be adjusted accordingly.

Dalteparin therapy is weight based dosing. Monthly weights should be performed and communicated with study staff. For patients experiencing more than 10% weight loss or gain, the dose of dalteparin will be adjusted to current body weight.

The dalteparin dose should be adjusted for patients experiencing kidney injury. An exclusion criterion for study enrollment is a creatinine clearance <30 ml/min. For those patients already enrolled who then develop worsening kidney function, the dalteparin dose will then be adjusted. For creatinine clearance between 15 and 30 ml/min, the dose of dalteparin should be reduced. During the first month of treatment when the patient is receiving 200IU/kg, the dose will be reduced to 150 IU/kg. During subsequent months, the dose of 150 IU/kg will be reduced to 100 IU/kg. Once the creatinine clearance improves to values > 30 ml/min, the standard dosing will be reintroduced.

For patients with severe kidney injury defined as creatinine clearance < 15 ml/min, dalteparin should be held and the patient should stop the study treatment and receive treatment per the attending physician.

For thrombocytopenia (> 50,000/microliter), no dose adjustment is necessary. For thrombocytopenia (25,000-50,000/microliter), dalteparin dose reduction to 5000 IU/day is necessary. For thrombocytopenia (< 25,000/microliter), dalteparin will be held until platelet count recovers. Once the platelet count improves, the dalteparin dose should be adjusted accordingly.

8.2 **Patients requiring an invasive procedure requiring temporary anticoagulant cessation will be managed as follows:**

(1) Date and type of procedure will be recorded on the CRF;
(2) Apixaban will be discontinued at least 48 hours prior to elective surgery or invasive procedures with a moderate or high risk of bleeding, with no drug given on the procedure date; For low bleeding risk procedures, apixaban will be discontinued at least 24 hours. Dalteparin dose will be reduced to 100 IU/kg and given on the morning prior to the procedure date with no drug given on the procedure date;
(3) Post procedure, the patient could receive prophylactic apixaban (2.5 mg twice daily) or dalteparin (5000 IU once daily) dosing for 48 hours; the first prophylactic dose will be given 24 hours after the procedure;
(4) Therapeutic apixaban or dalteparin will be withheld until 72 hours after the procedure and not initiated until adequate hemostasis is confirmed.

If apixaban or dalteparin treatment is temporality held, the reason will be recorded on the CRF and the patient can go back on study for up to day 180 of the original treatment schedule.

## 9.0 Ancillary Treatment/Supportive Care

9.1 Concomitant use of strong CYP3A4 inhibitors (e.g., HIV protease inhibitors, systemic ketoconazole (appendix II) should be discouraged. In the case of clinical necessity, for

those patients randomized to apixaban, the dose of apixaban will be reduced to 2.5 mg twice daily while the CYP3A4 inhibitor is given.

9.2 Non-steroid anti-inflammatory drugs (NSAIDs) and antiplatelet agents (aspirin) are discouraged but not prohibited. If aspirin use is required, then the dose should be ≤100 mg daily. The use of these drugs should be recorded on the CRF.

9.3 **Note:** Antiplatelet therapy with a thienopyridine (clopidogrel, prasugrel, or ticagrelor) is an exclusion criterion and not allowed while on protocol therapy.

## 10.0 Adverse Event (AE) Reporting and Monitoring

10.1 Adverse Event Characteristics

An Adverse Event [AE] is defined as any new untoward medical occurrence or worsening of a preexisting medical condition in a patient or clinical investigation subject administered an investigational (medicinal) product and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of investigational product, whether or not considered related to the investigational product.

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

10.11 Adverse event monitoring and reporting is a routine part of every clinical trial. First, identify and grade the severity of the event using the CTCAE version 4.0. Next, determine whether the event is expected or unexpected (see Section 10.2) and if the adverse event is related to the medical treatment or procedure (see Section 10.3). With this information, determine whether the event must be reported as an expedited report (see Section 10.4). Important: Expedited adverse event reporting requires submission of a Med Watch report(s). Expedited reports are to be completed within the timeframes and via the mechanisms specified in Sections 10.4 All AEs reported via expedited mechanisms must also be reported via the routine data reporting mechanisms defined by the protocol (see Sections 10.5 and 18.0).

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

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

10.2 Expected vs. Unexpected Events

- The determination of whether an AE is expected is based on agent-specific information provided in Section 15.0 of the protocol.

- Unexpected AEs are those not listed in the agent-specific information provided in Section 15.0 of the protocol.

**NOTE**: "Unexpected adverse experiences" means any adverse experience that is neither identified in nature, severity, or frequency of risk in the information provided for IRB review nor mentioned in the consent form.

10.3 Assessment of Attribution

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

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

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

10.31 **Special Situations for Expedited Reporting**

**10.311 Persistent or Significant Disabilities/Incapacities**

Any AE that results in persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions (formerly referred to as disabilities), congenital abnormities or birth defects, must be reported immediately if they occur at any time following treatment with an agent under an IND/IDE since they are considered to be a serious AE and must be reported to the sponsor as specified in 21 CFR 312.64(b).

**10.312 Death**

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

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

- **Reportable categories of Death**

  - Death attributable to a CTCAE term.

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

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

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

- Death due to progressive disease should be reported as **Grade 5 "Neoplasms benign, malignant and unspecified (incl cysts and polyps) – Other (Progressive Disease)"** under the system organ class (SOC) of the same name. Evidence that the death was a manifestation of underlying disease (e.g., radiological changes suggesting tumor growth or progression: clinical deterioration associated with a disease process) should be submitted.

