NCT #: NCT03594045

DF/HCC Protocol #: 18-153

TITLE: A Phase II study to evaluate the efficacy and safety of apixaban in the treatment of heparin induced thrombocytopenia (HIT).

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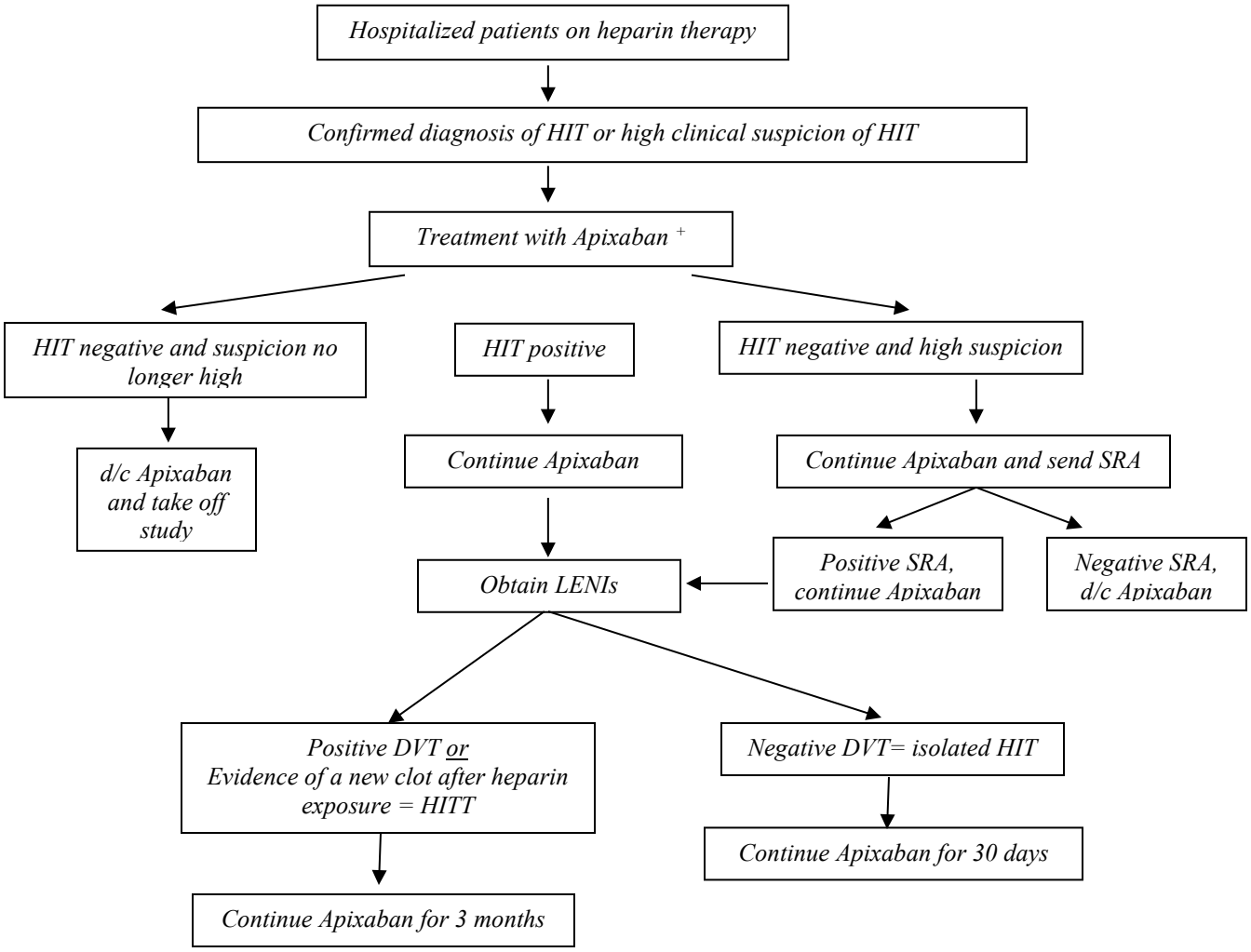
SCHEMA

Phase II prospective open label study



HIT: Heparin Induced Thrombocytopenia
SRA: Serotonin Release Assay
LENI: Lower extremity non invasives
DVT: deep vein thrombosis
HITT: Heparin Induced Thrombocytopenia with Thrombosis

+ Transition to apixaban
If patient is started on an alternative anticoagulant prior to study, please refer to appendix E for instructions on how to transition to apixaban.

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LIST OF ABBREVIATIONS

AE	Adverse Event
ALT	Alanine Aminotransferase
ANC	Absolute Neutrophil Count
aPTT	Activated Prothrombin Time
AST	Aspartate Aminotransferase
BMS	Bristol Meyer Squibb
BUN	Blood Urea Nitrogen
CBC	Complete Blood Count
CO_2	Carbon Dioxide
CRF	Case Report Form
DSMB	Data Safety Monitoring Board
DTI	Direct Thrombin Inhibitor
EIA	Enzyme-linked Immunoassay
FDA	Food and Drug Administration
HCG	Human Chorionic Gonadotropin
HIT	Heparin-induced Thrombocytopenia
HITT	Heparin-induced Thrombocytopenia and Thrombosis
IEC	Independent Ethics Committee
IND	Investigational New Drug
INR	International Normalization Ratio
IRB	Institutional Review Board
IV	Intravenous
K	Potassium
Kg	Kilogram
LMWH	Low Molecular Weight Heparin
Mg	Magnesium
mg	Milligram
MGH	Massachusetts General Hospital
Na	Sodium
Ng	Nanogram
NIH	National Institutes of Health
PF4	Platelet Factor 4
PO	Per os or by mouth
PT	Prothrombin Time
PTT	Partial Thromboplastin Time
RBC	Red Blood Cells
SAE	Serious Adverse Event
TEC	Thromboembolic Complications
UFH	Unfractionated Heparin
μg	Microgram
μL	Microliter
WBC	White Blood Cells

1. OBJECTIVES

1.1 Study Design

This is a prospective, open label, single center study designed to evaluate the activity and tolerability of apixaban for the treatment of hospitalized patients with a confirmed diagnosis of isolated heparin induced thrombocytopenia or heparin induced thrombocytopenia with thrombosis (HIT and HITT, respectively).

Hospitalized patients who have a confirmed diagnosis or highly suspicious symptoms of HIT will be treated with therapeutic dosing as approved by FDA of apixaban. Study length will be 30 days from the time of initiation of apixaban in patients with isolated HIT, defined as HIT without thrombosis, and 3 months for patients with HITT (heparin induced thrombocytopenia with thrombosis). Treatment will continue until completion of the study, unacceptable toxicity or at the discretion of the investigator and patient. Markers of disease activity (e.g. thrombocytopenia, TEC, death) will be assessed at baseline, daily during the initial treatment period with apixaban while patients are hospitalized and at 30-day follow-up for isolated HIT and 3 month follow up for HITT.

1.2 Primary Objectives

To evaluate the activity of apixaban as monotherapy in patients with isolated heparin induced thrombocytopenia and HITT, as defined by the incidence of new symptomatic thromboembolic complications (TEC) within 30 days of the time of initiation of apixaban.

1.3 Secondary Objectives

To evaluate the safety and efficacy of apixaban in the treatment of HIT and HITT within 30 days of enrollment, as defined by:

- the composite incidence of all-cause death, amputation and new TEC
- individual components of the composite endpoint
- composite incidence of new TEC and major bleeding
- the incidence of major bleeding
- the time to platelet recovery * as a surrogate index of the activity of apixaban.

