Apixaban for Primary Prevention of Venous Thromboembolism in Patients with Multiple Myeloma Receiving Immunomodulatory Therapy

Version 17.0

Protocol Version Date: November 8, 2017

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Protocol Version Record

Version 1.0	January 25, 2016
Version 2.0	January 26, 2016
Version 3.0	January 31, 2016
Version 4.0	February 2, 2016
Version 5.0	February 14, 2016
Version 6.0	March 4, 2016
Version 7.0	March 7, 2016
Version 8.0	April 8, 2016
Version 9.0	April 19, 2016
Version 10.0	April 24, 2016
Version 11.0	April 26, 2016
Version 12.0	May 16, 2016
Version 13.0	June 26, 2017
Version 14.0	July 30, 2017
Version 15.0	October 9, 2017
Version 16.0	October 26, 2017
Version 17.0	November 8, 2017

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Protocol Summary

Title: Apixaban for Primary Prevention of Venous Thromboembolism in Patients with Multiple Myeloma Receiving Immunomodulatory Therapy

Design: U.S.-based, single-center, single-arm, open-label, proof-of-concept study

Brief Treatment Description: Direct anti-factor Xa inhibition with apixaban 2.5 mg orally twice daily for primary prevention of VTE

Purpose: To determine the rate of major and clinically relevant non-major bleeding and the rate of symptomatic VTE in MM patients on immunomodulatory drugs (IMiDs) who are receiving apixaban 2.5 mg orally twice daily. This study will provide event rates that could inform the design of a larger randomized controlled trial.

Population: Outpatients with MM receiving IMiDs (i.e., thalidomide [Thalomid], lenalinomide [Revlimid], and pomalidomide [Pomalyst]).

Enrollment: 50 subjects

Clinical Site Locations: 1 center (Vanderbilt University Medical Center)

Study Duration: 22 months; enrollment period of up to 16 months with 6-month follow-up.

Primary Safety and Efficacy Outcomes:

Primary Safety Outcome: The 6-month rate of International Society on Thrombosis and Haemostasis major and clinically relevant non-major bleeding in MM patients receiving IMiDs who are prescribed apixaban 2.5 mg orally twice daily for primary prevention of VTE.

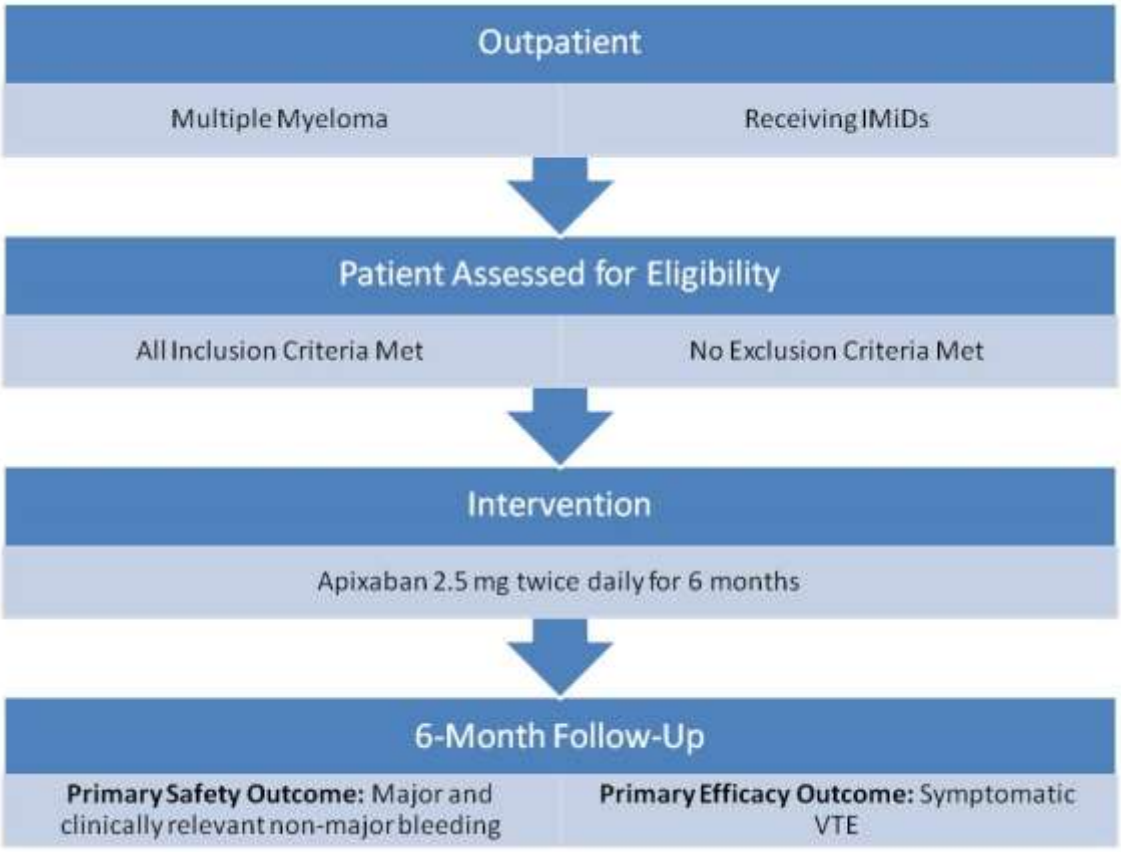
Secondary Safety Outcome: All-cause mortality at 6 months will be recorded. Cause of death will be classified as related to cancer, myocardial infarction, PE, or other disease state.

Primary Efficacy Outcome: The 6-month rate of symptomatic VTE in MM patients receiving IMiDs who are prescribed apixaban 2.5 mg orally twice daily for primary prevention of VTE.

Secondary Efficacy Objectives: The 6-month rate of myocardial infarction and stroke will also be calculated.

Follow-Up: Follow-up will consist of Electronic Health Record review at 6-months from study enrollment.

Study Flow Diagram



IMiDs, immunomodulatory drugs; VTE, venous thromboembolism

Abbreviations and Definitions

Listed in alphabetical order

DVT, deep vein thrombosis

eCRF, electronic case report form

IMiDs, immunomodulatory drugs (i.e., thalidomide [Thalomid], lenalinomide [Revlimid], and pomalidomide [Pomalyst])

ISTH, International Society on Thrombosis and Haemostasis

LMWH, low-molecular weight heparin

MM, multiple myeloma

NOACs, non-vitamin K oral anticoagulants

PE, pulmonary embolism

PI, Proteasome inhibitors

SAE, significant adverse event

UADE, unanticipated adverse drug effect

VTE, venous thromboembolism

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Specific Aims

Patients living with multiple myeloma (MM) have an increased risk of venous thromboembolism (VTE) due to the disease itself and the use of targeted therapies, including immunomodulatory drugs (IMiDs). Prevention of VTE has become a major management challenge during MM treatment. There is a paucity of data with respect to the non-vitamin K oral anticoagulants (NOACs) in the cancer population. However, the NOACs offer comparable efficacy but improved safety compared with warfarin. Apixaban has shown excellent safety and efficacy for treatment and prevention of recurrent VTE (1,2). The safety and efficacy of apixaban for primary prevention of VTE in MM patients has not been established.

Aim #1: To quantify the 6-month rate of major and clinically relevant non-major bleeding in MM patients receiving IMiDs who are prescribed apixaban 2.5 mg orally twice daily for primary prevention of VTE.

Hypothesis #1: The 6-month rate of major and clinically relevant non-major bleeding in MM patients receiving IMiDs who are prescribed apixaban 2.5 mg orally twice daily for primary prevention of VTE will be ≤3% (2). Although the MM population, in general, has a higher medical acuity than that of the previous large randomized controlled trials of apixaban, we will be selecting a stable population of MM patients who are appropriate for immunomodulatory therapy.

Aim #2: To quantify 6-month rate of symptomatic VTE in MM patients receiving IMiDs who are prescribed apixaban 2.5 mg orally twice daily for primary prevention of VTE.

Hypothesis #2: The 6-month rate of symptomatic VTE in MM patients receiving IMiDs who are prescribed apixaban 2.5 mg orally twice daily for primary prevention of VTE will be <7% (3). Although additional therapies for MM such as dexamethasone and erythropoietin-stimulating agents may further increase the risk of VTE, the rate of incident VTE should be reduced to <7% with apixaban.

Introduction and Background

Multiple myeloma (MM) is a plasma cell malignancy characterized by clonal proliferation of malignant plasma cells in the bone marrow microenvironment, monoclonal protein in the blood or urine, and associated organ dysfunction (4). Overall survival has improved due to the advent of novel targeted therapies, including immunomodulatory drugs (IMiDs) and proteasome inhibitors (PIs). As with other hematological malignancies, MM is associated with an increased risk of venous thromboembolism (VTE). The risk of VTE is further increased in the setting of IMiDs. Currently used IMiDs include thalidomide (Thalomid), lenalinomide (Revlimid), and pomalidomide (Pomalyst). A meta-analysis of more than 3000 MM patients showed that the risk of VTE increased nearly 3-fold when the IMiD thalidomide was prescribed and nearly 8-fold when thalidomide was combined with other chemotherapeutics (5). The risk of VTE is amplified when IMiDs are combined with a novel proteasome inhibitor, carfilzomib, that was recently approved by the U.S. Food and Drug Administration (6). Due to the increasing use of IMiD-based regimens, prevention of VTE has become a major management challenge during MM treatment (**Table 1**) (7). A systematic analysis of MM patients treated with IMiDs, especially in combination with other therapies, shows that VTE risk remains an important complication in this population (Piazza G and Moslehi J, unpublished data).