**10.313 Secondary Malignancy**

- A ***secondary malignancy*** is a cancer caused by treatment for a previous malignancy (e.g., treatment with investigational agent/intervention, radiation or chemotherapy). A secondary malignancy is not considered a metastasis of the initial neoplasm.

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

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

  - Myelodysplastic syndrome (MDS)

  - Treatment-related secondary malignancy

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

**10.314 Second Malignancy**

- A second malignancy is one unrelated to the treatment of a prior malignancy (and is NOT a metastasis from the initial malignancy). Second malignancies require ONLY routine reporting.

**10.315 Pregnancy**

If, following initiation of the investigational product, it is subsequently discovered that a study subject is pregnant or may have been pregnant at

the time of investigational product exposure, including during at least 5 half-lives after product administration, the investigational product will be permanently discontinued in an appropriate manner (eg, dose tapering if necessary for subject safety).

The site investigator must immediately notify ACCRU of this event via the Pregnancy Surveillance Form within 24 hours and in accordance with SAE reporting procedures.

Follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome and, where applicable, offspring information must be reported on a Pregnancy Surveillance Form.

Any pregnancy that occurs in a female partner of a male study participant should be reported to BMS. Information on this pregnancy may also be collected on the Pregnancy Surveillance Form.

Protocol-required procedures for study discontinuation and follow-up must be performed on the subject unless contraindicated by pregnancy (eg, x-ray studies). Other appropriate pregnancy follow-up procedures should be considered if indicated.

### 10.316 Overdose

An overdose is defined as the accidental or intentional administration of any dose of a product that is considered both excessive and medically important. All occurrences of overdose must be reported as SAEs.

### 10.317 Drug Induced Liver Injury (DILI)

Wherever possible, timely confirmation of initial liver-related laboratory abnormalities should occur prior to the reporting of a potential DILI event. All occurrences of potential DILIs, meeting the defined criteria, must be reported as SAEs.

Potential drug induced liver injury is defined as
1. AT (ALT or AST) elevation > 3 times upper limit of normal (ULN)
AND
2. Total bilirubin > 2 times ULN, without initial findings of cholestasis (elevated serum alkaline phosphatase),
AND
3. No other immediately apparent possible causes of AT elevation and hyperbilirubinemia, including, but not limited to, viral hepatitis, pre-existing chronic or acute liver disease, or the administration of other drug(s) known to be hepatotoxic.

### 10.318 Other Safety Considerations

Any significant worsening noted during interim or final physical examinations, electrocardiograms, x rays, and any other potential safety assessments, whether or not these procedures are required by the protocol, should also be recorded as a nonserious or serious adverse event, as appropriate, and reported accordingly.

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

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

**FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)**
**NOTE:** Investigators **MUST** immediately report to ACCRU **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)
An adverse event is considered serious if it results in **ANY** of the following outcomes:

1) Death
2) A life-threatening adverse event
3) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5) A congenital anomaly/birth defect.
6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

**ALL SERIOUS** adverse events that meet the above criteria **MUST** be immediately reported to ACCRU within the timeframes detailed in the table below.

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

**Expedited AE reporting timelines are defined as:**

- "24-Hour; 1 Business Day" - The AE must initially be reported via MedWatch within 24 hours of learning of the AE, followed by a complete expedited report within 1 business day of the initial 24-hour report.
- "1 Business Day" - A complete expedited report on the AE must be submitted within 1 business day of learning of the AE.

[1]Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:
**Expedited 24-hour notification followed by complete report within 1 business day for:**

- All Grade 4, and Grade 5 AEs

**Expedited 1 business day reports for:**

- Grade 2 adverse events resulting in hospitalization or prolongation of hospitalization
- Grade 3 adverse events

[2] For studies using PET or SPECT IND agents, the AE reporting period is limited to 10 radioactive half-lives, rounded UP to the nearest whole day, after the agent/intervention was last administered. Footnote "1" above applies after this reporting period.

Effective Date: May 5, 2011

Additional Instructions:
1. An increased incidence of an expected adverse event (AE) is based on the patients treated for this study at their site. A list of known/expected AEs is reported in the package insert or the literature, including AEs resulting from a drug overdose.

2. Follow site-specific reporting guidelines.

3. Submit MedWatch form 3500A to the ACCRU SAE Coordinator via fax [redacted]. The ACCRU SAE Coordinator will forward the report to Bristol-Myers Squibb via E-mail within 1 business day to [redacted] or [redacted] and will also forward to Pfizer via [redacted].