*Time to platelet recovery is defined in section 11.1.4

2. BACKGROUND

2.1 Study Disease(s)

Heparin-induced thrombocytopenia type-II (HIT) is a common and frequently severe syndrome characterized by thrombocytopenia and a prothrombotic state following exposure to unfractionated heparin (UFH) or low molecular weight heparin (LMWH).[1] The incidence of HIT ranges from 0.3-5.0% depending on the patient population and the type and route of heparin used.[1-4] It is an antibody-mediated reaction caused by the binding of platelet-activating IgG antibodies to platelet factor 4–heparin complexes on the surface of platelets, and it typically manifests 4-10 days after the initiation of heparin therapy, but it can occur as quickly as a few hours in patients who have received heparin within the previous 100 days.[5-7]

Patients diagnosed with HIT are at high risk for life-threatening thrombotic sequelae, up to 55% if untreated.[4] Recognition of the diagnosis, discontinuation of heparin therapy and immediate intervention with a non-heparin anticoagulant are critical for preventing thromboembolic complications (TEC) and restoring a normal platelet count. When HIT is accompanied by thrombosis, it is termed HITT; when it is not accompanied by thrombosis, it is termed isolated HIT. Without evidence of TEC at the time of recognition, patients are regarded as having "isolated" HIT. Such patients are recognized as having HIT due to a characteristic decline in the platelet count following the administration of heparin. This decrease in the platelet count may occur immediately, as with a history of recent prior exposure (and thus antibodies are already present when heparin is recommenced), or after a delay of approximately five to ten days in patients without antibodies at baseline who are newly or repeatedly exposed to heparin. The diagnosis may be confirmed objectively by one of a number of available laboratory tests including the serotonin-release assay, the platelet aggregation assay, or the heparin-platelet factor 4 (PF4) enzyme-linked immunoassay (EIA).[5,8,9] While diagnostic specificity can be augmented by the use of functional studies, the heparin-PF4 EIA is the present, accepted standard for confirming the diagnosis of HIT in the United States.[10]

Standard therapy in the United States for HIT(T) involves immediate administration of the direct thrombin inhibitor (DTI), argatroban.[10] Based on a significant reduction of a composite endpoint of thromboembolic events, limb amputation and death in patients with HIT(T) compared to a historical control, argatroban was approved by the FDA for use in patients with HIT or HIT with thrombosis (HITT). A review of the two prospective clinical studies reporting argatroban administration in the acute treatment of isolated HIT reveals an incidence of TEC ranging from 6-8% among treated patients.[11,12] However, two recently published studies report much higher TEC rates. A case series aimed at identifying risk factors associated with the development of TEC report a rate of 25%.[13] A "real world" analysis of 442 patients with a positive PF4 antibody test and heparin exposure had a composite endpoint of death, limb amputation or new thrombosis as the primary outcome. This composite endpoint occurred in 48% of the HITT patients and in 36% of the isolated HIT patients, of which 61% and 38% were treated with non-heparin anticoagulation, respectively.[14] These recent studies more accurately reflect current trends.

In the absence of thromboembolic disease, the duration of treatment is debated. Based on a

retrospective cohort analysis documenting a high (52.8%) VTE risk at 30 days following diagnosis, a minimum of four weeks of therapeutic anticoagulation after normalization of the platelet count is appropriate.[4] Early transition to warfarin is contraindicated due to the increased risk of microvascular thrombotic complications including skin necrosis and venous limb gangrene while patients are thrombocytopenic.[15,16] Therefore practice standards require therapeutic anticoagulation with a DTI until the platelet count has demonstrated recovery, followed by a period of 5 or more days of continuous intravenous therapy with a DTI while transitioning to oral warfarin. [10,17]

2.2 IND Agent: Apixaban

Apixaban is an ideal alternative for the treatment of HIT or HITT because it is administered orally with fixed dosing, requires no routine coagulation monitoring and is FDA approved in the treatment of venous and arterial thromboembolism in other settings.[18,19] It inhibits free and clot-bound FXa resulting in decreased thrombin generation and thrombus formation and is structurally unrelated to heparin. An in vitro study demonstrated that apixaban does not aggregate or activate platelets in the presence of HIT antibodies.[20] Furthermore, a recent case series of 22 HIT patients showed that treatment with a short course of argatroban followed by a new oral anticoagulant (NOAC) was safe and effective in normalization of platelets and prevention of thrombosis.[21] Moreover, there is one case report revealing that treatment with apixaban as monotherapy for the management of HIT was successful in terms of platelet recovery and lack of adverse events.[22] Thus, apixaban is attractive alternative to DTIs for the treatment of HIT and HITT.

2.3 Rationale

Heparin-induced thrombocytopenia type-II (HIT) is a common and often severe complication of heparin therapy. Although the central feature of HIT is thrombocytopenia, the more worrisome complication is the development of arterial or venous thrombosis often referred to as heparin-induced thrombocytopenia-thrombosis syndrome (HITT). The exact incidence of HIT associated thrombosis is not well established but studies demonstrate a range from 10% to as high as 55%.[4] In addition, the mortality associated with this complication has been reported to be as high as 20%.[4,9,10] Given this high rate of mortality and the awareness of prolonged thrombin generation even after heparin is discontinued, establishing the diagnosis, discontinuing heparin therapy and immediately intervening with a non-heparin anticoagulant are critical for preventing thromboembolic complications (TEC). [8]

Presently there is only one available alternative (Argatroban) to heparin that is FDA approved for HIT or HITT in this country that can be used as a bridge to coumadin.[9,10] Argatroban is a direct thrombin inhibitor (DTI), administered intravenously, requires continuous laboratory monitoring, can cause excessive bleeding and is extremely costly. Non FDA agents that are often used are fondaparinux or bivalirudin, the former requires an injection and the later is similar to Argatroban (and is approved for HIT in patients undergoing PCI). Practice standards require therapeutic anticoagulation with a DTI until platelet count recovery, followed by 5 or more days of overlap while transitioning to oral warfarin with goal INR 2-3 for 1 month for patients with HIT and 3 months for patients with HITT.[8,11] Thus, anticoagulating patients with HIT has

become a huge expense and burden on our health care system.

There are several potential benefits to apixaban therapy compared to treatment with the direct thrombin inhibitor, argatroban. Argatroban requires continuous intravenous administration, typically requiring protracted inpatient hospitalization for at least six to thirteen days based on the published mean duration of therapy with direct thrombin inhibitors reported in clinical trials. The oral route of apixaban allows for the potential outpatient treatment of HIT in selected patients, akin to the widespread use of subcutaneous danaparoid sodium in HIT prior to its withdrawal from the United States market. Whereas direct thrombin inhibitors are unfamiliar to many practitioners and require careful titration of coagulation parameters, apixaban has a reliable pharmacokinetic profile and does not require plasma monitoring. Furthermore, conversion to oral warfarin from a DTI, which is the current standard of care for HIT, is complicated by cessation of DTI anticoagulation while assessment of therapeutic warfarin dosing is determined. In addition to the requirement of inpatient hospitalization, direct thrombin inhibitors are costly medications compared to the cost of apixaban. Thus, apixaban appears attractive as an alternative to direct thrombin inhibitor therapy in the treatment of HIT.

Another desirable features of apixaban is the benefit of immediate anticoagulation in these highly prothrombotic and hypercoagulable patients. The incidence of TEC in HIT is greatest in the earliest phase of disease.[4] Immediate alternative anticoagulation is, therefore, indicated in all patients where HIT is suspected. However, therapeutic anticoagulation with a DTI may be difficult to achieve initially, in routine clinical practice. In a prospective trial of argatroban in the treatment of HIT, only 83% of patients ultimately achieved therapeutic anticoagulation.[11] Pharmacokinetic studies of apixaban suggest that peak plasma concentration is reached within 3 hours of administration, with a highly reproducible pharmacokinetic profile.[23] Therefore, patients treated with apixaban are more likely to be effectively anticoagulated earlier in the course of the most hazardous phase of their disease.

The ideal study would be a randomized controlled trial comparing apixaban with the FDA approved treatment for HIT, argatroban. However, this is impractical due to cost and time constraints as it would require a large sample size and take years to accrue. Although this is only a single site study, accruing to this study should not be difficult. HIT is a frequent diagnosis at Massachusetts General Hospital (MGH). There is an average of five positive HIT tests each week and over half of those are from patients who are in the hospital. Over a 5 month period, from Oct 2015 to March 2016, there were 52 patients at MGH who received an intravenous direct thrombin inhibitor (DTI) - either argatroban or bivalirudin. This number is likely an underestimate of the number of HIT patients requiring treatment as it does not include those patients who were treated with fondaparinux alone. Moreover, it is important to note that at MGH, patients diagnosed with HIT can only receive a DTI if approved by the hematology service. Therefore, the principle investigator will be alerted to every HIT patient who potentially requires a DTI and if eligible, can offer the trial instead.