Table 1. VTE incidence in IMiDs trials (7).

Treatment Regimen	VTE incidence (%) without thromboprophylaxis	VTE incidence (%) with thromboprophylaxis[a]
Thalidomide		
Alone	2-10	NA
Plus dexamethasone	2-26	8-25
Plus chemotherapy[b]	3-58	3-31
Lenalidomide		
Alone	0-33	NA
Plus dexamethasone	8-75	3-14
Plus chemotherapy[b]	14	5-9
Pomalidomide		
Alone	NA	2
Plus dexamethasone	NA	2-5

VTE, venous thromboembolism; NA, not applicable
[a]Aspirin (81-325mg daily), low molecular weight heparin (LMWH), fixed warfarin (1-1.25mg daily) and full-dose of warfarin (target INR 2-3) have been used for prophylaxis. Choice of thromboprophylaxis was largely based on physicians' discretion.

[b]Thalidomide and lenalidomide were used in combination with other therapeutic agents, including melphalan, doxorubicin and cyclophosphamide.

MM patients also have a higher risk of arterial thromboembolic events, including myocardial infarction and stroke (7). IMiDs also appear to increase the risk for arterial thromboembolic events. In the long-term follow-up of 704 MM patients in two phase 3, randomized clinical trials, the frequency of myocardial infarction and cerebrovacular events were 1.98% and 3.4%, respectively, in patients treated with lenalidomide and dexamethasone compared with 0.57% and 1.7%, in patients treated with dexamethasone alone (https://www.gov.uk/drug-safety-update/lenalidomide-risk-of-thrombosis-and-thromboembolism). Lenalidomide carries a black box warning of significant myocardial infarction and stroke risks in MM patients receiving lenalidomide and dexamethasone treatment.

Currently, there are no guidelines regarding the optimal thromboprophylactic regimen for MM patients receiving IMiDs. A broad-based VTE prevention guideline for cancer patients is too general to be of practical use in MM patients (8). In the case of MM, aspirin (81-325 mg daily), low-molecular weight heparin (LMWH), and warfarin (target INR 2-3) have all been prescribed for VTE prophylaxis. However, the specific prophylactic regimen is ultimately based on the treating clinician's best clinical judgment (7,9). The choice of VTE prophylaxis is further complicated due to frequent renal dysfunction in MM patients. Furthermore, these patients are often reluctant to undertake an extended duration prophylactic LMWH regimen of daily self-injections due to anxiety and injection-site discomfort. An unintended consequence of LMWH injections is that injectable prophylactic anticoagulant regimens are associated with decreased medication adherence (10).

There is a paucity of data with respect to the non-vitamin K oral anticoagulants (NOACs) in the cancer population. However, the NOACs have been shown to offer comparable efficacy but improved safety compared with warfarin. Apixaban has shown excellent safety and efficacy for treatment and prevention of recurrent VTE (1,2).

In a randomized, double-blind study (AMPLIFY), apixaban (administered as a loading dose of 10 mg twice daily for 7 days, followed by 5 mg twice daily) was compared with subcutaneously-administered enoxaparin followed by warfarin in 5395 patients with acute venous thromboembolism (1). The primary efficacy outcome of recurrent symptomatic VTE or VTE-related death occurred in 59 of 2609 patients (2.3%) in the apixaban group compared with 71 of 2635 (2.7%) in the warfarin group (relative risk, 0.84; 95% confidence interval [CI], 0.60 to 1.18; $p < 0.001$ for non-inferiority). Major bleeding occurred in 0.6% of patients who received apixaban and in 1.8% of those who received warfarin (relative risk, 0.31; 95% CI, 0.17 to 0.55; $p<0.001$ for superiority). A composite outcome of major bleeding and clinically relevant nonmajor bleeding occurred in 4.3% of the

patients in the apixaban group compared with 9.7% of those in the conventional-therapy group (relative risk, 0.44; 95% CI, 0.36 to 0.55; p<0.001).

In the randomized, double-blind AMPLIFY-EXT study, two doses of apixaban (2.5 mg and 5 mg, twice daily) were compared with placebo in patients with VTE who had completed 6 to 12 months of anticoagulation therapy and for whom there was clinical equipoise regarding the continuation or cessation of anticoagulation therapy (2). A total of 2486 patients underwent randomization. Symptomatic recurrent venous thromboembolism or death from venous thromboembolism occurred in 73 of the 829 patients (8.8%) who were receiving placebo versus 14 of the 840 patients (1.7%) who were receiving 2.5 mg of apixaban and 14 of the 813 patients (1.7%) who were receiving 5 mg of apixaban (p<0.001 for both comparisons). The rate of major and clinically relevant non-major bleeding in patients receiving apixaban 2.5 mg orally twice daily for extended-duration prevention of recurrent VTE was similar to that of placebo.

Though the stroke prevention in atrial fibrillation population is different, the AVERROES Trial also demonstrated the strong safety profile of apixaban, which had the same major bleeding rate as aspirin (11).

Rationale for the Proposed Study

MM is associated with an increased risk of venous thromboembolism (VTE). The use of targeted therapies, including immunomodulatory drugs (IMiDs), has improved outcomes for patients with MM but also increases the risk of VTE. Prevention of VTE has become a major management dilemma during MM treatment. There is a paucity of data with respect to the non-vitamin K oral anticoagulants (NOACs) in the cancer population, including patients with MM. However, the NOACs have been shown to offer comparable efficacy but improved safety compared with warfarin. Apixaban has shown excellent safety and efficacy for treatment and prevention of recurrent VTE (1,2). Compared with injectable thromboprophylactic regimens such as enoxaparin, apixaban offers the advantages of being orally administered and less reliant on renal clearance. The safety and efficacy of apixaban for primary prevention of VTE in MM patients has not been established. The current study will evaluate apixaban (2.5 mg twice daily) in a patient population without a history of prior VTE. Although the current study population is high risk for VTE, it is likely to be lower risk for VTE than those of the prior randomized controlled trials of apixaban for secondary prevention. Furthermore, current practice is to provide MM patients receiving IMiDs with prophylactic doses (not treatment doses) of low-molecular weight heparin (such as enoxaparin 40 mg injected daily). Accordingly, the rationale to test apixaban (2.5 mg twice daily) is consistent with the standard practice of prophylactic anticoagulation.

The current study will provide event rates that will inform the design of a larger randomized controlled trial. If safe and effective, apixaban will satisfy a critical unmet need and will represent a substantial advance and "game changer" in the prevention of VTE in this high risk patient population.

Study Objectives

Primary Safety Objective: To quantitatively assess the 6-month rate of major and clinically relevant non-major bleeding in MM patients receiving IMiDs who are prescribed apixaban 2.5 mg orally twice daily for primary prevention of VTE.

Primary Efficacy Outcome: To quantitatively assess the 6-month rate of symptomatic VTE in MM patients receiving IMiDs who are prescribed apixaban 2.5 mg orally twice daily for primary prevention of VTE.

Secondary Efficacy Outcome: To quantitatively assess the 6-month rate of myocardial infarction and stroke.

Study Design

50-patient U.S.-based, single-center, single-arm, open-label, proof-of-concept study of apixaban 2.5 mg orally twice daily for primary prevention of VTE.

Study Duration

The study will be completed in 24 months: 3 months for start-up (including Human Research Committee approval, hiring of additional staff, and finalizing the Case Report Form), 18 months for patient enrollment and data collection, and 3 months for data analysis and writing up the results (**Table 2**).

Table 2. Study timeline.

Milestone	**Duration (months)**
Start-up	3
Patient enrollment	12
Completion of data collection	6
Data analysis and completion of study report	3
TOTAL	**24**

Study Population

Patients who are > 18 years of age or older with newly diagnosed MM, relapsed MM, MM on maintenance therapy and receiving IMiDs (i.e., thalidomide [Thalomid], lenalinomide [Revlimid], and pomalidomide [Pomalyst]).

Study Inclusion Criteria

- Men and women
- Age > 18 years
- Current or prior diagnosis of symptomatic MM based on International Myeloma Working Group (IMWG) guidelines (http://imwg.myeloma.org/category/guidelines-2/) and will be starting or already receiving IMiD therapy with thalidomide [Thalomid], lenalinomide [Revlimid], or pomalidomide [Pomalyst]
- IMiD therapy given in the setting of newly diagnosed MM, relapsed MM, progressive MM, maintenance therapy or consolidation therapy as per IMWG criteria

Patients must have had measurable disease as defined by at least one of the following:**

- Serum M-protein ≥ 0.5 g/dL by serum electrophoresis (SPEP) or for IgA myeloma, by quantitative IgA (>750 mg/dl)
- Urinary M-protein excretion at least 200 mg/24 hours
- Serum Free Light Chain (FLC) whereby the involved light chain measures ≥ 10 mg/dL and with an abnormal light chain ratio.

**The patient must have met criteria for measurable disease at some point. Criteria do not have to be met at time of enrollment.