4. The ACCRU SAE Coordinator will forward to [redacted] as appropriate. The ACCRU IND Coordinator will assist the sponsor-investigator in notifying the FDA if required.

| EVENT TYPE | REPORTING PROCEDURE |
|---|---|
| Other Grade 4 or 5 Events and/or Any Hospitalizations During Treatment Not Otherwise Warranting an Expedited Report | Notification form: Grade 4 or 5 Non-AER Reportable Events/ Hospitalization Form to ACCRU within 5 working days[1] |

1. If FDA Form 3500A (MedWatch) was completed, this form need not be completed.

10.5 Other Required Reporting

10.51 Adverse events to be graded at each evaluation and pretreatment symptoms/conditions to be evaluated at baseline per the CTCAE v4.0 grading unless otherwise stated in the table below:

| System Organ Class (SOC) | Adverse event/Symptoms | Baseline | Each evaluation | Non CTCAE Grading Scale (major bleeding scale based on ISTH) See appendix IV |
|---|---|---|---|---|
| Vascular disorder | Other, specify: Bleeding | X | X | X |
| General disorders and administration site conditions | Injection site reaction | | X | |
| Investigations | Decreased platelet count | X | X | |

10.52 Submit via appropriate Academic and Community Cancer Research United (ACCRU) Case Report Forms (i.e., paper or electronic, as applicable) the following AEs experienced by a patient and not specified in Section 10.5:

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

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

10.523 Grade 5 AEs (Deaths)

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

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

10.55 Refer to the instructions in the Forms Packet (or electronic data entry screens, as applicable) regarding the submission of late occurring AEs following completion of the Active Monitoring Phase (i.e., compliance with Test Schedule in Section 4.0).

10.56 Research Coordinating Center will reconcile the clinical database SAE cases received from ACCRU Sites with the SAE cases that have been transmitted to BMS Global Pharmacovigilance (GPV&E). Frequency of reconciliation will occur no more frequently than quarterly for a maximum of twelve (12) reconciliations and will occur no less than once prior to study database lock. BMS GPV&E will e-mail upon request from the investigator, the GPV&E reconciliation report. Requests for reconciliation should be sent to aepbusinessprocess@bmscom. The data elements listed on the GPV&E reconciliation report will be used for case identification purposes. If the investigator determines a case was not transmitted to BMS GPV&E, the case will be sent immediately.

## 11.0 Treatment Evaluation Using RECIST Guideline – Not Applicable

## 12.0 Descriptive Factors – Not Applicable

## 13.0 Treatment/Follow–up Decision at Evaluation of Patient

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

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

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

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

## 14.0 Body Fluid Biospecimens – Not applicable

## 15.0 Drug Information

15.1 Apixaban (Eliquis®) IND Exempt

- Package Insert is available on the ACCRU web site.

15.11 Background: Apixaban (Eliquis) is an oral direct factor Xa inhibitor which impairs coagulation by inhibiting the conversion of prothrombin to thrombin. It does not require antithrombin for antithrombotic activity and inhibits both free and clot-bound FXa. Apixaban has a half-life of about 12 hours and thus is dosed twice-daily. Bioavailability is approximately 50% after oral dosing with maximum concentrations at 4 hours post ingestion. The pharmacokinetics are linear and plasma protein binding in humans is high at nearly 87% with a volume of distribution of approximately 21 liters. Apixaban is metabolized in the liver mainly via the CYP3A4 pathway. Renal excretion accounts for about 27% of total clearance. Approximately 25% of the drug is eliminated in the urine and feces.

15.12 Formulation: Apixaban (Eliquis®) tablets are available for oral administration in strengths of 2.5 mg and 5 mg of apixaban with the following inactive ingredients: anhydrous lactose, microcrystalline cellulose, croscarmellose sodium, sodium lauryl sulfate, and magnesium stearate. The film coating contains lactose monohydrate, hypromellose, titanium dioxide, triacetin, and yellow iron oxide (2.5 mg tablets) or red iron oxide (5 mg tablets).

15.13 Preparation and storage: Store at room temperature 20°C to 25°C (68°F-77°F); excursions permitted between 15°C and 30°C (59°F-86°F). Please see package insert.

15.14 Administration: Apixaban will be provided in bottles containing 74 tablets of 5 mg for the first 30 days of treatment (28 tablets for days 1-7; 46 tablets for days 8-30). For subsequent months, patients will receive 74 tablets of 5 mg strength.

Administer without regards to meals. If patient is unable to swallow tablets whole, 2.5 or 5 mg tablets may be crushed and suspended in 60 mL of dextrose 5% in water followed by immediate delivery through a nasogastric tube. Apixaban tablets may also be crushed and suspended in water, or 5% dextrose in water (D5W), or apple juice or mixed with apple puree and immediately administered orally. Crushed apixaban tablets are stable in water, D5W, apple juice, and apple puree for up to 4 hours.

15.15 Appearance: Yellow, round, biconvex, film-coated tablets with “893” debossed on one side and “5” on the other side.

15.16 Pharmacokinetic information:
a) Absorption – Time to peak after oral administration is 3 to 4 hours; bioavailability is approximately 50% for doses up to 10 mg.

b) Distribution – Plasma protein binding in humans is approximately 87%. The steady-state volume of distribution is approximately 21 L.

c) Metabolism – Approximately 25% of an orally administered apixaban dose is recovered in urine and feces as metabolitesApixaban is metabolized mainly via CYP3A4 and to a lesser extent via CYP1A2, 2C8, 2C9, 2C19, and 2J2

d) Excretion Apixaban is eliminated in both urine and feces. Renal excretion accounts for about 27% of total clearance.

e) Half-life Elimination – approximately 12 hours

15.17 Drug interactions: Apixaban is a substrate of both CYP3A4 and P-gp. Inhibitors of CYP3A4 and P-gp increase exposure to apixaban and increase the risk of bleeding. Inducers of CYP3A4 and P-gp decrease exposure to apixaban and increase the risk of stroke

Strong Dual Inhibitors of CYP3 A4 and P-gp
The dose if ELIQUIS should be decreased to 2.5 mg twice daily then when is coadministered with drugs that are strong dual inhibitors of CYP3A4 and P-gp.(e.g.; ketoconazole, itraconazole, ritonavir, or clarithromycin).