3 PARTICIPANT SELECTION

The potential participants in this study are hospitalized patients who receive heparin or low molecular weight therapy for various indications. When a clinical diagnosis or high suspicion for HIT is apparent, heparin therapy should be discontinued. Before a patient starts apixaban, they will be screened to determine their eligibility to participate in the study based on the following inclusion/exclusion criteria:

3.1 Eligibility Criteria

3.1.1 Hospitalized patients at MGH and participating Dana Farber/Harvard Cancer Center (DF/HCC) sites.

3.1.2 Patient must have a 4 T score of ≥ 5 as calculated by the following criteria:

- **Thrombocytopenia**
  - Platelet count fall >50 percent and nadir ≥20,000/microL – 2 points
  - Platelet count fall 30 to 50 percent or nadir 10 to 19,000/microL – 1 points
  - Platelet count fall <30 percent or nadir <10,000/microL – 0 points
- **Timing of platelet count fall**
  - Clear onset between days 5 and 10 or platelet count fall at ≤1 day if prior heparin exposure within the last 30 days – 2 points
  - Consistent with fall at 5 to 10 days but unclear (eg, missing platelet counts), onset after day 10, or fall ≤1 day with prior heparin exposure within 30 to 100 days – 1 point
  - Platelet count fall at <4 days without recent exposure – 0 points
- **Thrombosis or other sequelae**
  - Confirmed new thrombosis, skin necrosis, or acute systemic reaction after intravenous unfractionated heparin bolus – 2 points
  - Progressive or recurrent thrombosis, non-necrotizing (erythematous) skin lesions, or suspected thrombosis that has not been proven – 1 point
  - None – 0 points
- **Other causes for thrombocytopenia**
  - None apparent – 2 points
  - Possible – 1 point
  - Definite – 0 points

3.1.3 Patient must meet one of the following:

- Have a confirmed diagnosis of HIT by Heparin-PF4 EIA or other accepted confirmatory test (serotonin-release assay, platelet aggregation assay).
- Have a high clinical suspicion of HIT (either Heparin-PF4 result is pending, or Heparin-PF4 result is negative or not obtained but a confirmatory test is pending)

Testing for HIT at MGH and participating DF/HCC sites *is extremely reliable. MGH and participating DF/HCC sites currently use an extensively validated PF4-H IgG-based ELISA for HIT which has 94% specificity with a negative predictive value of 99.7% and a sensitivity that is close to 95%.*

3.1.4 Patients can be treated with a non-heparin anticoagulant (such as argatroban, bivalirudin, or fondaparinux) for up to 7 days prior to enrollment.

3.1.5 Age 18 years or older.

3.1.6 ECOG performance status ≤2

3.1.7 Participants must have organ and marrow function as defined below:

- absolute neutrophil count ≥1,500/mcL
- AST(SGOT) and ALT(SGPT) ≤2.5 × institutional upper limit of normal
- creatinine clearance (Per Cockcroft-Gault formula) ≥25 mL/min as was used in the AMPLIFY trial[16]

3.1.8 The effects of apixaban on the developing human fetus are unknown. For this reason, women of child-bearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry and for the duration of study participation. Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study, she should inform her treating physician immediately. Men treated or enrolled on this protocol must also agree to use adequate contraception prior to the study, for the duration of study participation, and 4 months after completion of apixaban administration.

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

3.2 Exclusion Criteria

3.2.1 Patient requires anticoagulation for a mechanical heart valve.

3.2.2 Patient requires:
- dual antiplatelet therapy,
- treatment with aspirin at a dose of more than 162 mg daily

3.2.3 Patient has signs of active or ongoing clinically significant hemorrhage.

3.2.4 Patient has hereditary or acquired coagulopathy or bleeding disorder.

3.2.5 Patient has a contraindication to apixaban.

3.2.6 Participants receiving any medications or substances that are inhibitors or inducers of cytochrome P-450 3A4 or p-glycoprotein are ineligible. Because the lists of these agents are constantly changing, it is important to regularly consult a frequently-updated list such as http://medicine.iupui.edu/clinpharm/ddis/table.aspx; medical reference texts such as the Physicians' Desk Reference may also provide this information. As part of the enrollment/informed consent procedures, the patient will be counseled on the risk of interactions with other agents, and what to do if new medications need to be prescribed or if the patient is considering a new over-the-counter medicine or herbal product.

3.2.7 Patient has severe renal insufficiency (CrCl <25 ml/min–as used in the AMPLIFY trial) [16]

3.2.8 Patient has hepatic disease (including Child-Pugh B and C) associated with coagulopathy or clinically relevant bleeding risk. See appendix F for definition

3.2.9 Recent (previous seven days), or complicated lumbar puncture or epidural catheter placement or removal.

3.2.10 Patient has high potential need to undergo a surgical or major invasive procedure in the near future.

3.2.11 Patient has a history of uncorrected cerebral aneurysm, intracranial tumor or hemorrhagic cerebrovascular accident.

3.2.12 Patient refuses to receive transfused blood products should this intervention become clinically indicated.

3.2.13 Patient is taking or has been taking an investigational drug within the previous 30 days prior to enrollment.

3.2.14 In the judgment of the investigator, any disease or circumstance that would interfere with the objectives of the study, that places the patient at undue, increased risk by enrolling in the study, or which limits the ability either to provide signed informed consent or comply with the trial protocol.

3.2.15 Participants with known brain metastases should be excluded from this clinical trial because of their poor prognosis and because they often develop progressive neurologic dysfunction that would confound the evaluation of neurologic and other adverse events.

3.2.16 History of allergic reactions attributed to compounds of similar chemical or biologic composition to apixaban.

3.2.17 Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.

3.2.18 Pregnant women are excluded from this study because apixaban is a Class B agent with unknown potential for teratogenic or abortifacient effects. It is unknown whether apixaban or its metabolites are excreted in human milk. Because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with apixaban, breastfeeding should be discontinued if the mother is treated with apixaban.

3.2.19 Prior treatment with a non-heparin anticoagulant while awaiting study enrollment is not an exclusion.

3.3 Inclusion of Women and Minorities

Both men and women of all races and ethnic groups are eligible for this trial.

4 REGISTRATION PROCEDURES

4.1 General Guidelines for DF/HCC Institutions

Institutions will register eligible participants in the Clinical Trials Management System (CTMS) OnCore. Registrations must occur prior to the initiation of any protocol-specific therapy or intervention. Any participant not registered to the protocol before protocol-specific therapy or intervention begins will be considered ineligible and registration will be denied.

An investigator will confirm eligibility criteria and a member of the study team will complete the protocol-specific eligibility checklist.

Following registration, participants may begin protocol-specific therapy and/or intervention. Issues that would cause treatment delays should be discussed with the Overall Principal Investigator (PI). If the subject does not receive protocol therapy following registration, the subject must be taken off-study in the CTMS (OnCore) with an appropriate date and reason entered.

4.2 Registration Process for DF/HCC Institutions

DF/HCC Standard Operating Procedure for Human Subject Research Titled *Subject Protocol Registration* (SOP #: REGIST-101) must be followed.

5 TREATMENT AND/OR IMAGING PLAN

5.1 Treatment Regimen

Patients eligible for the study will receive the standard of care and FDA approved dosing of apixaban. Platelet count recovery in patients with HIT is typically 5-7 days. Warkentin demonstrated that patients with isolated HIT (HIT without thrombosis) have an increased risk of thrombosis for up to 30 days after diagnosis.[4] Therefore, for patients with isolated HIT (HIT without thrombosis), patients will receive apixaban, 10 mg twice a day for 7 days followed by 5 mg twice a day for 23 days, for a total of 30 days of apixaban dosing. For patients with HITT, patients will receive apixaban, 10 mg twice a day for 7 days followed by 5 mg twice a day for 83 days, for a total of 90 days of apixaban dosing, which are the current CHEST guidelines for duration of treatment for patients with provoked VTE.[24] The proposed apixaban dosing regimen is taken from the current FDA approved dosing schedule for the treatment of venous thromboembolism [VTE] with apixaban which is 10 mg twice daily for 7 days followed by 5 mg twice daily thereafter.

Treatment will initially be administered on an inpatient basis but once patient is medically cleared to be discharged, the remaining treatment will be administered on an outpatient basis. Reported adverse events and potential risks are described in Section 7. Appropriate dose modifications are described in Section 6. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the participant.

Regimen Description					
Agent	***Premedications; Precautions***	***Dose***	***Route***	***Schedule****	***Length of treatment***
Apixaban	*No premedications required*	*10 mg twice a day*	*Oral*	*For the first 7 days***	*1 month (30 days) total for HIT patients and 3 months (90 days) total for HITT patients*
Apixaban	*No premedications required*	*5 mg twice a day*	*Oral*	*To start this dose after patient completes the first 7 days with the 10 mg twice a day dose.***	
** This is the FDA approved dose for apixaban for prevention and treatment of venous thromboembolism.* *** Patients will not start the 5 mg dose prior to 7 days as this is the FDA approved dosing structure.*					

NOTE: Patients will be requested to maintain a medication diary of each dose of medication. The medication diary will be returned to clinic staff at the end of the study (one month for HIT patients and 3 months for HITT patients).