- Willing to provide written informed consent
- Eastern Cooperative Oncology Group (ECOG) functional status ≤ 2
- Providers must plan to treat the patient with IMiD therapy for a minimum of 6 cycles

Study Exclusion Criteria

- Pregnancy
- Breastfeeding
- Women of child-bearing potential who are unwilling or unable to use an acceptable method of birth control (such as oral contraceptives, other hormonal contraceptives [vaginal products, skin patches, or implanted or injectable products], or mechanical products such as an intrauterine device or barrier methods [diaphragm, condoms, spermicides]) to avoid pregnancy for the entire study
- Any prior venous thromboembolism
- Contraindication to anticoagulant therapy

- Conditions for which serious bleeding may occur including:
    - Current or within last 6 months: intracranial bleeding, intraocular bleeding, gastrointestinal bleeding, endoscopically documented ulcer disease
    - Current or within last month: head trauma or other major trauma, major surgery
    - Current or within last 2 weeks: stroke, neurosurgical procedure
    - Current: gross hematuria, major unhealed wound, major surgery planned during the trial period, intracranial mass, vascular malformation, or aneurysm, overt bleeding, blood dyscrasia
    - CNS involvement of MM or other history of CNS malignancy
- Active and clinically significant liver disease
- Uncontrolled hypertension: systolic blood pressure >180 mm Hg or diastolic blood pressure >100 mm Hg
- Current endocarditis
- Requirement for ongoing anticoagulant therapy, including mechanical heart valve replacement and atrial fibrillation
- Severe valvular heart disease, including rheumatic heart disease and mitral stenosis
- Bioprosthetic heart valve replacement
- Requirement for dual antiplatelet therapy or single agent antiplatelet therapy with clopidogrel, prasugrel, or ticagrelor
- Requirement for aspirin at a dose higher than 165 mg daily.
- Hemoglobin < 9 mg/dL at time of screening
- Platelet count < 100,000/mm^3 at time of screening
- Serum calculated creatinine clearance (CrCl) < 25 ml/m at time of screening
- Alanine aminotransferase or aspartate aminotransferase level > 2 times the upper limit of the normal at time of screening
- Total bilirubin level > 1.5 times the upper limit of the normal at time of screening
- Life expectancy < 12 months or hospice care
- Prisoners or subjects who are involuntarily incarcerated
- Subjects who are compulsorily detained for treatment of either a psychiatric or physical (e.g., infectious disease) illness
- Receiving concurrent non-FDA-approved or investigational agents or has received an investigational agent within the past 30 days prior to the first dose of study treatment (with the exception of approved medications being used for an approved indication, e.g., investigating a new dosing regimen for an approved indication).
- Any condition, which in the opinion of the investigator, would put the subject at an unacceptable risk from participating in the study
- Any other medical, social, logistical, or psychological reason, which in the opinion of the investigator, would preclude compliance with, or successful completion of, the study protocol

Enrollment of Women of Childbearing Potential and Partners

Although it is highly unlikely that a male or female patient of childbearing potential would be enrolled in this trial, the following criteria must be met for women of childbearing potential and their partners:

a) Women of childbearing potential must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) within 24 hours prior to the start of study drug.
b) Women must not be breastfeeding.
c) Women of childbearing potential must agree to follow instructions for method(s) of contraception for the duration of treatment with study drug 6 months plus 5 half-lives of study drug (2.5 days) plus 30 days (duration of ovulatory cycle) for a total of 212.5 days post-treatment completion.
d) Males who are sexually active with women of childbearing potential must agree to follow instructions for method(s) of contraception for the duration of treatment with study drug 6 months plus 5 half-lives of the study drug (2.5 days) plus 90 days (duration of sperm turnover) for a total of 272.5 days post-treatment completion.
e) Azoospermic males and women of childbearing potential who are continuously not heterosexually active are exempt from contraceptive requirements. However, women of childbearing potential who are continuously not heterosexually active must still undergo pregnancy testing.

Investigators will counsel women of childbearing potential and male subjects who are sexually active with women of childbearing potential on the importance of pregnancy prevention and the implications of an unexpected pregnancy Investigators will advise women of childbearing potential and male subjects who are sexually active with women of childbearing potential 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:

- Male condoms with spermicide
- Hormonal methods of contraception including combined oral contraceptive pills, vaginal ring, injectables, implants and hormone-impregnated intrauterine devices (IUDs) by women of childbearing potential subject. 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

- 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 alternative methods of highly effective contraception must be discussed in the event that the subject chooses to forego complete abstinence

A woman of childbearing potential 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. In addition, females under the age of 55 years must have a serum follicle stimulating hormone, (FSH) level > 40mIU/mL to confirm menopause.

*Females treated with hormone replacement therapy, (HRT) are likely to have artificially suppressed FSH levels and may require a washout period in order to obtain a physiologic FSH level. The duration of the washout period is a function of the type of HRT used. The duration of the washout period below are suggested guidelines and the investigators should use their judgement in checking serum FSH levels. If the serum FSH level is >40 mIU/ml at any time during the washout period, the woman can be considered postmenopausal:

- 1 week minimum for vaginal hormonal products (rings, creams, gels)
- 4 week minimum for transdermal products
- 8 week minimum for oral products

Other parenteral products may require washout periods as long as 6 months.

Screening Procedures

When a potential study subject is identified, the following screening procedures will be followed:

1. The Principal Investigator or designee at the study site where the potentially eligible patient is receiving care will be contacted by the responsible provider to initiate screening.

2. The Principal Investigator or designee will confirm that patient is > 18 years of age or older, has MM, and is receiving an IMiD (i.e., thalidomide [Thalomid], lenalinomide [Revlimid], and pomalidomide [Pomalyst]).

3. The Principal Investigator or designee will also confirm the absence of all exclusion criteria.

4. The Principal Investigator or designee will provide the potential study subject with the study Informed Consent Form to review, sign, and date. Informed consent must be obtained from a subject with the capacity for medical decision-making and/or the subject's legally authorized representative. The process for obtaining informed consent must be in compliance with the local ethics committee guidelines and policies. Informed consent may be obtained by the Principal Investigator, co-investigators, study coordinators, or an appointed designee. Potential study subjects will not be enrolled if informed consent cannot be obtained. A copy of the signed Informed Consent Form must be provided to the subject or the subject's legally authorized representative. Signed Informed Consent Forms must remain in each subject's study file and must be available for verification at all times.

5. The study coordinator will enter the patient demographic data into the screening portion of the electronic case report form (eCRF).

6. **Subjects who agree to participate in the study and sign the Informed Consent Form will be considered for enrollment in the study and should undergo baseline data acquisition** which includes:
    a. History and physical examination
    b. Serum (β-HCG) or urine pregnancy test (u-HCG) for women of child-bearing potential

7. If the potential study subject does not meet all of the inclusion criteria or meets any of the exclusion criteria, the rationale for exclusion from the study will be recorded in the screening section of the electronic case report form (eCRF).

Treatment Description

Patients will begin prophylactic anticoagulation within 3 weeks of passing the screening procedure. Patients with MM receiving IMiDs will be assigned to receive apixaban 2.5 mg orally twice daily for primary prevention of VTE for a duration of 6 months.

If patients come off IMiD therapy during the 6-month study period due to progression of disease or therapy failure, apixaban will be discontinued.

If during the study period the patient requires an invasive procedure or surgery that necessitates the discontinuation of anticoagulation (study drug), apixaban should be held as per the prescribing guidelines (**Appendix**,

http://packageinserts.bms.com/pi/pi_eliquis.pdf). If appropriate based on the judgment of the responsible clinician, apixaban should be restarted when safe to do so postoperatively.

Safety Outcomes

Primary Safety Outcome

The primary safety outcome is the 6-month rate of major and clinically relevant non-major bleeding in MM patients receiving IMiDs who are prescribed apixaban 2.5 mg orally twice daily for primary prevention of VTE.

Using the ISTH classification, bleeding is defined as major if it is overt and associated with a decrease in the hemoglobin level of 2 g/dL or more, requires the transfusion of 2 or more units of blood, occurs into a critical site, or contributes to death (12).

Using the ISTH classification, clinically relevant nonmajor bleeding is defined as overt bleeding not meeting the criteria for major bleeding but associated with medical intervention, surgical intervention, or interruption of the study drug.

Secondary Safety Outcome

All-cause mortality at 6 months will be recorded. Cause of death will be classified as related to cancer, myocardial infarction, PE, other cardiovascular or other disease state. Death will be attributed to PE if there is evidence to support an association with PE.

Efficacy Outcomes

Primary Efficacy Outcome

The primary efficacy outcome is the 6-month rate of symptomatic VTE in MM patients receiving IMiDs who are prescribed apixaban 2.5 mg orally twice daily for primary prevention of VTE.

DVT is diagnosed as a noncompressible venous segment or segments on ultrasonography or a filling defect on computed tomographic (CT) venography, magnetic resonance (MR) venography, or contrast venography.

PE is diagnosed on the basis of a mismatched perfusion defects on ventilation perfusion scan, the presence of a pulmonary artery filling defect on contrast-

enhanced chest CT, a finding of intraluminal filling defect on invasive pulmonary angiography, or evidence of PE at autopsy.

Secondary Efficacy Outcome

MM patients have an increased risk of atherothrombotic events, including myocardial infarction and stroke. The risk of atherothrombotic events is further increased with IMiDs. Accordingly, the 6-month rates of myocardial infarction and stroke will also be calculated.