In patients already taking ELIQUIS at a dose of 2.5 mg twice daily, avoid coadministration with strong dual inhibitors of both CYP3A4 and P-gp.

Strong Dual Inducers of CYP3A4 and P-gp
Avoid concomitant use of ELIQUIS with strong dual inducers of CYP3A4 and P-gp (e.g. e.g., rifampin, carbamazepine, phenytoin, St. John's wort) because such drugs will decrease exposure to apixaban.

Coadministration of antiplatelet agents, fibrinolytics, heparin, aspirin, and chronic NSAID use increases the risk of bleeding.

Please consult current drug reference sources for a complete list of potential drug interactions.

15.18 Please consult the package insert for the most current and complete adverse event information.

15.19a Drug procurement: Bristol Myers-Squibb will supply the drug to Biologics, Inc. Each participating ACCRU treating location will order the drug from Biologics, Inc. Fax the Drug Order Request Form (found in the forms packet) to:

Biologics, Inc.
Attn. Clinical Research Services
Fax: [redacted]

Each participating ACCRU treating location will be responsible for monitoring the supply of apixaban and will use the Drug Order Request Form to order additional supplies as needed.

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

15.19b Nursing guidelines

- Assess patient's concomitant medications including OTC, and herbal products. There are several drug to drug interactions that may interfere with the absorption of agent. Additionally, warn patient to avoid taking medication with any other anti-platelet agents (i.e. aspirin, NSAIDS, etc.)
- Warn patients of risk of bleeding, (including serious life- threatening internal bleeding). Instruct patients to report these to the study team
- Patients should discuss any procedures with the study team and/or any provider prior to proceeding, due to the risk of post procedure bleeding.
- Rarely patients may have nausea, treat symptomatically and monitor for effectiveness
- Rarely LFT's may be elevated. Follow any monitoring as recommended by the study protocol.

15.2 Dalteparin (Fragmin®) Commercial supply

Package Insert is available on the ACCRU web site.

15.21 Background: Dalteparin is a low molecular weight heparin with antithrombotic properties. It acts by enhancing the inhibition of Factor Xa and thrombin by antithrombin. In humans, dalteparin potentiates preferentially the inhibition of coagulation Factor Xa, while only slightly affecting the activated partial thromboplastin time (APTT).

Dalteparin is used for the prevention of deep vein thrombosis (DVT) which may lead to pulmonary embolism, in patients requiring abdominal surgery who are at risk for thromboembolism complications (eg, patients >40 years of age, obesity, patients with malignancy, history of DVT or pulmonary embolism, and surgical procedures requiring general anesthesia and lasting >30 minutes); prevention of DVT in patients undergoing hip-replacement surgery; patients immobile during an acute illness; prevention of ischemic complications in patients with unstable angina or non-Q-wave myocardial infarction on concurrent aspirin therapy; in patients with cancer, extended treatment (6 months) of acute symptomatic venous thromboembolism (DVT and/or PE) to reduce the recurrence of venous thromboembolism.

15.22 **Formulation:** Dalteparin sodium injection (Fragmin®) is available as single dose prefilled syringes in the following sizes: 2,500 IU/0.2 mL, 5,000 IU/0.2 mL, 7,500 IU/0.3 mL, 12,500 IU/0.5 mL, 15,000 IU/0.6 mL, and 18,000 IU/0.72 mL. It is also available as a single-dose graduated syringe of 10,000 IU/1 mL, and is available as a multiple dose vial containing 95,000 IU/3.8 mL (25,000 IU/mL).

Each prefilled syringe also contains Water for Injection and sodium chloride, when required, to maintain physiologic ionic strength. The prefilled syringes are

preservative-free. Each multiple-dose vial also contains Water for Injection and 14 mg of benzyl alcohol per mL as a preservative. The pH of both formulations is 5.0 to 7.5

15.23 **Preparation and storage**: Store at controlled room temperature 20° to 25°C (68° to 77°F)Store at 20°C to 25°C (68°F-77°F) [see USP]. Please see package insert.

15.24 **Administration:** Dalteparin will be given 200 IU/kg/day subcutaneously. The dosage will be calculated on the patient's current weight in kilograms, rounded to the nearest whole kilogram. The syringe dose will be chosen based on the weight adjusted calculation (see table 7.11). . The patient will be taught by on site nursing staff how to "waste" from each syringe such that the appropriate weight adjusted dose is delivered. After the first month, dalteparin will be given 150 IU/kg/day subcutaneously. Dalteparin will be dispensed in one month supply aliquots to the patient. Dalteparin will be stored according to the package insert. Patient instructions on proper subcutaneous injection techniques are included in appendix IX.

15.25 **Appearance:** Colorless solution in single-dose, prefilled syringes preassembled with a needle guard device. Each syringe contains 2,500, 5,000, 7,500, 10,000, 12,500, 15,000 or 18,000 anti-Factor Xa international units (IU).