5.2 Pre-Treatment Criteria

Prior to initiation of treatment on D1, participants' labs must re-meet eligibility. Participants must have organ and marrow function as defined by absolute neutrophil count ≥1,500/mcL, AST(SGOT) and ALT(SGPT) ≤2.5 × institutional upper limit of normal and creatinine clearance ≥25 mL/min (as was used in the AMPLIFY trial).

5.3 Schedule and Description of Study Procedures (requirements also detailed in study calendar)

5.3.1 **Screening and Pre-Enrollment Procedures (Day -7 to Day 1)**

Patients with suspected heparin-induced thrombocytopenia will be screened to determine if they meet study eligibility criteria. Prior to initiation of any study procedures, a written IRB–approved informed consent will be obtained. Much of the information listed below will be obtained at the time of determining eligibility. Eligibility is verified after consent, and patients are enrolled only after eligibility is determined.

The window for baseline screening/assessment is up to 7 days prior to start of treatment.

Upon consent, the following study procedures will be performed:

5.3..1 Confirmatory Laboratory Test for the Diagnosis of HIT

- Heparin-PF4 EIA or accepted other confirmatory test (e.g. serotonin-release assay, platelet aggregation assay) is required if not already recorded in the 7 days prior to study treatment initiation.
- If the patient's initial HIT confirmatory test is negative, but the patient presentation is highly suspect for HIT, perform a serotonin release assay.
- Result may be pending at the time of enrollment.

5.3..2 Demographic and Medical History

- Date of birth, gender, race, hospital service.
- Past medical history of significant medical/surgical disease and previous hospitalization.
- History of thrombotic event(s).
- History of HIT and/or previous exposure to heparin/LMWH.
- Reason for initial hospitalization.
- Reason for initiation of heparin/LMWH.
- Type of heparin treatment, route of administration and length of therapy.
- Previous use of other anticoagulation therapy
- Concomitant medications.

5.3..3 Physical Examination, including:

- Height, weight. (Height documented within the month prior to D1 is acceptable)
- ECOG

- Vital signs (temperature, pulse, respirations, blood pressure, oxygen saturation).
- Clinical assessment for signs and symptoms of thromboembolic complications and any significant findings.

5.3..4 Laboratory Tests

- Record pre-heparin CBC with platelet count and blood coagulation profile.
- Urine or serum HGC pregnancy test in women of childbearing age (acceptable if performed within 7 days prior to initiation of study drug regimen).
- CBC: hemoglobin, hematocrit, WBC with differential, and platelet count.
- Blood coagulation profile: Activated partial thromboplastin time (aPTT), prothrombin time/international normalized ratio (PT/INR).
- Serum Chemistries: creatinine, BUN, Na, K, CO2 and glucose.
- Hepatic Profile: total bilirubin, AST, ALT.

5.3.2 **Imaging (Day -7 to Day +3)**

- As part of standard of care, all patients with confirmed HIT or high suspicion of HIT undergo bilateral lower extremity non invasive testing to rule out deep vein thrombosis. LENI is not required if the patient is diagnosed with a Pulmonary Embolism.
- This can occur anytime from Day -7 to Day +3. Only one test is required.

5.3.3 **Initiation of Therapy: Day 1**

Once the patient has been consented and is determined to meet inclusion/exclusion criteria as described above in Section 3.1 and 3.2, the following study procedures will be performed. These assessments do not need to be repeated if Screening was conducted on D1.

- Physical Exam
- Clinical Assessment for signs and symptoms of TEC and any significant findings
- Vital signs
- Weight
- ECOG
- Laboratory tests:
    - CBC: hemoglobin, hematocrit, WBC with differential, and platelet count
    - Chemistries: creatinine, BUN, Na, K, CO2 and glucose
    - Hepatic panel: total bilirubin, AST, ALT
    - Coagulation profile: aPTT, PT/INR
- Record Concomitant Medications
- Assess and Record Adverse Events
- Initiation of Therapy: dispense study medication and diary
    - Administer study medication: Apixaban
    - Initiate daily oral therapy at 10 mg twice daily for 7 days followed by 5 mg twice daily thereafter.

5.3.4 **Hospital Course: Day 2 - Day of Discharge:**

The following procedures will be done on a daily basis until discharge from the hospital:

- Clinical Assessment for signs and symptoms of thromboembolic complications and any significant findings.
- Vital signs
- Laboratory Tests:
  - CBC: hemoglobin, hematocrit, WBC with differential, and platelet count
  - Chemistry Panel: creatinine, BUN, Na, K, CO2 and glucose
- Assess and record Adverse Events
- Record Concomitant Medications
- Record all doses of administered Apixaban (from the day it was initiated).

Before discharge, ensure enough study medication is dispensed to last at least until the 30 Day Follow Up visit (for HIT) or the 90 Day Follow Up visit (for HITT).

5.3.5 **Follow-up: Day 30 (+/- 5 days)**

The patient will be assessed on Day 30 (± 5 days) from initiation of therapy, preferably in clinic. If clinic follow up is feasible, all of the following data must be recorded. If patient is unable to come to clinic (ie due to living in another city or unable to travel), day 30 follow up can be completed by telephone interview and the labs, exam and vitals will not be recorded.

The following data must be recorded:

- Summary of patient's clinical course
- Any adverse events that occurred between Day of Discharge through Day 30 including signs and symptoms of TEC.
- CBC, chemistries, coagulation profile*
- Physical exam and vital signs*
- Concomitant Medications
- For patients discharged on apixaban:
  - Retrieve study medication and diary
  - Record the stop date of discontinuation of apixaban.

**unable to obtain if follow up is telephone interview*

5.3.6 **Follow-up for patients with HITT: Day 90 (+/- 5 days)**

The patient will be assessed on Day 90 (± 5 days), from initiation of therapy, preferably in clinic. If clinic follow up is feasible, all of the following data must be recorded. If patient is unable to come to clinic (ie due to living in another city or unable to travel), day 90 follow up can be completed by telephone interview and the labs, exam and vitals will not be recorded.

The following data must be recorded:

- Summary of patient's clinical course
- Any adverse events that occurred between Day of Discharge through Day 90 including signs and symptoms of TEC.
- CBC, chemistries, coagulation profile*
- Physical exam and vital signs*
- Concomitant Medications
- For patients discharged on apixaban:
  - Retrieve study medication and diary
  - Record the stop date of discontinuation of apixaban.

**unable to obtain if follow up is telephone interview*

5.3.7 **Follow-up 30 days after last dose of therapy (+/- 5 days)**

The patient will be assessed on 30 days (± 5 days), after last dose of therapy. If clinic follow up is feasible, all of the following data must be recorded. If patient is unable to come to clinic (ie due to living in another city or unable to travel), this follow up can be completed by telephone interview and the labs, exam and vitals will not be recorded.

The following data must be recorded:

- Summary of patient's clinical course
- Any adverse events through 30 days after the last dose of therapy including signs and symptoms of TEC.
- CBC, chemistries*
- Physical exam and vital signs*
- Concomitant Medications

**unable to obtain if follow up is telephone interview*

5.3.8 **Unscheduled Additional Visits**

For any unscheduled visits, between Day of Discharge and Day 30 for isolated HIT and Day 90 for HITT, that are related to HIT and require hospitalization and treatment, the following procedures should be performed if possible (ie will not be possible if patient is admitted to an outside hospital or over the weekend/evening and discharged before study team available)

- Clinical Assessment for signs and symptoms of thromboembolic complications and any significant findings.
- Physical exam
- Vitals
- Summary of patient's clinical course, including any imaging if performed
- Laboratory Tests:
    - CBC: hemoglobin, hematocrit, WBC with differential, and platelet count
    - Chemistries: creatinine, BUN, Na, K, CO2 and glucose
    - Hepatic panel: total bilirubin, AST, ALT
    - Blood coagulation profile: aPTT, PT/INR
- Assess and record Adverse Events
- Record Concomitant Medications
- Record all doses of apixaban.

5.3.9 Evaluation of Symptomatic Thromboembolic Complications (TEC).

Patients will be evaluated for thrombotic events at each visit. The diagnosis of symptomatic, venous or arterial thrombosis will be determined by the primary investigator and/or treating physician based on established clinical signs and symptoms and where indicated (as for VTE) by a confirmatory, objective diagnostic test per the accepted standard of care.

5.3.10 Treatment of Symptomatic Thromboembolic Complications (TEC).

Treatment of symptomatic TEC will be instituted by the primary investigator and/or treating physician per their standard of care. Patients who develop symptomatic TEC, which is the primary endpoint for this study, will be followed for safety throughout the study follow-up period.