An acute MI is defined as the presence of at least 2 of the 3 following conditions (13):

- The detection of a rise and/or fall of cardiac biomarkers, with at least one of the values being elevated [preferably cardiac troponin (cTn) with at least one value above the 99th percentile upper reference limit] and with at least one of the following:
    (1) symptoms of myocardial ischemia;
    (2) new (or presumably new) significant ST-segment/T-wave changes or left bundle branch block;
    (3) development of pathological Q waves on ECG;
    (4) new loss of viable myocardium or regional wall motion abnormality by imaging;
    (5) identification of intracoronary thrombus by angiography or autopsy

An acute stroke was defined as a new, focal neurologic deficit of sudden onset, lasting at least 24 hours, not due to a readily identifiable nonvascular cause (i.e. brain tumor, trauma), as confirmed by a neurologist (2). All strokes during the study were assessed by imaging or autopsy, and classified as primary hemorrhagic, non-hemorrhagic, infarction with hemorrhagic conversion, or unknown, as defined by the American College of Cardiology.

• **Primary hemorrhagic:** a stroke with documentation on imaging (e.g., CT scan or magnetic resonance imaging) of hemorrhage in the cerebral parenchyma, or subarachnoid hemorrhage. Evidence of hemorrhagic stroke obtained from lumbar puncture, neurosurgery, or autopsy can also confirm the diagnosis.
• **Non-hemorrhagic:** an ischemic focal neurological deficit (and not due to hemorrhage) that appears and is still partially evident at 24 hours.
• **Infarction with hemorrhagic conversion:** no evidence of hemorrhage on an initial scan, but found on a subsequent scan and is clinically relevant to the event, as determined by a neurologist.
• **Unknown type/no imaging performed:** the type of stroke could not be determined by imaging or other means (lumbar puncture, neurosurgery).

<u>Follow-up</u>

Follow-Up Evaluation

Routine follow-up visits with study personnel will not be required. Study patients will be encouraged to follow-up with their primary care providers and other appropriate clinicians, including oncologists. Data regarding study outcomes will be abstracted from the Electronic Health Record.

We will assess medication adherence via pill count. Medication adherence will be calculated as the total number of doses taken divided by the total number of doses prescribed ([x / 336] x 100 = medication adherence [%]).

Subjects will be given a study diary to fill out at home each day. Subjects will write down the time they take their study drug and any side effects. The study diary will be collected at a regularly scheduled office visit at conclusion of the study period.

Subject Retention, Withdrawal, and Termination

Continued participation of study subjects will be encouraged at the time of outpatient evaluation through the 6-month follow-up interval. However, study subjects will be informed that they retain the right to withdraw from the study at any time without compromise to their current or subsequent medical care. Subjects will be terminated from the study if they expire or elect to withdraw.

If study subjects elect to withdraw, they will be asked for permission to do the following:

1. Be contacted by telephone **AND**
2. Have a family member contacted **AND**
3. Have their physicians contacted

Withdrawal criteria will include:

1. Patient requests to withdraw
2. Reasons related to SAE:
    a. Initiating or continuing study drug places the subject at undue hazard as determined by the Investigator;
    b. SAE or other safety concern that is related to study drug treatment;
    c. Major or life-threatening bleeding (as defined in the protocol)
    d. ALT or AST ≥ 3 ULN, if suspected to be due to the study drug
    e. Calculated CrCL decreased to < 30 mL/min confirmed by repeat testing at least one week later, or need for dialysis
    f. Subjects in whom multiple myeloma is felt to be refractory to therapy or who have transitioned to a palliative treatment strategy
3. Pregnancy;
4. Patient develops severe hepatic impairment (Child-Pugh class C) during the trial;

5. Death;
6. Lost to follow-up (every attempt will be made by the Investigator not to have subjects "lost to follow-up");
7. Study terminated by sponsor (termination of all or part of the study by the sponsor, in concert with the study leadership)

Assessment and Reporting of Adverse Events

Definitions

Adverse events

An adverse event (AE) is defined as any new untoward medical occurrence or worsening of a pre existing 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. The causal relationship to study drug is determined by a physician and should be used to assess all AEs.

Adverse events can be spontaneously reported or elicited during open-ended questioning, examination, or evaluation of a subject. (In order to prevent reporting bias, subjects should not be questioned regarding the specific occurrence of one or more adverse events).

All SAEs that occur following the subject's written consent to participate in the study through 30 days of discontinuation of dosing will be reported to BMS Worldwide Safety.

Serious Adverse Events

A serious adverse event (SAE) is any untoward medical occurrence at any dose that:

- results in death
- is life-threatening (defined as an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- requires inpatient hospitalization or causes prolongation of existing hospitalization
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect

- is an important medical event, defined as a medical event that may not be immediately life-threatening or result in death or hospitalization but, based on appropriate medical and scientific judgment, may jeopardize the subject or may require intervention (e.g., medical, surgical) to prevent one of the other serious outcomes listed above. Examples of such events include but are not limited to intensive treatment in an emergency department or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization.

Suspected transmission of an infectious agent (eg, pathogenic or non-pathogenic) via the study drug is an SAE. Although pregnancy, overdose, and cancer are not always serious by regulatory definition, these events must be handled as SAEs.

The following hospitalizations are not considered SAEs:

- A visit to the emergency room or other hospital department lasting less than 24 hours that does not result in admission (unless considered an "important medical event" or a life-threatening event)
- Elective surgery planned before signing consent
- Admissions as per protocol for a planned medical/surgical procedure
- Routine health assessment requiring admission for baseline/trending of health status (eg, routine colonoscopy)
- Medical/surgical admission other than remedying ill health state that was planned before study entry. Appropriate documentation is required in these cases
- Admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (e.g., lack of housing, economic inadequacy, caregiver respite, family circumstances, administrative reason)

Adverse Events of Special Interest

In this study, the following adverse events will to be reported to BMS, regardless of whether these reports are classified as serious or unexpected.

- Potential or suspected cases of liver injury including but not limited to liver test abnormalities, jaundice, hepatitis or cholestasis.

Pre-Existing Medical Conditions

A pre-existing medical condition is one that is present at the start of the study. Pre-existing medical conditions should be recorded in the baseline and demographic data section of the electronic case report form (eCRF). Pre-existing medical conditions should be reassessed during the trial and reported as an adverse event or severe adverse event only if the frequency, severity, or

character of the conditions worsens significantly or unexpectedly during the study. When reporting such adverse events, the description should convey that the pre-existing condition has changed by including applicable descriptors (for example, “more frequent” headaches). Previously scheduled hospitalizations and hospitalizations required for diagnostic or elective surgical procedures for the management of unchanged pre-existing medical condition should not be considered adverse events.

Serious Adverse Event Collecting and Reporting

Following the subject’s written consent to participate in the study, all SAEs, whether related or not related to study drug, must be collected, including those thought to be associated with protocol-specified procedures. All SAEs must be collected that occur during the screening period and within 30 days of discontinuing dosing. If applicable, SAEs must be collected that relate to any later protocol-specific procedure (such as follow-up skin biopsy). The investigator should report any SAE occurring after these time periods that is believed to be related to study drug or protocol-specified procedure. An SAE report should be completed for any event where doubt exists regarding its status of seriousness. If the investigator believes that an SAE is not related to study drug, but is potentially related to the conditions of the study (such as withdrawal of previous therapy, or a complication of a study procedure), the relationship should be specified in the narrative section of the SAE Report Form.

SAEs, whether related or unrelated to the study drug, and pregnancies must be reported to BMS within 24 hours:

SAE Email Address: Worldwide.Safety@BMS.com
SAE Fax Number: 609-818-3804

SAEs must be recorded on the FDA MedWatch Form 3500A. Pregnancies must be reported on a Pregnancy Surveillance Form.

If only limited information is initially available, follow-up reports are required. (Note: Follow-up SAE reports should include the same investigator term(s) initially reported.)

If an ongoing SAE changes in its intensity or relationship to study drug or if new information becomes available, a follow-up SAE report should be sent within 24 hours to the BMS (or designee) using the same procedure used for transmitting the initial SAE report. All SAEs should be followed to resolution or stabilization.

SAE Reconciliation

The investigator will reconcile the clinical database SAE cases transmitted to BMS Global Pharmacovigilance (GPV&E). Frequency of reconciliation will be

done every three months and 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@bms.com. 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.

Health Authority Reporting (US FDA IND)

Investigators must adhere to local Health Authority Reporting Requirements. For studies conducted under an investigator sponsored US FDA IND, provide details of the following:

- Any event that is both serious and unexpected must be reported to the Food and Drug Administration (FDA) as soon as possible and no later than 7 days (for a death or life-threatening event) or 15 days (for all other SAEs) after the investigator's or institution's initial receipt of the information.
- BMS will be provided with a simultaneous copy of all adverse events filed with the FDA. SAEs should be reported on MedWatch Form 3500A, which can be accessed at: http://www.accessdata.fda.gov/scripts/medwatch/.

MedWatch SAE forms should be sent to the FDA at:

MEDWATCH
5600 Fishers Lane
Rockville, MD 20852-9787
Fax: 1-800-FDA-0178 (1-800-332-0178)
http://www.accessdata.fda.gov/scripts/medwatch/

All SAEs should simultaneously be faxed or e-mailed to BMS at:

Global Pharmacovigilance & Epidemiology
Bristol-Myers Squibb Company
Fax Number: 609-818-3804
Email: Worldwide.safety@bms.com

Non-Serious Adverse Events

A non-serious adverse event is an AE not classified as serious.

Non-Serious Event Collecting and Reporting

The collection of non-serious adverse event (NSAE) information should begin at initiation of study drug. Nonserious AEs should be followed to resolution or stabilization, or reported as SAEs if they become serious. Follow-up is also required for nonserious AEs that cause interruption or discontinuation of study drug, or those that are present at the end of study treatment as appropriate.