15.26 **Pharmacokinetic information:**

a) Onset of action - Anti-Xa activity: Within 1-2 hours
b) Duration - >12 hours
c) Distribution - Vd: 40-60 mL/kg
d) Protein binding - Low affinity for plasma proteins
e) Bioavailability - SubQ: 81% to 93%
f) Half-life elimination (route dependent) - Anti-Xa activity: 2-5 hours; prolonged in chronic renal insufficiency: 3.7-7.7 hours (following a single 5000 unit dose)
g) Time to peak, serum - Anti-Xa activity: ~4 hours
h) Excretion - Primarily renal

15.27 **Potential drug interactions:** Dalteparin should be used with care in patients receiving oral anticoagulants, platelet inhibitors, and thrombolytic agents because of increased risk of bleeding.

Please consult current drug reference sources for a complete list of potential drug interactions.

15.28 **Known potential toxicities**: As with all anticoagulants, bleeding is the major adverse effect of dalteparin. Hemorrhage may occur at virtually any site. Risk is dependent on multiple variables. Please consult the package insert for the most current and complete information.

Adverse effects by frequency:

>10%:

Hematologic & oncologic: Hemorrhage (3% to 14%), thrombocytopenia (including heparin-induced thrombocytopenia, <1%; cancer clinical

trials: ~11%)

1% to 10%:
Hematologic & oncologic: Major hemorrhage (≤6%), wound hematoma (3%)

Hepatic: Increased serum ALT (>3 x ULN: 4% to 10%), increased serum AST (>3 x ULN: 5% to 9%)

Local: Pain at injection site (≤12%), hematoma at injection site (≤7%)

<1% (Limited to important or life-threatening):
Alopecia, anaphylactoid reaction, gastrointestinal hemorrhage, hemoptysis, hypersensitivity reaction (fever, pruritus, rash, injections site reaction, bullous eruption), postoperative wound bleeding, skin necrosis, subdural hematoma, thrombosis (associated with heparin-induced thrombocytopenia). Spinal or epidural hematomas can occur following neuraxial anesthesia or spinal puncture, resulting in paralysis.

15.29a **Drug procurement:** Pfizer will supply the drug to Biologics, Inc. Each participating ACCRU treating location will order the drug from Biologics, Inc. Fax the Drug Order Request Form (found in the forms packet) to:
Biologics, Inc.
Attn. Clinical Research Services
Fax: [redacted]

Each participating ACCRU treating location will be responsible for monitoring the supply of dalteparin and will use the Drug Order Request Form to order additional supplies as needed.

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

15.29b Nursing guidelines:
- Instruct patients on self-injection technique.
- Warn patient of increased risk of bleeding, including life threatening hemorrhage. Patients should report excessive bruising and/or bleeding to the study team.
- Monitor LFT's and alert study team to changes in values.
- Instruct patients that they need to notify their provider prior to any procedures, as their risk for bleeding is significantly increased.

## 16.0 Statistical Considerations and Methodology

16.1 Sample Size Determination

The primary objective of this study is to determine whether apixaban therapy has less major bleeding than low molecular weight heparin (dalteparin) in the treatment of patients with active cancer and confirmed acute deep-vein thrombosis (DVT) or pulmonary embolism (PE). Important assumptions include a major bleeding rate of 6% over 6 months with clinically relevant non-major bleeding rates of 11-14% for those

patients assigned to dalteparin. **The incidence of major bleeding ( or DVT) will be computed using the cumulative incidence funtion treating death without major bleeding ( or without DVT) as the competing risk. Rationale: to prevent potential bias in the comparison due to the difference in mortality rates between the two arms. Unstratified Cox models will be used in all analyses instead of stratified Cox models. Rationale: Based on data from previous studies which are used to design this trial, the incidence of major bleeding is extremely low. There will substantial loss of power with the use of stratified Cox models which the study was not powered for. Since this is a randomized study and the randomization is stratified by cancer stage and risk; we expect minimal confounding effect from these variables.** This assumption is based on available published trial data summarized in the table:

| Author | LMWH | F/U (months) | LMW VTE | LMW Death | LMW major bleed |
|---|---|---|---|---|---|
| Lee (18) | 336 | 6 | 9% | 39% | 6% |
| Kakkar (28) | 334 | 12 | 13.2% | | 8.4% |
| Hull (22) | 100 | 12 | 16% | 47% | |
| Monreal (29) | 203 | 3 | 9% | | 5.4% |
| Deitcher (21) | 122 | 7 | 6.6% | | |

The published rates of major and clinically relevant non-major bleeding for apixaban for VTE treatment (AMPLIFY trial) are 0.6% and 4.3% respectively.

A superiority trial design is proposed. Sample sizes, power estimates, and hazard ratios have been calculated with EAST 6.3 (Cytel Inc.). Patients will be randomized in a 1:1 fashion. Other assumptions used to determine the trial sample size include:

- one sided significance = 0.05
- power = 80%
- 6 month bleeding rate on control arm (dalteparin) = 6.0%
- accrual rate: 10 patients per month
- anticipated follow-up period: minimum of 6 months for each patient
- assuming the 6 months major bleed rate in experimental arm (apixaban) is 1.4% and assuming major bleeding follows an exponential distribution, this corresponds to a hazard ratio (HR) of 0.22

Based on the assumptions above, a sample size of 300 patients (150 per arm) would be required. We would accrue an additional maximum of 5% to account for ineligible patients and patients who withdraw from the study prior to receiving treatment. Hence the total maximum target accrual would be 315 (= 1.05 x 300) patients.
The anticipated accrual period (assuming 10 patients per month) would be 30 months or approximately 2.5 years. It is anticipated that the primary analysis can take place after the last accrued patient was followed for 6 months or when 11 major bleeds have been observed.