5.4 Agent Administration.

Apixaban will be supplied by BMS**.**

5.4.1 Administration and Dosing.

Apixaban will be initiated at 10 mg twice a day orally for the first 7 days. After 7 days, the dose of apixaban will be changed to 5 mg twice daily. This dosing regimen is the FDA approved dose per package insert. Per FDA approved guidelines, there is no requirements for dose modifications once patients meets inclusion and exclusion criteria.

For patients who are unable to swallow whole tablets, 5 mg APIXABAN tablets may be crushed and suspended in water, 5% dextrose in water (D5W), or apple juice, or mixed with applesauce and promptly administered orally. Alternatively, APIXABAN tablets may be crushed and suspended in 60 mL of water or D5W and promptly delivered through a nasogastric tube. Crushed APIXABAN tablets are stable in water, D5W, apple juice, and applesauce for up to 4 hours.

No hydration or pre-medications are required prior to administration of apixaban. There are no dietary restrictions when taking apixaban. There are no specific precautions necessary when administering apixaban.

5.4.2 Dosage Forms and Strengths

- 5 mg, pink, oval-shaped, biconvex, film-coated tablets with "894" debossed on one side and "5" on the other side.

- Drug may be dispensed per institutional standard, including repackaging.

5.4.3 Drug Diary

Patients will be requested to maintain a medication diary of each dose of medication. The medication diary will be returned to clinic staff at the end of the study (one month for HIT patients and 3 months for HITT patients).

5.4.4 Missed Dose or Vomited Dose

If a dose of APIXABAN is not taken at the scheduled time, the dose should be taken as soon as possible on the same day and twice-daily administration should be resumed. The dose should not be doubled to make up for a missed dose.

For vomited dose(s): If a single episode of vomiting, the dose should be taken at the next scheduled dose timings. If repeated vomiting and the patient is unable to retain any oral medications, the patient should contact his/her doctor immediately and he/she may need to be either temporarily discontinued from the study medication or permanently discontinued from the study drug. An alternative medication will be necessary if apixaban is stopped.

5.5 Other Modalities or Procedures

Once patients are diagnosed with HIT as part of standard of care or there is high suspicion of HIT, patients will undergo bilateral lower extremity non invasive ultrasound (LENI) to determine the presences of deep vein thromboses. If DVTs are identified, there will be no change in therapy. Presence of DVT will affect the length of anticoagulation. If patients have DVT, this would qualify as HITT and the patient will require 3 months of apixaban instead of 30 days as indicated for isolated HIT. If LENI is negative for DVT, but patient develops and is diagnosed with a clot elsewhere after heparin exposure, this would also qualify as HITT and will require 3 months of apixaban. The LENI is not required if the patient is diagnosed with a Pulmonary Embolism.

5.6 General Concomitant Medication and Supportive Care Guidelines

Because there is a potential for interaction of apixaban with other concomitantly administered drugs through the cytochrome P450 system or the p-glycoprotein system, the case report form must capture the concurrent use of all other drugs, over-the-counter medications, or alternative therapies. Appendix C presents guidelines for identifying medications/substances that could potentially interact with the study agent(s).

The following medications are **not** permitted in the protocol:

- Any other drug or biological agent with anticoagulation action.
- Any other drug that is known to interact negatively with the study drug.
- Investigational agents.
- Myelosuppressive chemotherapy.
- Treatment with aspirin at a dose of more than 162 mg daily.

5.7 Criteria for Taking a Participant Off Protocol Therapy

Duration of therapy will be one month for patients with isolated HIT and 3 months for patients with HITT. In the absence of treatment delays due to adverse event(s), treatment may continue for 1 month for isolated HIT and 3 months for HITT or until one of the following criteria applies:

- Patient had initial high clinical suspicion for HIT as defined in section 3.1.2 but testing with PF4 or other accepted confirmatory test (serotonin-release assay, platelet aggregation assay) returned negative.
- New symptomatic TEC
- Intercurrent illness that prevents further administration of treatment
- Major bleed (See Section 6)
- Patient becomes pregnant
- Unacceptable adverse event(s)

- Participant demonstrates an inability or unwillingness to comply with the oral medication regimen and/or documentation requirements

- Patient refuses to receive transfused blood products should this intervention become clinically indicated

- Participant decides to withdraw from the protocol therapy

- General or specific changes in the participant's condition render the participant unacceptable for further treatment in the judgment of the treating investigator. It is requested that premature discontinuation of a patient should be discussed immediately with the principal investigator, Dr. Rachel Rosovsky, 617-726-2000.

Participants will be removed from the protocol therapy when any of these criteria apply. The reason for removal from protocol therapy, and the date the participant was removed, must be documented in the case report form (CRF). Alternative care options will be discussed with the participant.

When a participant is removed from protocol therapy and/or is off of the study, the relevant Off-Treatment/Off-Study information will be updated in OnCore.

5.8 Duration of Follow Up

Participants will be followed for 30 days after last dose of study drug. Patients who are not hospitalized at the time of follow up will be seen in the outpatient clinic. Participants removed from protocol therapy for unacceptable adverse event(s) will be followed until resolution or stabilization of the adverse event.

5.9 Criteria for Taking a Participant Off Study

Participants will be removed from study when any of the following criteria apply:

- Lost to follow-up
- Withdrawal of consent for data submission
- Death

The reason for taking a participant off study, and the date the participant was removed, must be documented in the case report form (CRF). In addition, the study team will ensure Off Treatment/Off Study information is updated in OnCore in accordance with DF/HCC policy REGIST-101.

5.10 Early Withdraw

Any patient who is enrolled in the study, but withdraws prematurely at any time for any reason before the end of their Day 30 follow-up visit (or phone call) for isolated HIT or Day 90 follow up visit (or phone call) for HITT, is considered an early withdraw and will not be replaced. A

complete set of data including the reason for the early withdraw will be collected on each patient through the time of withdraw. Every effort will be made to ascertain patient safety and survival information at the Day 30 follow-up time-point for isolated HIT and Day 90 for HITT.

Note: Date of follow up refers to the total days since initiation of treatment.

6 DOSING CHANGES

Dose changes will be made as indicated in the following table(s). The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for dose changes. A copy of the CTCAE version 4.0 can be downloaded from the CTEP website http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

Bleeding	Management of Patient	Management Of Apixaban
≤ Grade 1	Mild, intervention not indicated	Continue apixaban and monitor closely
Grade 2	Symptomatic and medical intervention indicated	Stop apixaban, take off protocol
Grade 3	Transfusion, interventional radiology, endoscopic, or operative intervention indicated; radiation therapy (i.e., hemostasis of bleeding site)	Stop apixaban, take off protocol
Grade 4	Life-threatening consequences; major urgent intervention indicated	Stop apixaban, take off protocol
Grade 5	Death	Stop apixaban, take off protocol

Apixaban will also be stopped and patient will be taken off protocol for any major bleed. Decisions regarding further treatment for patients who experience a major hemorrhagic event will be deferred to the primary team. They will be followed to the end of the study in an intention-to-treat analysis.

Major bleeding is defined as overt bleeding and:

- associated with a decrease in hemoglobin of ≥ 2 g/dL, or
- leading to a transfusion of ≥ 2 units of packed red blood cells or whole blood, or
- occurring in a critical site: intracranial, intraspinal, intraocular, pericardial, intra-articular, intramuscular with compartment syndrome, retroperitoneal, or
- contributing to death.

6.1 Reversal of Anticoagulation Effect

A specific antidote for Apixaban is not available, and there is no established way to reverse bleeding in patients taking Apixaban. The pharmacodynamic effect of APIXABAN can be

expected to persist for at least 24 hours after the last dose, i.e., for about two drug half-lives. Use of procoagulant reversal agents, such as prothrombin complex concentrate (PCC), activated prothrombin complex concentrate or recombinant factor VIIa, has not been evaluated in clinical studies. Activated oral charcoal reduces absorption of apixaban, thereby lowering apixaban plasma concentration *[see Overdosage below]*. Hemodialysis does not appear to have a substantial impact on apixaban exposure. Protamine sulfate and vitamin K are not expected to affect the anticoagulant activity of apixaban. There is no experience with antifibrinolytic agents (tranexamic acid, aminocaproic acid) in individuals receiving apixaban. There is no experience with systemic hemostatic agents (desmopressin and aprotinin) in individuals receiving apixaban and they are not expected to be effective as a reversal agent.

Because there is no specific antidote to reverse the effect of apixaban, the following steps are recommended for subjects with ongoing life-threatening bleeding (bleeding resulting in hemodynamic compromise requiring intervention or any intracranial hemorrhage):

- Withhold study drug and all antiplatelets/anticoagulants;
- Institute standard of care for life-threatening bleeding (large bore IV or central venous line, type and crossmatch blood, admit to the intensive care unit, provide hemodynamic and respiratory support);
- Administer packed red blood cells (or whole blood) as needed.