Nonserious Adverse Events are provided to BMS via annual safety reports (if applicable), and interim or final study reports.

Laboratory Test Abnormalities

The following laboratory abnormalities should be captured and reported as appropriate:

- Any laboratory test result that is clinically significant or meets the definition of an SAE
- Any laboratory test result abnormality that required the subject to have study drug discontinued or interrupted
- Any laboratory test result abnormality that required the subject to receive specific corrective therapy.

It is expected that wherever possible, the clinical rather than the laboratory term will be used by the reporting investigator (e.g., use the term anemia rather than low hemoglobin value). Laboratory test abnormalities are provided to BMS via annual safety reports (if applicable), and interim or final study reports.

Pregnancy

If, following initiation of apixaban, it is subsequently discovered that a study subject is pregnant or may have been pregnant at the time of apixaban exposure, including during at least 5 half-lives after product administration, the investigational product will be permanently discontinued in an appropriate manner. The investigator must immediately notify WorldwideSafety@BMS.com 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. Other appropriate pregnancy follow-up procedures should be considered if indicated.

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.

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 non-serious or serious adverse event, as appropriate, and reported accordingly.

Documentation of Adverse Events

Information about potential adverse events should be reviewed during the 6-month follow-up period. Subjects should be encouraged to report adverse events spontaneously or in response to non-directed questioning by their usual healthcare providers. If it is determined that an adverse event has occurred, the study staff member entering data into the eCRF should obtain all of the information necessary to complete the Adverse Event section. All observed or reported adverse events, regardless of the suspected causal relationship to study treatment must be recorded in the Adverse Event section of the eCRF. The Sponsor will be notified when an event has been entered into the database.

Duration of Adverse Event Reporting Period

Bleeding adverse events and other serious adverse events must be reported throughout the 6-month follow-up period. All observed or reported serious adverse events occurring through the 6-month follow-up period, regardless of the suspected causal relationship with treatment, must be recorded in the appropriate section of the eCRF. Procedures to expedite reporting serious adverse events are described later in this section.

Specific Adverse Event Reporting Guidelines

Study investigators should follow the following guidelines to ensure the quality and precision of adverse event reporting:

1. Use recognized medical terms.
2. Avoid the use of colloquialisms and non-standard abbreviations
3. If known at the time of adverse event reporting, a diagnosis should be reported instead of individual symptoms and signs (for example, record only “pneumonia” rather than “productive cough” and “elevated white blood cell count”).
4. If the reported symptoms and signs cannot be medically characterized as a single diagnosis or syndrome at the time of adverse event reporting, the information that is available should be reported. If a diagnosis is subsequently established, it should be reported as follow-up information as described earlier.
5. A cascade of clinical events (such as sequelae of an adverse event) should be identified as the primary, causative event. The cascade of events can be further described in the adverse event narrative. For example, when recording a death, the event or condition that caused or contributed to the fatal outcome should be reported as the serious adverse event. If the cause of death is unknown and cannot be determined at the time of reporting, “unknown cause of death” should be recorded.
6. Any adverse event that results in inpatient hospitalization or prolongs a hospitalization should be reported as a serious adverse event. If a subject is hospitalized to undergo a medical or surgical procedure as a result of an adverse event, the event responsible for the procedure (not the procedure itself) should be reported as the serious adverse event. For example, if a subject is hospitalized to undergo exploratory surgery as a result of a major bleeding event, record the major bleeding event that necessitated surgery as the serious adverse event.

All Serious Adverse Events (SAEs) that occur following the subject’s written consent to participate in the study through 30 days of discontinuation of dosing must be reported to BMS Worldwide Safety.

Categorization of Adverse Events

All adverse events must be classified according to intensity or severity, expectedness, relatedness, outcome, and treatment or action taken.

Intensity or Severity

The following categories for intensity or severity of an adverse event should be used in reporting:

Mild	Awareness of a symptom or sign that does not interfere with the patient’s usual activity or is transient and resolves without

	treatment and without sequelae
Moderate	Interferes with the patient's usual daily activities, but he or she is still able to function
Severe	Interrupts a patient's usual daily activities and generally requires medication, surgery, or other intervention for treatment

Expectedness

Each adverse event should be evaluated as to whether it was expected or unexpected as follows:

Expected	The specificity and severity of the event is consistent with applicable information on apixaban.
Unexpected	The specificity or severity of the event is not consistent with applicable information on apixaban.
Unanticipated Adverse Device Effect (**UADE)**	Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, apixaban, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application or any other unanticipated serious problem associated with apixaban that relates to the rights, safety, or welfare of subjects.

Relatedness

Each adverse event should be evaluated as to whether it was related to the study procedures or apixaban as follows:

Definite	An adverse event is clearly related to apixaban
Probable	An adverse event has a reasonable causal relationship to the use of apixaban; another etiology is significantly less likely
Possible	An adverse event has a reasonable causal relationship to the use of apixaban; an alternative etiology is equally or less likely
Unlikely	An adverse event has little or no causal relationship to the use of apixaban; an alternative etiology is more likely
Not related	An adverse event is not related to the use of apixaban; there is no temporal relationship or a much more likely alternative etiology exists

The term "reasonable causal relationship" means there is evidence to suggest a causal relationship.

Outcome

The clinical course of all adverse events should be followed until a medical outcome is determined (resolution, stabilization, or determination that it was unrelated to study participation). If a subject is pregnant or becomes pregnant within 30 days of receiving apixaban, follow-up should be obtained from the medical record to determine the outcome of the pregnancy (successful live-birth, etc.). The clinical outcome of all adverse events should be recorded as follows:

Death	Patient expired
Recovered	Patient returned to baseline health and functional status
Not yet recovered	Patient did not recover and symptoms or sequelae persist
Recovered with sequelae	Patient did recover but continues to experience clinical sequelae from the adverse event

Treatment or Action Taken

Adverse events and serious adverse events will be categorized by the actions taken in response to the event:

Intervention	Surgery or other invasive procedure
Non-surgical treatment	Drug initiation, interruption, dose reduction, dose increase, or discontinuation
None	No action was taken

Expedited Reporting of Serious Adverse Events (SAE)

The study investigators must use the following procedure for reporting serious adverse events:

1. Report any serious adverse event that occurs to the Sponsor within 24 hours of knowledge of the event (Monday through Friday). If the investigator does not have all information regarding the SAE, ***he/she will not wait to receive additional information before notifying the Sponsor*** of the event and completing the eCRF. The investigator shall provide an event update when additional information is received.
   NOTE: The Sponsor will automatically be notified when an adverse event or serious adverse event has been entered into the database when the investigator fills in an eCRF.

2. In the reporting of serious adverse events, the study investigator shall provide any potentially relevant information including:
   a. Subject demographics
   b. Pre-existing conditions
   c. The complete description of the adverse event.
   d. Date and time of adverse event onset
   e. Severity

f. Treatment
g. Results of diagnostic testing
h. Duration of sequelae
i. Outcome (if known)
j. Date and time of adverse event resolution.
k. Information on suspected medications including dose, route of administration, frequency, dates, lot number, expiration date, and concomitant medications

3. When reporting a death, the primary event or condition that caused or contributed to the fatal outcome shall be reported as the serious adverse event. Death will be reported as the outcomes of the serious adverse event. If the cause of death is unknown at the time of reporting, report "unknown cause of death."

4. The investigator shall report unanticipated adverse device effects (UADEs) to the sponsor and Institutional Review Board within 10 working days after the investigator first learns of the event.

Sponsor Unanticipated Adverse Drug Effects (UADEs) Reporting Responsibilities

Any serious adverse event determined to be caused by apixaban will be reviewed for possible reporting to the U.S. Food and Drug Administration and IRBs. Upon notice of an unanticipated adverse drug effect (UADE), the sponsor shall immediately conduct an evaluation of the UADE and report the results of the evaluation to the FDA, all reviewing IRBs, and participating investigators within 10 days of first receiving the report.

Data Reporting, Processing, and Quality Control

Data Acquisition, Monitoring, and Quality Control

Subject data will be collected using a web-based centralized electronic case report form (eCRF). Database monitoring and quality control will be performed by the Study Coordinating Center (BWH).

Monitoring Plan

Monitoring procedures will consist of the following:

Site Initiation

At the initial site visit, the Study Coordinating Center shall conduct a full site qualification and training. Study Coordinating Center shall review the terms of the protocol with the site investigator and confirm the investigators access to

facilities required to conduct the study. The Study Coordinating Center will answer any questions the investigator may have concerning the clinical study or protocol and instruct the investigator on how to complete the eCRFs.

During the Study

During the study, the Study Coordinating Center shall perform monthly random reviews of data submitted by investigators with checks for accuracy and completeness and document that corrective actions have been taken in response to protocol deviations or other forms of non-compliance. Investigators will be contacted and asked to submit any missing information or clarify any questionable data. Notes from telephone conversations and copies of written correspondence between the Study Coordinating Center and the Investigators will be maintained in the Study File.

Independent Study Safety Monitor

A physician with relevant expertise whose primary responsibility is to protect the safety of study subjects and to provide ongoing, critical, and unbiased evaluation of the progress of the study will be appointed as an independent study safety monitor for the duration of the study. The safety monitor will operate in a manner similar to that of a Clinical Events Committee/Data and Safety Monitoring Board.