16.2 Primary Hypothesis:

We hypothesize that apixaban is associated with a significantly lower rate of major bleed compared to dalteparin in the treatment of patients with active cancer and confirmed acute deep-vein thrombosis (DVT) or pulmonary embolism (PE).

There are two changes made to the analysis plan as of Amendment 3. The original analysis plan was formulated by the previous study statistician. The following changes are proposed by the current study statistician for reasons explained below without knowledge of the outcome data. The changes and rationale for those changes are summarized below.

1. The incidence of major bleeding (or DVT) will be computed using the cumulative incidence function treating death without major bleeding (or without DVT) as the competing risk. Rationale: to prevent potential bias in the comparison due to the difference in mortality rates between the two arms.

2. Unstratified Cox models will be used in all analyses instead of stratified Cox models. Rationale: Based on data from previous studies which are used to design this trial, the incidence of major bleeding is extremely low. There will be substantial loss of power with the use of stratified Cox models which the study was not powered for. Since this is a randomized study and the randomization is stratified by cancer stage and risk, we expect minimal confounding effect from these variables.

16.21 Primary Safety Analysis:

All patients who received at least one dose of either apixaban or dalteparin will be included in the primary analysis. Patients will be analyzed according to the drug they received because this is a safety analysis rather than an efficacy analysis. The analysis of major bleeding events will primarily focus on those events which occurred during treatment or within 7 days of treatment discontinuation. Major bleeding events observed later will be described separately. Patients who did not have a bleeding event during the predefined time of treatment and follow-up period, who were lost to follow-up, or who withdrew informed consent before the end of the predefined study duration and who did not have a bleeding event will be censored at the appropriate time. The frequency of major bleeding events will be summarized separately by treatment arm. The cumulative incidence of major bleeding at 6 months from treatment initiation and its associated 95% confidence interval will be estimated separately by treatment arm using a cumulative incidence function, treating death without bleeding as a cometing risk.~~.~~ A Cox proportional hazard model will be used to determine the point estimate for the HR (comparing apixaban to dalteparin) and the p-value for the comparison between the two arms. If the one-sided p-value is less than 0.05, then apixaban will be declared to have a lower major bleeding rate in this population

16.22 Secondary Safety Analysis:

A sensitivity analysis of the primary safety endpoint will be performed using the intent-to-treat population. Cox's proportional hazard model will be used to compare the major bleed events between the two. As before, a one-sided p-value will be used to determine whether apixaban has superior safety (i.e. smaller major bleed event rate than the control).

The secondary safety endpoint analysis will be on a treatment received basis. In this analysis, the composite endpoint of bleeding event defined as a major bleed or a clinically relevant non-major bleed will be used. For this analysis we will only include events that occurred during treatment or 7 days after treatment termination A similar analysis as described for the primary safety analysis will be used. The impact of baseline covariates on the safety outcome will be Explored by adjusting for them in the Cox models. The frequencies of the separate components contributing to the safety outcome will be described. Other safety outcomes include all deaths and other vascular events. AEs will be coded using the MedDRA Dictionary. Emergent adverse events will be defined as AEs occurring or worsening after randomization but not more than 7 days after study medication discontinuation. Events occurring during the 30 day follow up period will be described.

16.23 Secondary Efficacy Analysis:

For the secondary efficacy analysis, the time to the first event of the composite DVT/PE outcome will be analyzed using the same methods described above for the primary endpoint. The impact of baseline covariates (location of DVT, renal clearance, age, sex, mobility at randomization, pulmonary disease, and cardiac disease) on the efficacy outcome will be explored adjusting for them in the Cox models. Since this is a secondary endpoint, there is no adjustment for multiple comparisons. This analysis will be conducted at the one-sided type I error of 0.05.

The assumption of proportional hazards will be checked for all Cox models (including primary and secondary endpoints~~and secondary analyese~~) using graphical methods aslog(-log)-plots and plots of scaled Schoenfeld residuals.

16.3 Handling of Missing Data:

Monitoring and auditing procedures should be followed, in order to comply with GCP guidelines. Each center will be audited at regular intervals to ensure compliance with the protocol, GCP and legal aspects. This will include on-site checking of the CRF for completeness and clarity, cross-checking with source documents, and clarification of administrative matters.

16.4 Interim Analysis and Study Monitoring:

No formal interim analysis is planned. Risk-benefit will be evaluated by the Mayo Clinic Data Safety and Monitoring Board (DSMB), which will give regular recommendation to the executive committee. Early termination of accrual will be considered if there is evidence of a significant difference in major bleeding rates between the comparators. Access to interim tabular risk benefit data will be restricted.

16.5 Adeverse Event Stopping Rule:

The stopping rule specified below is based on the knowledge available at study development. We do note that the Adverse Event Stopping Rule may be adjusted in the event of either (1) the study re-opening to accrual or (2) at any time during the conduct of the trial and in consideration of newly acquired information regarding the adverse event profile of the treatment(s) under investigation. The study team may choose to suspend

accrual because of unexpected adverse event profiles that have not crossed the specified rule below.