If life-threatening bleeding persists, it is recommended to contact the PI to discuss subject management.

6.2 Overdose

There is no antidote to Apixaban. Overdose of Apixaban increases the risk of bleeding. In controlled clinical trials, orally administered apixaban in healthy subjects at doses up to 50 mg daily for 3 to 7 days (25 mg twice daily for 7 days or 50 mg once daily for 3 days) had no clinically relevant adverse effects.

In healthy subjects, administration of activated charcoal 2 and 6 hours after ingestion of a 20-mg dose of apixaban reduced mean apixaban AUC by 50% and 27%, respectively. Thus, administration of activated charcoal may be useful in the management of apixaban overdose or accidental ingestion.

7 ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

An Adverse Event (AE) is defined as any new untoward medical occurrence or worsening of a preexisting medical condition in a clinical investigation participant administered study drug and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (such as an abnormal laboratory finding), 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 adverse events (AE).
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 AEs.)

An abnormal laboratory value will not be assessed as an AE unless that value leads to discontinuation or delay in treatment, dose modification, therapeutic intervention, meets the definition of an SAE or AESI, or is considered by the investigator to be a clinically significant change from baseline.

7.1 Nonserious Adverse Event

A nonserious adverse event is an AE not classified as serious.

- Nonserious Adverse Events are to be provided to BMS in aggregate via interim or final study reports as specified in the agreement or, if a regulatory requirement [e.g. IND US trial] as part of an annual reporting requirement.

7.1.1 Nonserious Adverse Event Collection and Reporting

The collection of nonserious AE information should begin following the subject's written consent to participate in the study. All nonserious adverse events (not only those deemed to be treatment-related) should be collected continuously during the treatment period and for a minimum of 30 days following the last dose of study treatment.

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 and for those 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.

7.2 Laboratory Test Abnormalities

All laboratory test results captured as part of the study should be recorded following institutional procedures. Test results that constitute SAEs should be documented and reported as such.

The following laboratory abnormalities should be documented and reported appropriately:

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

It is expected that wherever possible, the clinical rather than laboratory term would be used by the reporting investigator (eg, anemia versus low hemoglobin value).

7.3 Serious Adverse Event

A Serious Adverse Event (SAE) is any untoward medical occurrence that at any dose:

- results in death
- is life-threatening (defined as an event in which the participant 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 (see **NOTE** below)
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect
- is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the subject or may require intervention [eg, medical, surgical] to prevent one of the other serious outcomes listed in the definition above.) Examples of such events include, but are not limited to, intensive treatment in an emergency room 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 nonpathogenic) via the study drug is an SAE.

Although pregnancy, overdose, potential drug-induced liver injury (DILI) and cancer are not always serious by regulatory definition, these events must be handled as SAEs.

Any component of a study endpoint that is considered related to study therapy should be reported as an SAE if it meets the above SAE definition (eg, death is an endpoint, if death occurred due to anaphylaxis, anaphylaxis must be reported).

NOTE: The following hospitalizations are not considered SAEs:

- a visit to the emergency room or other hospital department < 24 hours, that does not result in admission (unless considered an important medical or life-threatening event)
- elective surgery, planned prior to 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 to remedy ill health and planned prior to entry into the study. 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 (eg, lack of housing, economic inadequacy, caregiver respite, family circumstances, administrative reason).

7.4 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.

7.5 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.

7.6 Adverse Events of Special Interest

In this study, the following adverse events are 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.

7.7 Expected Toxicities

7.7.1 Adverse Events List for Apixaban

The safety of APIXABAN has been evaluated in non HIT or non HITT venous thromboembolism patient populations in the AMPLIFY and AMPLIFY-EXT studies, including 2676 patients exposed to APIXABAN 10 mg twice daily, 3359 patients exposed to APIXABAN 5 mg twice daily, and 840 patients exposed to APIXABAN 2.5 mg twice daily.

Common adverse reactions (≥1%) were gingival bleeding, epistaxis, contusion, hematuria, rectal hemorrhage, hematoma, menorrhagia, and hemoptysis.

AMPLIFY Study
The mean duration of exposure to APIXABAN was 154 days and to enoxaparin/warfarin was 152 days in the AMPLIFY study. Adverse reactions related to bleeding occurred in 417 (15.6%) APIXABAN-treated patients compared to 661 (24.6%) enoxaparin/warfarin treated patients. The discontinuation rate due to bleeding events was 0.7% in the APIXABAN-treated patients compared to 1.7% in enoxaparin/warfarin-treated patients in the AMPLIFY study.

In the AMPLIFY study, APIXABAN was statistically superior to enoxaparin/warfarin in the primary safety endpoint of major bleeding (relative risk 0.31, 95% CI [0.17, 0.55], P-value <0.0001).

Adverse reactions occurring in 1-3% of patients in the AMPLIFY study include: epistaxis, contusion, hematuria, menorrhagia, hematoma, hemoptysis, rectal hemorrhage, gingival bleeding.

AMPLIFY-EXT Study
The mean duration of exposure to APIXABAN was approximately 330 days and to placebo was 312 days in the AMPLIFY-EXT study. Adverse reactions related to bleeding occurred in 219 (13.3%) APIXABAN-treated patients compared to 72 (8.7%) placebo-treated patients. The discontinuation rate due to bleeding events was approximately 1% in the APIXABAN-treated patients compared to 0.4% in those patients in the placebo group in the AMPLIFY-EXT study.

Adverse reactions occurring in 1-2% of patients in the AMPLIFY-EXT study include: epistaxis, contusion, hematuria, hematoma, gingival bleeding.

Other Adverse Reactions
Less common adverse reactions in APIXABAN-treated patients in the AMPLIFY or AMPLIFYEXT studies occurring at a frequency of ≥0.1% to <1%:

Blood and lymphatic system disorders: hemorrhagic anemia

Gastrointestinal disorders: hematochezia, hemorrhoidal hemorrhage, gastrointestinal hemorrhage, hematemesis, melena, anal hemorrhage

Injury, poisoning, and procedural complications: wound hemorrhage, postprocedural hemorrhage, traumatic hematoma, periorbital hematoma

Musculoskeletal and connective tissue disorders: muscle hemorrhage

Reproductive system and breast disorders: vaginal hemorrhage, metrorrhagia, menometrorrhagia, genital hemorrhage

Vascular disorders: hemorrhage

Skin and subcutaneous tissue disorders: ecchymosis, skin hemorrhage, petechiae

Eye disorders: conjunctival hemorrhage, retinal hemorrhage, eye hemorrhage

Investigations: blood urine present, occult blood positive, occult blood, red blood cells urine positive

General disorders and administration-site conditions: injection-site hematoma, vessel puncture-site hematoma

Please refer to the approved apixaban U.S prescribing information for a complete listing of adverse events

7.8 Adverse Event Characteristics

- **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.

- **For expedited reporting purposes only:**
  - AEs for the agent(s) that are listed above should be reported only if the adverse event varies in nature, intensity or frequency from the expected toxicity information which is provided.
  - Other AEs for the protocol that do not require expedited reporting are outlined in the next section (Expedited Adverse Event Reporting) under the sub-heading of Protocol-Specific Expedited Adverse Event Reporting Exclusions.

- **Attribution** of the AE:
  - Definite – The AE *is clearly related* to the study treatment.
  - Probable – The AE *is likely related* to the study treatment.
  - Possible – The AE *may be related* to the study treatment.
  - Unlikely – The AE *is doubtfully related* to the study treatment.
  - Unrelated – The AE *is clearly NOT related* to the study treatment.

7.9 Expedited Adverse Event Reporting

7.9.1 In the event of an unanticipated problem or life-threatening complications treating investigators must immediately notify the Overall PI.

7.9.2 Investigators **must** report to the Overall PI any serious adverse event (SAE) that occurs after the initial dose of study treatment, during treatment, and within 30 days after the last dose of treatment.

7.9.3 DF/HCC Expedited Reporting Guidelines

Investigative sites within DF/HCC will report AEs directly to the DFCI Office for Human Research Studies (OHRS) per the DFCI IRB reporting policy.

7.9.4 Protocol-Specific Expedited Adverse Event Reporting Exclusions:

None

7.10 Expedited Reporting to BMS

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 of awareness of the event. SAEs must be recorded on the FDA MedWatch Form 3500A; Pregnancies on a Pregnancy Surveillance Form.

SAE Email Address: [redacted]

SAE Fax Number: [redacted]

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.