The safety monitor will:

- Provide independent safety evaluation of events and adjudicate all actual and potential serious adverse events experienced by study subjects during this study;
- Review aggregate safety data including the frequency of adverse safety outcomes, particularly death, symptomatic VTE and major bleeding; and can recommend premature stopping of the study to the Sponsor and Principal Investigator at any time.

Interim Safety and Efficacy Analysis

The safety monitor will review the safety and efficacy outcomes for the first 10 patients enrolled in the study. The need for dose adjustment will be made based in this interim analysis. The safety monitor will review the safety and efficacy outcomes again at the completion of the study.

Stopping Criteria

The study will be terminated by the safety monitor, sponsor, and principal investigator if the following stopping criterion is met:

- An excess of morbidity or mortality is observed in patients receiving apixaban.
    a. When 2 patients receiving apixaban experience an unprovoked intracranial hemorrhage, confirmed by independent adjudication, and did not have a protocol violation such that he/she cannot be considered as representative of the intended patient population.
    b. When 3 of the subjects receiving apixaban experience an unprovoked major bleed (including fatal hemorrhagic events) and did not have a protocol violation such that he/she cannot be considered as representative of the intended patient population.

Protocol Violations

The Study Coordinating Center will rapidly and firmly address any protocol violations. If a protocol violation is detected or suspected, the study site investigator(s) will first be asked to provide a written explanation. After reviewing the available information, the Study Coordinating Center will categorize protocol violations as either major (eligibility or primary/secondary endpoint determination compromised or indefinite) or minor (data still able to be used for endpoint determination), and will record and track them.

The Study Coordinating Center will communicate with the study enrollment site personnel to confirm that a process is in place to ensure that further protocol violations do not recur.

Data Confidentiality

Hardcopy and electronic subject data will be maintained in a locked office at each investigational site and will only be available to the study site personnel and sponsor personnel during monitoring visits. Patient identifiers including names and other personal information will be kept separate from the study data.

Compliance with Laws and Regulations

The study will be conducted in accordance with this protocol, Title 21 Code of Federal Regulations, Parts 10, 50, 54,56 and 812, International Harmonized Standards- E6 Good Clinical Practices Guidance, and local ethical and legal requirements.

Statistical Methods

Sample Size Calculation

The sample size estimate is completed using the 95% confidence interval (CI) method. We propose a sample size of 50 patients. It generates a half-width of CI less than 10% if the blood clot rate is <15%. Since our study expects an 80% risk reduction in VTE, our estimated VTE rate is about 5%. If based on the 5% VTE incidence rate, the half-width CI will be <6%. Therefore, the precision will be improved with narrower CI, since we expect an incidence much lower than 15%.

Statistical Analysis Plan

For this proof-of-concept study, we will calculate:

1) the 6-month rate of major and clinically relevant non-major bleeding
2) the 6-month rate of symptomatic VTE

We will also calculate 6-month rates of myocardial infarction and stroke.

The primary analysis will be intention-to-treat. Although study eligibility criteria warrant that the provider plans to treat the patient with IMiDs for at least 6 cycles, we will include any patient who has received at least 2 cycles in a modified intention-to-treat analysis.

Means, medians, and frequency distributions will be calculated for continuous variables. Number and percentages will be reported for binary and categorical variables. Differences between subgroups of interest will be examined using the chi-square or Fisher's exact test for binary and categorical variables and t-test or Wilcoxon Rank Sum for continuous variables (if the subgroups are of sufficient size for statistical comparison). Potential subgroup analysis will include patients newly diagnosed vs. recurrent/relapsed disease and concomitant medications (dexamethasone, etc.).

All tests will be two tailed and a p-value of <0.05 assumed to represent statistical significance. All analyses will be performed using SAS software.

Investigator Responsibilities

Study Initiation

Before enrollment of the first subject at the study site, the following documents must be on file with the Study Sponsor:

1. Current *curriculum vitae* of the principal investigator and all co-investigators
2. Current, dated Institutional Review Board (IRB) membership list

3. Written documentation of IRB protocol approval (protocol number/title and approval date) and Informed Consent Form (protocol number/title and approval date)
4. A copy of the IRB-approved Informed Consent Form (The Informed Consent Form must be reviewed by the study Principal Investigator prior to IRB submission.)

Study Completion

The following data and materials must be on file at the study site before the study can be considered complete or terminated:

1. Completed electronic case report forms (eCRFs) for all study subjects.
2. All regulatory documents including:
    a. C*urriculum vitae* for each investigator and study staff member.
    b. Signed confidentiality agreement
    c. Study protocol and protocol amendments
    d. Institutional Review Board approval letter (s) for initial protocol and any protocol amendments; as well as continuing review approval letters.
    e. All Institutional Review Board correspondence
    f. Study termination letter
    g. Institutional Review Board membership list
    h. Site personnel signature list
    i. Financial Disclosure and Conflict of Interest forms for all site investigators
    j. Patient screening and enrollment logs
    k. Signed study Informed Consent Forms for each subject
    l. Supporting source documentation for values and responses in case report forms
    m. Supporting source documentation for adverse events

Informed Consent

A template for the Informed Consent Form will be provided to the study site by the Study Coordinating Center. The Informed Consent Form must be signed by the subject or his or her legally authorized representative before enrollment into the study. A hardcopy of the Informed Consent Form must be provided to the subject or his or her legally authorized representative. If applicable, informed consent should be obtained using Interpreter Services. If an interpreter is required to explain the study, the informed consent presented to the patient for signature must be in the language in which the patient is literate.

Signed Informed Consent Forms must remain in each subject's study file and be available for verification by the Study Sponsor at all times. Documentation of the date informed consent was obtained and a notation that a signed copy of the

Informed Consent Form was provided to the study subject should be recorded. The informed consent process must always be conducted in a non-coercive manner.

Disclosure of Data

Subject data obtained for this study will be maintained as confidential, and disclosure to parties other than study personnel will be prohibited. Upon the study subject's permission, medical information may be given to his or her physician or other medical personnel for his or her welfare.

Retention of Records

Records and documents pertaining to the conduct of this study including case report forms, signed informed consent forms, protocol and amendments, supporting source documentation for values and responses in the case report forms, and supporting documentation for adverse events must be retained by the investigators for at least two years after conclusion of the study.

Feasibility

Brigham and Women's Hospital

Brigham and Women's Hospital (BWH) is a 777-bed acute tertiary care facility providing medical and surgical care for patients with general medical, cardiothoracic, orthopedic, oncologic, neurologic, obstetric, gynecologic, and gastrointestinal conditions. BWH's affiliation with the Dana Farber Cancer Institute (DFCI) has resulted in a large population of oncology patients receiving care in the inpatient wards and in the Cardiovascular Medicine clinics. DFCI provides care to a large population of MM patients who travel from around the world. With the opening of the Heart and Vascular Center in 2014, BWH has solidified its position as a world leader in cardiovascular care and research, supporting an integrated care model in a single location. BWH is one of the world-leaders in the rapidly growing field of cardio-oncology. Dr. Piazza's cardiovascular medicine outpatient practice, which is based in the Heart and Vascular Center, includes a large number of referrals for thrombosis in the setting of malignancy.

The BWH Thrombosis Research Group

The Thrombosis Research Group, directed by Samuel Z. Goldhaber, MD, Professor of Medicine, Harvard Medical School and Section Head of Vascular Medicine at Brigham and Women's Hospital, is based at BWH and Harvard Medical School. The Thrombosis Research Group has a decades-long

commitment to improving the care for patients with cancer and increased thrombosis risk.

The Thrombosis Research Group has an infrastructure of experienced leadership, with trained personnel in a multidisciplinary academic team (pharmacists, fellows, research nurses, research coordinators, biostatisticians, administrators, and medical informatics specialists). Data storage and computing resources, as well as a network of regional, national, and international collaborating investigators, facilitate our execution of ongoing research projects and our planning of future research projects. The Thrombosis Research Group has studied all aspects of thrombosis in malignancy, including epidemiology, diagnosis, and VTE prevention. According to www.pubmed.gov, the Group has authored more than 90 Original Reports since 2010. Dr. Piazza appreciates the burden of thrombosis on the cancer population through registries that he has led (14) and high-impact reviews that he has published on the subject (7,15). Drs. Piazza and Goldhaber have extensive experience leading large randomized controlled trials focused on prevention of thromboembolic disease. Examples of major Thrombosis Research Group-led trials in thrombosis prevention include the 2500-patient multicenter Electronic Alert Trial (16), the 2500-patient multicenter Physician Alert Trial (17), and the 2500-patient Discharge Alert Trial (18).

For this trial, the Clinical Coordinating Center of the Thrombosis Research Group will draft and finalize the study protocol, informed consent, and case report form, obtain Institutional Review Board approval, create an electronic data repository, assist the clinical centers with local IRB approval, file the IND, ensure scientific and financial integrity, approve site payments, plan and host an Investigators Meeting, perform the data analysis, and draft and submit for publication the study manuscript.

Vanderbilt Cardio-Oncology Program

Vanderbilt University Medical Center will be the Study Enrollment Center. The proposed study will be feasible because Vanderbilt is a large Center of Excellence for MM care with active clinical research programs. Specifically, the Vanderbilt Cardio-Oncology program, directed by Dr. Javid Moslehi, brings together physicians and scientists with a focus on cardiac, vascular and thrombotic complications that occur as a result of cancer and cancer therapies. The integrative and collaborate nature of the Vanderbilt Cardio-Oncology program is illustrated by the care of MM patients. The laboratory of Dr. Moslehi is investigating the mechanisms of vascular and thrombotic toxicity associated with IMiDs and PIs. At the same time, the group is already embarking on several clinical and translation studies focused on cardiovascular effects of MM treatments. Dr. Javid Moslehi, Director of Cardio-Oncology at Vanderbilt University Medical Center will work closely with colleagues in oncology, including Dr. Robert. F. Cornell in spearheading the recruitment effort.