Accrual will be temporarily suspended to this study if at any time we observe events that the study team considers to be at least possibly related to study treatment (i.e., an adverse event with attribute specified as "possible," "probable," or "definite") that satisfy the following:

- If 5 or more patients in the first 20 treated patients of either of the study arms (or 20% of all patients after 20 are accrued) experience a grade 4 or higher non-hematologic adverse event.

We note that we will review grade 4 and 5 adverse events deemed "unrelated" or "unlikely to be related" to verify their attribution and to monitor the emergence of a previously unrecognized treatment-related adverse event.

## 17.0 Pathology Considerations/Tissue Biospecimens – Not applicable

## 18.0 Records and Data Collection Procedures

All data must be entered by Remote Date Entry (RDE) and completed by qualified and authorized personnel. All data on the CRF must reflect the corresponding source document. Please refer to the ACCRU website for instructions [redacted]

### 18.1 Submission Timetable

**Initial Material(s)**

| **CRF** | **Active-Monitoring Phase** (Compliance with Test Schedule Section 4.0) |
|---|---|
| On-Study | ≤2 weeks after registration |
| Adverse Event - Baseline | |
| Selected Concomitant Medication - Baseline | |
| End of Active Treatment/Cancel Notification | Submit ≤2 weeks after registration if withdrawal/refusal occurs prior to beginning protocol therapy |
| Patient Questionnaire Booklet | ≤ 2 weeks after registration - Patient questionnaire booklet **must** be used; copies are not acceptable for this submission. |
| Patient Questionnaire Booklet Compliance | ≤ 2 weeks after registration - This form **must** be completed only if the patient questionnaire booklet contains absolutely **NO** patient provided assessment information. |

**Test Schedule Material(s)**

| **CRF** | **Active-Monitoring Phase** (Compliance with Test Schedule Section 4.0) | | |
|---|---|---|---|
| | At each monthly evaluation during treatment | At end of treatment | Observation (3 months) |
| Evaluation/Treatment Form (Arm A: Apixaban) (Cycle 1 Only) | X | | |

| CRF | Active-Monitoring Phase (Compliance with Test Schedule Section 4.0) | | |
|---|---|---|---|
| | At each monthly evaluation during treatment | At end of treatment | Observation (3 months) |
| Evaluation/Treatment Form (Arm A: Apixaban) | X | X | |
| Evaluation/Treatment Form (Arm B: Dalteparin)(Cycle 1 only) | X | | |
| Evaluation/Treatment Form (Arm B: Dalteparin) | X | X | X |
| Evaluation/Observation Form | | | X |
| Recurrent Venous Thrombosis | X | X | X |
| Adverse Event | X | X | X |
| Non-CTCAE Bleeding Grading | X | | |
| Selected Concomitant Medication | X | X | |
| Laboratory | X | X | |
| Patient Questionnaire Booklet | X[1] | X | |
| Booklet Compliance | X[2] | X | |
| Patient Compliance Questionnaire | X | X | |
| End of Active Treatment/Cancel Notification | | X | |
| Notification Form – Grade 4 or 5 Non-AER Reportable Events/Hospitalization | At each occurrence (see Section 10.0) | | |
| ADR/AER | At each occurrence (see Section 10.0) | | |

1. Patient questionnaire booklet **must** be used; copies are not acceptable for this submission.
2. This form must be completed **only** if the Patient Questionnaire booklet contains absolutely **NO** patient provided assessment information.

## 19.0 Budget

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

19.2 Tests to be research funded: none.

19.3 Other budget concerns: The study drug, apixaban, will be supplied free of charge by Bristol Myers-Squibb. The comparator drug, dalteparin, will be provided free of charge by Pfizer.