7.10.1 SAE Reconciliation

The investigator will reconcile the clinical database SAE cases transmitted to BMS Global Pharmacovigilance (GPV&E). Reconciliation will occur every three months and once just prior to database lock/Final Study Report (FSR). The investigator will request a safety data reconciliation report to [redacted]. BMS GPV&E will e-mail upon request from the investigator, the GPV&E reconciliation report. The data elements listed on the GPV&E safety data 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.

7.10.2 Pregnancy

If, following initiation of the investigational product, it is subsequently discovered that a study participant 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 participant).

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

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

Follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome and, where applicable, offspring information must be reported on the Pregnancy Surveillance Form [provided upon request from BMS]

Any pregnancy that occurs in a female partner of a male study participant should be reported to BMS. Information on this pregnancy will be collected on the Pregnancy Surveillance Form. In order for Sponsor or designee to collect any pregnancy surveillance information from the female partner, the female partner must sign an informed consent form for disclosure of this information.

7.11 Expedited Reporting to the Food and Drug Administration (FDA)

The Overall PI, as study sponsor, will be responsible for all communications with the FDA. The Overall PI will report to the FDA, regardless of the site of occurrence, any serious adverse event that meets the FDA's criteria for expedited reporting following the reporting requirements and timelines set by the FDA.

7.12 Expedited Reporting to Hospital Risk Management

Participating investigators will report to their local Risk Management office any participant safety reports or sentinel events that require reporting according to institutional policy.

7.13 Routine Adverse Event Reporting

All Adverse Events **must** be reported in routine study data submissions to the Overall PI on the toxicity case report forms. **AEs reported through expedited processes (e.g., reported to the IRB, FDA, etc.) must <u>also</u> be reported in routine study data submissions.**

8 PHARMACEUTICAL AGENT INFORMATION

A list of the adverse events and potential risks associated with the investigational or other agents administered in this study can be found in Section 7.7.

8.1 Mechanism of Action.

Apixaban is a selective inhibitor of FXa. It does not require antithrombin III for antithrombotic activity. Apixaban inhibits free and clot-bound FXa, and prothrombinase activity. Apixaban has no direct effect on platelet aggregation, but indirectly inhibits platelet aggregation induced by thrombin. By inhibiting FXa, apixaban decreases thrombin generation and thrombus development.

8.2 Pharmacodynamics

As a result of FXa inhibition, apixaban prolongs clotting tests such as prothrombin time (PT), INR, and activated partial thromboplastin time (aPTT). Changes observed in these clotting tests at the expected therapeutic dose, however, are small, subject to a high degree of variability, and not useful in monitoring the anticoagulation effect of apixaban.

The Rotachrom® Heparin chromogenic assay was used to measure the effect of apixaban on FXa activity in humans during the apixaban development program. A concentration dependent increase in anti-FXa activity was observed in the dose range tested and was similar in healthy subjects and patients with AF. This test is not recommended for assessing the anticoagulant effect of apixaban.

8.3 Specific Populations

Renal impairment:
Anti-FXa activity adjusted for exposure to apixaban was similar across renal function categories.

Hepatic impairment:
Changes in anti-FXa activity were similar in patients with mild-to-moderate hepatic impairment and healthy subjects. However, in patients with moderate hepatic impairment, there is no clear understanding of the impact of this degree of hepatic function impairment on the coagulation cascade and its relationship to efficacy and bleeding. Patients with severe hepatic impairment were not studied.

Cardiac Electrophysiology
Apixaban has no effect on the QTc interval in humans at doses up to 50 mg.

8.4 Pharmacokinetics

Apixaban demonstrates linear pharmacokinetics with dose-proportional increases in exposure for oral doses up to 10 mg.

Absorption
The absolute bioavailability of apixaban is approximately 50% for doses up to 10 mg of APIXABAN. Food does not affect the bioavailability of apixaban. Maximum concentrations (Cmax) of apixaban appear 3 to 4 hours after oral administration of

APIXABAN. At doses ≥25 mg, apixaban displays dissolution-limited absorption with decreased bioavailability. Following oral administration of 10 mg of apixaban as 2 crushed 5 mg tablets suspended in 30 mL of water, exposure was similar to that after oral administration of 2 intact 5 mg tablets. Following oral administration of 10 mg of apixaban as 2 crushed 5 mg tablets mixed with 30 g of applesauce, the Cmax and AUC were 20% and 16% lower, respectively, when compared to administration of 2 intact 5 mg tablets. Following administration of a crushed 5 mg APIXABAN tablet that was suspended in 60 mL D5W and delivered through a nasogastric tube, exposure was similar to that seen in other clinical trials involving healthy volunteers receiving a single oral 5 mg tablet dose.

Distribution
Plasma protein binding in humans is approximately 87%. The volume of distribution Vss) is approximately 21 liters.

Metabolism

Approximately 25% of an orally administered apixaban dose is recovered in urine and feces as metabolites. Apixaban is metabolized mainly via CYP3A4 with minor contributions from CYP1A2, 2C8, 2C9, 2C19, and 2J2. O-demethylation and hydroxylation at the 3-oxopiperidinyl moiety are the major sites of biotransformation. Unchanged apixaban is the major drug-related component in human plasma; there are no active circulating metabolites.

Elimination

Apixaban is eliminated in both urine and feces. Renal excretion accounts for about 27% of total clearance. Biliary and direct intestinal excretion contributes to elimination of apixaban in the feces. Apixaban has a total clearance of approximately 3.3 L/hour and an apparent half-life of approximately 12 hours following oral administration. Apixaban is a substrate of transport proteins: P-gp and breast cancer resistance protein.

Drug Interaction Studies

In vitro
Apixaban studies at concentrations significantly greater than therapeutic exposures, no inhibitory effect on the activity of CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2D6, CYP3A4/5, or CYP2C19, nor induction effect on the activity of CYP1A2, CYP2B6, or CYP3A4/5 were observed. Therefore, apixaban is not expected to alter the metabolic clearance of co-administered drugs that are metabolized by these enzymes. Apixaban is not a significant inhibitor of P-gp.

In dedicated studies conducted in healthy subjects, famotidine, atenolol, prasugrel, and enoxaparin did not meaningfully alter the pharmacokinetics of apixaban. In studies conducted in healthy subjects, apixaban did not meaningfully alter the pharmacokinetics of digoxin, naproxen, atenolol, prasugrel, or acetylsalicylic acid.

Specific Populations

Gender: A study in healthy subjects comparing the pharmacokinetics in males and females showed no meaningful difference.

Race: The results across pharmacokinetic studies in normal subjects showed no differences in apixaban pharmacokinetics among White/Caucasian, Asian, and Black/ African American subjects. No dose adjustment is required based on race/ethnicity.

Hemodialysis in ESRD subjects: Systemic exposure to apixaban administered as a single 5 mg dose in ESRD subjects dosed immediately after the completion of a 4-hour hemodialysis session (post-dialysis) is 36% higher when compared to subjects with normal renal function. The systemic exposure to apixaban administered 2 hours prior to a 4-hour hemodialysis session with a dialysate flow rate of 500 mL/min and a blood flow rate in the range of 350 to 500 mL/min is 17% higher compared to those with normal renal function. The dialysis clearance of apixaban is approximately 18 mL/min. The systemic exposure of apixaban is 14% lower on dialysis when compared to not on dialysis. Protein binding was similar (92%-94%) between healthy controls and ESRD subjects during the on-dialysis and off-dialysis periods.

It is important to note that clinical efficacy and safety studies with ELIQUIS did not enroll patients with end-stage renal disease (ESRD) on dialysis. In patients with ESRD maintained on intermittent hemodialysis, administration of ELIQUIS at the usually recommended dose *[see Dosage and Administration (2.1)]* will result in concentrations of apixaban and pharmacodynamic activity similar to those observed in the ARISTOTLE study *[see Clinical Pharmacology (12.3)]*. It is not known whether these concentrations will lead to similar stroke reduction and bleeding risk in patients with ESRD on dialysis as was seen in ARISTOTLE

8.5 Pharmaceutical Section for Apixaban:

Please refer to package insert for additional details.

https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/202155s000lbl.pdf

8.5.1 **Description**

The chemical name is: (-)-cis-2-(2-chorophnyl-5,7-dihydroxy-8-(4R-3S-hydroxy-1-methyl) piperidinyl-4H-1benzopyran-4-one,hydrochloride. Flavopiridol is also known as HMR 1275 and is a synthetic flavone. The molecular formula is C21H20CINO3 HCL. The molecular weight is 438.29.