Potential Risks and Benefits

Potential benefits to the subject

The potential benefit of prophylaxis with apixaban in patients with MM receiving IMiDs is prevention of VTE, including fatal PE.

Potential Benefits to Society

The major potential benefit to society of the proposed trial of apixaban for primary prevention of VTE in patients with MM receiving IMiDs is that if successful, the study will provide the foundation for a novel regimen that avoids the discomfort of the currently used injectable anticoagulant strategies. The data acquired from the current study will inform the design of a larger randomized controlled trial focused on clinical outcomes.

Potential Risks to the Subject

The foreseeable risk of apixaban for primary prevention of VTE in patients with MM receiving IMiDs is major or clinically relevant non-major bleeding.

Risks of Research Procedures Performed on Subjects

The risk of research procedures include psychological discomfort from participating in a clinical trial (less likely) and loss of confidentiality of medical records or economic data (rare).

Women of childbearing potential (able to get pregnant) must have a negative pregnancy test before being considered for the study. It is not known how apixaban could affect an unborn child. Women of childbearing potential must use an effective method of birth control while participating in this research, as directed by their physician.

Anticipated Risks of Drug

Anticipated risks of apixaban are categorized as likely, less likely, and rare.

Likely

1. Anxiety related to participating in a clinical trial
2. Discomfort or bruising at sites for blood draws

Less likely

1. Major bleeding requiring transfusion of blood products
2. Clinically-relevant non-major bleeding
3. Nausea and vomiting

4. Non-severe adverse drug reaction to apixaban

Rare
1. Severe allergic reaction (such as anaphylaxis) to apixaban
2. Thromboembolism
3. Fatal, life-threatening, or intracranial hemorrhage or stroke
4. Severe internal bleeding (such as gastrointestinal or retroperitoneal) that requires surgical or interventional laboratory intervention
5. Death
6. Other rare or unforeseen adverse effects

Protection of Subjects against the Risks of Research Procedures

Before Study Enrollment

A rigorous screening process will be utilized to ensure that subjects with an increased risk of harm due to enrollment in the study are excluded from the study. This will include performing a detailed history and physical examination (to ensure that enrolled subjects truly fulfill all eligibility criteria) and carefully reviewing the results of laboratory testing (in particular, hematocrit, platelet count, INR, and serum creatinine).

During Follow-Up

Changes in health status during the 6-month follow-up period will be evaluated by the patient's primary physician, oncologist, and other routine providers. As apixaban is an FDA-approved drug commonly used for thromboprophylaxis and does not require routine follow-up clinical or laboratory monitoring for toxicity, the study will not mandate any follow-up visits or procedures other than those required for the patient's routine myeloma care.

Protection against Loss of Confidentiality

Subject confidentiality will be protected by maintaining all paper records in locked file cabinets in locked offices and all electronic records in password-protected computer files. All study data will be de-identified for storage in the electronic data repository. In addition, any identifying information will be removed from images or other data used in publication or presentations. All database information will be stored on computer systems that are located behind an electronic firewall, which will only permit access to certified study personnel. Access to study data files will be password-protected.

Use of Information and Publication

All information concerning and relating to the study is considered confidential information. This information includes the clinical investigational plan, case report forms (CRFs), training materials, and scientific data.

Ethical Considerations

In this prospective, single-arm, single-center clinical study, we will be evaluating the impact of apixaban for primary prevention of VTE in patients with MM receiving IMiDs. The benefits of apixaban for primary prevention of VTE in patients with MM receiving IMiDs have not been assessed. The risk of bleeding in MM patients receiving apixaban has not been determined. Currently used thromboprophylactic regimens for primary prevention of VTE in MM patients receiving IMiDs largely consist of injectable anticoagulant regimens, such as enoxaparin and dalteparin. These regimens have not been well-evaluated for primary prevention of VTE in the MM population and are associated with patient discomfort, inconvenience, and limited medication adherence. Apixaban 2.5 mg orally twice daily has been shown to be safe and effective for prevention of VTE in a large general medical population. Therefore, a solid foundation for investigation of this thromboprophylactic regimen and equipoise for the proposed clinical trial exist. A successful trial has the potential to provide clinicians and patients with a more convenient, more comfortable, and potentially safer prophylactic regimen.

Because the proposed clinical trial involves a novel application of a U.S. FDA-approved anticoagulant, we will obtain written consent from all study subjects and Institutional Review Board approval at all study sites.

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Table 1. Study Calendar

Procedure	Screening[a]	6-month Visit
Informed Consent	**X**	
Inclusion/Exclusion	**X**	
Demographics	**X**	
Medical History	**X**	
Prior/Concomitant Medications	**X**	
Urine Pregnancy (if clinically indicated)	**X**	
Multiple Myeloma History	**X**	
Cardio-vascular History	**X**	
Thrombosis Evaluation		**X**
Bleeding Evaluation		**X**
Pill Diary Collection		**X**

[a]Screening is D-21 through D1 prior to enrollment

Case Report Form

Screening	
Inclusion criteria (all must be checked)	[ ] Diagnosis of multiple myeloma [ ] Receiving immunomodulatory therapy (either thalidomide [Thalomid], lenalinomide [Revlimid], and pomalidomide [Pomalyst]) [ ] 18 years of age or older [ ] Willing and able to provide written informed consent
Exclusion criteria (NONE must be checked)	[ ] Pregnancy [ ] Breastfeeding [ ] Women of child-bearing potential who are unwilling or unable to use an acceptable method of birth control to avoid pregnancy for the entire study [ ] Any prior venous thromboembolism [ ] Contraindication to anticoagulant therapy [ ] Conditions for which serious bleeding may occur including: o Current or within last 6 months: intracranial bleeding, intraocular bleeding, gastrointestinal bleeding, endoscopically documented ulcer disease o Current or within last month: head trauma or other major trauma, major surgery o Current or within last 2 weeks: stroke, neurosurgical procedure o Current: gross hematuria, major unhealed wound, major surgery planned during the trial period, intracranial mass, vascular

	malformation, or aneurysm, overt bleeding, blood dyscrasia [ ] Active and clinically signficant liver disease [ ] Uncontrolled hypertension: systolic blood pressure >180 mm Hg or diastolic blood pressure >100 mm Hg [ ] Current endocarditis [ ] Requirement for ongoing anticoagulant therapy including mechanical heart valve replacement and atrial fibrillation [ ] Severe valvular heart disease, including rheumatic heart disease and mitral stenosis [ ] Bioprosthetic heart valve replacement [ ] Requirement for dual antiplatelet therapy or single agent antiplatelet therapy with clopidogrel, prasugrel, or ticagrelor [ ] Requirement for aspirin at a dose higher than 165 mg daily. [ ] Hemoglobin < 9 mg/dL [ ] Platelet count < 100,000/mm^3 [ ] Calculated creatinine clearance (CrCl) < 25 ml/m [ ] Alanine aminotransferase or aspartate aminotransferase level > 2 times the upper limit of the normal [ ] Total bilirubin level > 1.5 times the upper limit of the normal [ ] Life expectancy < 12 months or hospice care [ ] Prisoners or subjects who are involuntarily incarcerated [ ] Subjects who are compulsorily detained for treatment of either a psychiatric or physical (eg, infectious disease) illness [ ] Receiving concurrent investigational agents or has received an investigational agent within the past 30 days prior to the first dose of study treatment (with the exception of approved medications being used for an approved indication, e.g., investigating a new dosing regimen for an approved indication). [ ] Any condition, which in the opinion of the investigator, would put the subject at an unacceptable risk from participating in the study [ ] Any other medical, social, logistical, or psychological reason, which in the opinion of the investigator, would preclude compliance with, or successful completion of, the study protocol
STOP HERE AND DO NOT ENROLL PATIENT IF ANY OF THE INCLUSION CRITERIA ARE ABSENT OR ANY EXCLUSION CRITERIA ARE PRESENT	
Eligible	[ ] Yes [ ] No
Written informed	[ ] Yes

consent signed	[ ] No

Patient Demographics	
Study ID number	_ _ _ _ _ _
Date of enrollment	_____/_____/_____ MM DD YYYY
Date of birth	_____/_____/_____ MM DD YYYY
Gender	[ ] Male [ ] Female
Ethnicity	[ ] Hispanic/Latino [ ] Non-Hispanic/Non-Latino
Race	[ ] American Indian or Alaskan Native [ ] Asian [ ] White [ ] Hispanic or Latino [ ] Native Hawaiian or Pacific Islander [ ] Black or African-American [ ] Mixed race [ ] Other, specify:_____
Weight (enter either weight and height OR BMI)	_____(kg)
Height	_____(cm)
BMI calculated	_____(kg/m²)