**References**

1. Prandoni, P., A. Piccioli, and A. Girolami, Cancer and venous thromboembolism: an overview. Haematologica, 1999. 84(5): p. 437-45.
2. Nordstrom, M., et al., Deep venous thrombosis and occult malignancy: an epidemiological study. Bmj, 1994. 308(6933): p. 891-4.
3. Prandoni, P., et al., Deep-vein thrombosis and the incidence of subsequent symptomatic cancer. N Engl J Med, 1992. 327(16): p. 1128-33.
4. Cormack, J., Phlegmasia alba dolens., in Trousseau A. Lectures on clinical medicine, delivered at the Hotel-dieu, Paris. 1872. p. 281-95.
5. Heit, J.A., et al., Risk factors for deep vein thrombosis and pulmonary embolism: a population-based case-control study. Arch Intern Med, 2000. 160(6): p. 809-15.
6. Heit, J.A., Risk factors for venous thromboembolism. Clin Chest Med, 2003. 24(1): p. 1-12.
7. Khorana, A.A., et al., Thromboembolism is a leading cause of death in cancer patients receiving outpatient chemotherapy. J Thromb Haemost, 2007. 5(3): p. 632-4.
8. Sorensen, H.T., et al., Prognosis of cancers associated with venous thromboembolism. N Engl J Med, 2000. 343(25): p. 1846-50.
9. Chew, H.K., et al., Incidence of venous thromboembolism and its effect on survival among patients with common cancers. Arch Intern Med, 2006. 166(4): p. 458-64.
10. McBane RD, Wysokinski WE, Daniels PR, et al. Periprocedural anticoagulation management of patients with venous thromboembolism. Arterioscler Thromb Vasc Biol. 2010;30(3):442–448.
11. Ashrani AA, Heit JA. Risk factors for thrombosis in cancer patients. Cancer Treat Res. 2009;148:95–114.
12. Noble S, Pasi J. Epidemiology and pathophysiology of cancer-associated thrombosis. Br J Cancer. 2010;102(suppl 1):S2–S9.
13. Ashrani AA, Rajkumar SV. Chemotherapy-associated thrombosis. Cancer Treat Res. 2009;148:181–206.
14. Prandoni P, Trujillo-Santos J, Surico T, Dalla Valle F, Piccioli A, Monreal M; RIETE Investigators. Recurrent thromboembolism and major bleeding during oral anticoagulant therapy in patients with solid cancer: findings from the RIETE registry. Haematologica. 2008;93(9):1432–1434.
15. Trujillo-Santos J, Nieto JA, Ruíz-Gamietea A, et al; RIETE Investigators. Bleeding complications associated with anticoagulant therapy in patients with cancer. Thromb Res. 2010;125(suppl 2):S58–S61.
16. Tafur AJ, Wysokinski WE, McBane RD, et al. Cancer effect on periprocedural thromboembolism and bleeding in anticoagulated patients. Ann Oncol. 2012;23(8):1998–2005.
17. Kearon C, Akl EA, Comerota AJ, Prandoni P, Bounameaux H, Goldhaber SZ, Nelson ME, Wells PS, Gould MK, Dentali F, Crowther M, Kahn SR. Antithrombotic therapy for VTE disease: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest 2012;141:e419S-94S.
18. Lee AYY, Levine MN, Baker RI et al. Low-Molecular-Weight Heparin versus a Coumarin for the Prevention of Recurrent Venous Thromboembolism in Patients with Cancer. N Engl J Med 2003;349:146-153.
19. Lee AY, Rickles FR, Julian JA, Gent M, Baker RI, Bowden C, Kakkar AK, Prins M, Levine MN. Randomized comparison of low molecular weight heparin and coumarin derivatives on the survival of patients with cancer and venous thromboembolism. J Clin Oncol. 2005;23:2123-9.
20. Meyer G, Marjanovic Z, Valcke J, Lorcerie B, Gruel Y, Solal-Celigny P, Le Maignan C, Extra JM, Cottu P, Farge D. Comparison of low-molecular-weight heparin and warfarin for the secondary prevention of venous thromboembolism in patients with cancer: a randomized controlled study. Arch Intern Med. 2002;162:1729-35.
21. Deitcher SR, Kessler CM, Merli G, Rigas JR, Lyons RM, Fareed J; ONCENOX Investigators. Secondary prevention of venous thromboembolic events in patients with active cancer: enoxaparin

alone versus initial enoxaparin followed by warfarin for a 180-day period. Clin Appl Thromb Hemost. 2006;12:389-96.

22. Hull RD, Pineo GF, Brant RF, Mah AF, Burke N, Dear R, Wong T, Cook R, Solymoss S, Poon MC, Raskob G; LITE Trial Investigators. Long-term low-molecular-weight heparin versus usual care in proximal-vein thrombosis patients with cancer. Am J Med. 2006;119:1062-72.
23. Agnelli G, Buller HR, Cohen A, Curto M, Gallus AS, Johnson M, Masiukiewicz U, Pak R, Thompson J, Raskob GE, Weitz JI; the AMPLIFY Investigators. Oral Apixaban for the Treatment of Acute Venous Thromboembolism. N Engl J Med. 2013 Jul 1 (ahead of print).
24. Agnelli G, Buller HR, Cohen A, Curto M, Gallus AS, Johnson M, Porcari A, Raskob GE, Weitz JI; AMPLIFY-EXT Investigators. Apixaban for extended treatment of venous thromboembolism. N Engl J Med. 2013;368:699-708.
25. Einstein Investigators. Oral rivaroxaban for symptomatic venous thromboembolism. N Engl J Med 2010;363:2499-510.
26. Einstein PE Investigators. Oral rivaroxaban for the treatment of symptomatic pulmonary embolism. N Engl J Med 2012;366:1287-97.
27. Khorana AA, Kuderer NM, Culakova E, Lyman GH, Francis CW. Development and validation of a predictive model for chemotherapy-associated thrombosis. Blood. 2008;111:4902-7.
28. Kakkar AK, Levine MN, Kadziola Z, Lemoine NR, Low V, Patel HK, Rustin G, Thomas M, Quigley M, Williamson RC. Low molecular weight heparin, therapy with dalteparin, and survival in advanced cancer: the fragmin advanced malignancy outcome study (FAMOUS). J Clin Oncol. 2004;22:1944-8.
29. Monreal M, Falgá C, Valdés M, Suárez C, Gabriel F, Tolosa C, Montes J; Riete Investigators. Fatal pulmonary embolism and fatal bleeding in cancer patients with venous thromboembolism: findings from the RIETE registry. J Thromb Haemost. 2006;4:1950-6.
30. Pocock SJ, Simon R. Sequential Treatment Assignment with Balancing for Prognostic Factors in the Controlled Clinical Trial. Biometrics 31(1):103-115, 1975 Mar.
31. Chee CE, Ashrani AA, Marks RS, Petterson TM, Bailey KR, Melton LJ 3rd, Heit JA. Predictors of venous thromboembolism recurrence and bleeding among active cancer patients: a population-based cohort study. Blood. 2014;123(25):3972-3978.
32. Frost et al, Clinical Pharmacology: Advances and Applications 2014:6 179–187.