Multiple Myeloma Characteristics	
Date of diagnosis	_____/_____/_____ MM DD YYYY
Diagnosis status	[ ] New diagnosis (diagnosis within the last 30 days) [ ] Recurrent/relapsed disease
Diagnostic criteria	International Myeloma Working Group (IMWG) criteria Must have at least one of the following: [ ] Serum M-protein ≥ 0.5 g/dL by serum electrophoresis (SPEP) or for IgA myeloma, by quantitative IgA (>750 mg/dl) [ ] Urinary M-protein excretion at least 200 mg/24 hours [ ] Serum Free Light Chain (FLC) whereby the involved light chain measures ≥ 10 mg/dL and with an abnormal light chain ratio.
Stage	[ ] R-ISS I – ISS stage I (B2M <3.5 mg/L and serum albumin ≥3.5 g/dL) and normal LDH and no del(17p), t(4;14), or

	t(14;16) by FISH. [ ] R-ISS II – Neither stage I nor stage III. [ ] R-ISS III – ISS stage III (B2M ≥5.5 mg/L) plus LDH above normal limits and/or detection of one of the following by FISH: del(17p), t(4;14), or t(14;16).
Immunomodulatory therapy (check one)	[ ] thalidomide [Thalomid] [ ] lenalinomide [Revlimid] [ ] pomalidomide [Pomalyst]
Other therapies	[ ] proteasome inhibitors (PIs) (i.e., bortezomib [Velcade] and carfilzomib [Kyprolis]) [ ] corticosteroids (including dexamethasone) If yes, provide specific regimen (drug, dose, and frequency):_____ [ ] chemotherapy [ ] hematopoietic cell transplantation [ ] erythropoiesis stimulating agents [ ] other

Comorbid Conditions	
Cardiovascular disease	[ ] Cardiomyopathy/diminished left ventricular systolic function If yes, EF (%) ____ [ ] Heart failure [ ] Coronary artery disease If yes, CABG [ ] Coronary stent(s) [ ] Prior MI [ ] Unstable angina [ ] Stable angina [ ] [ ] Rheumatic heart disease [ ] Valvular heart disease [ ] Atrial fibrillation or atrial flutter [ ] Congenital cardiac abnormality [ ] Pulmonary hypertension [ ] Other structural cardiac disease
Valvular disease	[ ] Aortic Stenosis [ ] Aortic regurgitation [ ] Mitral regurgitation [ ] Mitral Stenosis [ ] Other If yes, Any severe valve disease?

	[ ] Yes [ ] No
Hypertension	[ ] Yes [ ] No
Peripheral vascular/artery disease	[ ] Yes [ ] No
Carotid occlusive disease	[ ] Yes [ ] No
Cerebrovascular accident (strokes or TIAs)	[ ] Yes [ ] No
Family history of VTE	[ ] Yes [ ] No
History of bleeding	[ ] Yes [ ] No
Hypercholesterolemia	[ ] Yes [ ] No
Current alcohol consumption	[ ] None [ ] 1-2 drinks per day [ ] >2 drinks per day
Chronic liver disease (as noted in chart)	[ ] Yes [ ] No If yes, cirrhosis [ ] yes [ ] no
History of falls	[ ] Yes [ ] No
Cigarette smoking (check only 1)	[ ] Current smoker [ ] Former smoker [ ] Never smoker
Major surgery within the past 3 months	[ ] Yes [ ] No If yes, date _____/_____/_____ MM DD YYYY **If within the last month, patient should not be enrolled.**
Prior hospitalization within 30 days	[ ] Yes [ ] No
COPD	[ ] Yes [ ] No
Diabetes mellitus (Type I or II)	[ ] Yes [ ] No
Serum creatinine > 2.5 mg/dL	[ ] Yes [ ] No If yes, is patient on dialysis? [ ] Yes

	[ ] No **If yes, patient should not be enrolled.** If no, creatinine clearance (Cockroft-Gault) = _ _ _ mg/dL
Concomitant medications	[ ] aspirin If yes, dose = _ _ _ mg/daily **If > 165 mg/daily, patient should not be enrolled.** [ ] daily NSAID use
Prior thromboprophylaxis regimen	[ ] Yes [ ] No If yes, check all that apply: [ ] LMWH [ ] Fondaparinux [ ] Unfractionated heparin [ ] Warfarin [ ] NOAC [ ] Aspirin [ ] Other: _____

Study Treatment	
Date study drug started	____/____/_____ MM DD YYYY
Date study drug stopped	____/____/_____ MM DD YYYY Completed full 6 months of study drug? [ ] Yes [ ] No If did not stay on drug for 6 months, reason why not? [ ] Fulfilled criteria for a primary study outcome (VTE or major/clinically relevant non-major bleed) [ ] Patient expired [ ] Adverse drug event or side-effect [ ] Change in clinical status (such as change in goals of care, comfort measures, hospice care) [ ] Patient preference/withdrawal of consent

Medication adherence (via pill count)	Total doses taken/total doses prescribed = (__ / 336) x 100 = _ _ _ %

Six-Month Study Outcomes	
Deep vein thrombosis	[ ] Yes [ ] No If yes, date ____/____/_____ MM DD YYYY Confirmed by diagnostic imaging: [ ] Yes [ ] No If yes, by? [ ] Ultrasound [ ] CT [ ] MRI [ ] Venography Location: [ ] Upper extremity If checked: [ ] Right [ ] Left [ ] Bilateral or SVC [ ] Lower extremity If checked: [ ] Right [ ] Left [ ] Bilateral or IVC [ ] Proximal (popliteal or higher) [ ] Calf Hospitalized? [ ] Yes [ ] No Treatment: [ ] Anticoagulation [ ] Pharmacomechanical (catheter-based) therapy [ ] Surgery [ ] IVC filter

Superficial vein thrombosis	[ ] Yes [ ] No If yes, date ____/____/_____ MM DD YYYY
Other venous thrombosis (mesenteric, cerebral sinus, gonadal, etc.)	[ ] Yes [ ] No If yes, date ____/____/_____ MM DD YYYY
Pulmonary embolism	[ ] Yes [ ] No If yes, date ____/____/_____ MM DD YYYY Confirmed by diagnostic imaging: [ ] Yes [ ] No If yes, by? [ ] CT [ ] MRI [ ] Pulmonary angiography [ ] V/Q scan Location: [ ] Left [ ] Right [ ] Bilateral RV dysfunction on echocardiogram or CT? [ ] Yes [ ] No Associated with hemodynamic instability (syncope, shock, hypotension, cardiac arrest)? [ ] Yes [ ] No Fatal? [ ] Yes [ ] No Hospitalized?

	[ ] Yes [ ] No Treatment: [ ] Anticoagulation [ ] Systemic fibrinolysis [ ] Pharmacomechanical (catheter-based) therapy [ ] Surgical embolectomy [ ] IVC filter
Death	[ ] Yes [ ] No If yes, date ____/____/_____ MM DD YYYY Cause of death: [ ] PE [ ] Myocardial infarction [ ] Other cardiovascular [ ] Cancer-related [ ] Non-cardiovascular, non-cancer
Major or clinically relevant non-major bleed	[ ] Yes [ ] No If yes, date ____/____/_____ MM DD YYYY
Major bleed	[ ] Yes [ ] No If yes, date ____/____/_____ MM DD YYYY Location: [ ] Intracranial [ ] Surgical/operative site [ ] Gastrointestinal [ ] Genitourinary [ ] Retroperitoneal [ ] Pericardial [ ] Pulmonary [ ] Other thoracic [ ] Musculoskeletal [ ] Nasopharyngeal

	[ ] Hematocrit or hemoglobin decrease without clear source [ ] Other Fatal? [ ] Yes [ ] No Hospitalized? [ ] Yes [ ] No Associated with hemodynamically instability? [ ] Yes [ ] No Treatment: [ ] Blood products [ ] Surgery [ ] Invasive procedure [ ] Medical therapy (PCC, andexanet, etc.)
Clinically relevant non-major bleed	[ ] Yes [ ] No If yes, date ____/____/_____ MM DD YYYY Location: [ ] Intracranial [ ] Surgical/operative site [ ] Gastrointestinal [ ] Genitourinary [ ] Retroperitoneal [ ] Pericardial [ ] Pulmonary [ ] Other thoracic [ ] Musculoskeletal [ ] Nasopharyngeal [ ] Hematocrit or hemoglobin decrease without clear source [ ] Other: _____ Hospitalized? [ ] Yes [ ] No Treatment:

	[ ] Blood products [ ] Surgery [ ] Invasive procedure [ ] Medical therapy (PCC, andexanet, etc.)
Non-bleed adverse drug reaction	[ ] Yes [ ] No If yes, date ____/____/_____ MM DD YYYY Type of reaction: [ ] Anaphylaxis [ ] Cutaneous (rash, etc.) [ ] Liver function abnormalities [ ] Other: _____ Hospitalized? [ ] Yes [ ] No Study drug discontinuation? [ ] Permanent stop [ ] Temporary stop [ ] Not discontinued
Myocardial infarction	[ ] Yes [ ] No If yes, date ____/____/_____ MM DD YYYY Type: [ ] ST elevation [ ] Non-ST elevation Fatal? [ ] Yes [ ] No Treatment: [ ] Systemic fibrinolysis [ ] Percutaneous coronary intervention (angioplasty, stenting, etc.) [ ] CABG [ ] Medical management

Stroke/TIA	[ ] Yes [ ] No If yes, date ____/____/_____ MM DD YYYY TIA? [ ] Yes [ ] No Stroke? [ ] Yes [ ] No If yes, type of stroke: [ ] Ischemic [ ] Hemorrhagic [ ] Other Fatal stroke? [ ] Yes [ ] No Treatment: [ ] Systemic fibrinolysis [ ] Percutaneous thrombectomy [ ] Surgery [ ] Other

Appendix

1. Apixaban Package Insert
2. Informed Consent