Apixaban displays prolonged absorption. Thus, despite a short clearance half-life of about 6 hours, the apparent half-life during repeat dosing is about 12 hours, which allows

twice-daily dosing to provide effective anticoagulation, but it also means that when the drug is stopped for surgery, anticoagulation persists for at least a day.

Absorption
The absolute bioavailability of apixaban is approximately 50% for doses up to 10 mg of ELIQUIS. Food does not affect the bioavailability of apixaban. Maximum concentrations (Cmax) of apixaban appear 3 to 4 hours after oral administration of ELIQUIS. Apixaban is absorbed throughout the gastrointestinal tract with the distal small bowel and ascending colon contributing about 55% of apixaban absorption. Apixaban demonstrates linear pharmacokinetics with dose-proportional increases in exposure for oral doses up to 10 mg. At doses ≥25 mg, apixaban displays dissolution-limited absorption with decreased bioavailability.

Distribution
Plasma protein binding in humans is approximately 87%. The volume of distribution (Vss) is approximately 21 liters.

Metabolism
Approximately 25% of an orally administered apixaban dose is recovered in urine and feces as metabolites. Apixaban is metabolized mainly via CYP3A4 with minor contributions from CYP1A2, 2C8, 2C9, 2C19, and 2J2. O-demethylation and hydroxylation at the 3-oxopiperidinyl moiety are the major sites of biotransformation. Unchanged apixaban is the major drug-related component in human plasma; there are no active circulating metabolites.

Elimination
Apixaban is eliminated in both urine and feces. Renal excretion accounts for about 27% of total clearance. Biliary and direct intestinal excretion contributes to elimination of apixaban in the feces.

Following intravenous administration, apixaban is eliminated with a dominant half-life of ~ 5 hours. Following oral administration, the apparent half-life is ~12 hours because of prolonged absorption.

Apixaban is a substrate of transport proteins: P-gp and breast cancer resistance protein.

8.5.2 **Form**

Apixaban is available in 2.5 mg, yellow, round, biconvex, film-coated tablets with “893” debossed on one side and “2½” on the other side and 5 mg, pink, oval-shaped, biconvex, film-coated tablets with “894” debossed on one side and “5” on the other side

8.5.3 **Storage and Stability**

Store at 20°C to 25°C (68°F-77°F); excursions permitted between 15°C and 30°C (59°F-86°F) [see USP Controlled Room Temperature].

8.5.4 **Compatibility**

N/A

8.5.5 **Handling**

Qualified personnel, familiar with procedures that minimize undue exposure to themselves and the environment, should undertake the preparation, handling, and safe disposal of the agent in a self-contained and protective environment.

8.5.6 **Availability**

Apixaban is commercially available and will be supplied by Bristol-Myers Squibb

8.5.7 **Preparation**

For patients who are unable to swallow whole tablets, 5 mg ELIQUIS tablets may be crushed and suspended in water, 5% dextrose in water (D5W), or apple juice, or mixed with applesauce and promptly administered orally [see U.S. Prescribing Information Clinical Pharmacology(12.3)].

Alternatively, ELIQUIS tablets may be crushed and suspended in 60 mL of water or D5W and promptly delivered through a nasogastric tube [see U.S. Prescribing Information, Clinical Pharmacology (12.3)].

Crushed ELIQUIS tablets are stable in water, D5W, apple juice, and applesauce for up to 4 hours.

8.5.8 **Administration**

NOTE: These instructions must be consistent with protocol section 5: TREATMENT AND/OR IMAGING PLAN.

Apixaban will be initiated at 10 mg twice a day orally for the first 7 days. After 7 days, the dose of apixaban will be changed to 5 mg twice daily. This dosing regimen is the FDA approved dose per package insert. Per FDA approved guidelines, there is no requirements for dose modifications once patients meets inclusion and exclusion criteria.

For patients who are unable to swallow whole tablets, 5 mg APIXABAN tablets may be crushed and suspended in water, 5% dextrose in water (D5W), or apple juice, or mixed with applesauce and promptly administered orally.

Alternatively, APIXABAN tablets may be crushed and suspended in 60 mL of water or D5W and promptly delivered through a nasogastric tube.

Crushed APIXABAN tablets are stable in water, D5W, apple juice, and applesauce for up to 4 hours.

No hydration or pre-medications are required prior to administration of apixaban. There are no dietary restrictions when taking apixaban. There are no specific precautions necessary when administering apixaban.

8.5.9 **Ordering**

Commercially available apixaban will be ordered via study drug order form supplied by Bristol-Myers Squibb. Please allow up to 5 business days for processing.

8.5.10 **Accountability**

The investigator, or a responsible party designated by the investigator, should maintain a

careful record of the inventory and disposition of the agent using the NCI Drug Accountability Record Form (DARF) or another comparable drug accountability form. (See the NCI Investigator's Handbook for Procedures for Drug Accountability and Storage.)

8.5.11 Destruction and Return

Per institutional destruction policy. Returns are not accepted by BMS.

9 BIOMARKER, CORRELATIVE, AND SPECIAL STUDIES:

None

10 STUDY CALENDAR

Baseline evaluations are to be conducted within 7 days prior to start of protocol therapy, unless otherwise noted. Assessments must be performed prior to administration of any study agent.

Procedure	Day -7 to Day 1: Screening and Enrollment	Day 1: Initiation of Therapy[10]	Daily for Day 2 through and including Day of Discharge	30 Day Follow-up (± 5 days) [11]	90 Day Follow-up for isolated HITT (± 5 days) [11]	30 Day after discontinuation of all treatment (± 5 days) [11]	Unscheduled Visits [12]
Informed Consent	x						
Demographics	x						
Medical History	x						
Physical Exam	x	x		x	X	X	X
Height[14]	x						
Weight	x	x					
Clinical Assessment for signs and symptoms of TEC or other significant findings[1]	x	x	x	x	X	X	X
Vital Signs (temperature, pulse, respirations, blood pressure, oxygen saturation)	x	x	x	x	X	X	X
ECOG Performance Status	x	x					
CBC w/ Platelets[2]	x	x	x	x	X	X	X
Serum Chemistry Panel[3]	x	x	x	x	X	X	X
Urine or Serum HCG (as appropriate)[4]	x						
Hepatic Profile[5]	x	x					X
HIT Confirmatory Test[6]	x						
Lower Extremity Non-invasive [7]	X						
Administer Apixaban [8]		x	x				
Coagulation Profile[9]	x	x		x	x		X
Concomitant Medications	x	x	x	x	X	X	X
Adverse Events		X	x	x	X	X	X
Summary of Patient's Clinical Course				x	X	X	X
Drug/Diary Dispensing[13]		X					
Drug/Diary Return				x	x		

1. Assessment for any significant findings or any signs and symptoms of TEC. For the purposes of this study, TEC is defined as any thromboembolic complication (venous or arterial, and including skin necrosis)
2. CBC (Hemoglobin, hematocrit, WBC with differential, platelet count)
3. Serum Chemistry(Creatinine, BUN, Na, K, CO_2, glucose)
4. Acceptable if performed within 7 days prior to initiation of study drug regimen

5. Hepatic Profile (Total Bilirubin, AST, ALT)
6. HIT Confirmatory Test (HIT Antibody Titers (EIA PF4 or Serotonin-Release Assay [SRA]). If negative and high clinical suspicion, perform SRA if initial test was EIA PF4.
7. LENI: As part of standard of care, all patients with confirmed HIT or high suspicion of HIT undergo lower extremity non invasive testing to rule out deep vein thrombosis, ONE TIME – can be done Day -7 to Day +3. LENI is not required if the patient is diagnosed with a Pulmonary Embolism.
8. Anticoagulant Therapy: Upon clinical diagnosis or high suspicion of HIT, obtain informed consent, determine inclusion/exclusion eligibility, enroll subject, and initiate apixaban.
9. Coagulation Profile: PT, INR, PTT
10. These do not need to be repeated if completed for screening on day 1.
11. The procedures will be performed for patients able to come to a follow up clinic visit. Otherwise, subjects will be contacted by phone.
12. Assessments for unscheduled visits recommended if feasible (ie if patient admitted to outside hospital, these assessments will not be possible.
13. Patients will be dispensed with enough drug prior to discharge to last until the 30 Day Follow Up visit (for HIT) or the 90 Day Follow Up visit (for HITT).
14. Height documented within the month prior to D1 is acceptable

11 MEASUREMENT OF EFFECT

11.1 Other Response Parameters

11.1.1 Definition of Symptomatic Thromboembolic Complications

Any symptomatic new thrombosis, skin necrosis and/or new thromboembolism, venous and/or arterial, in any part of the vascular system (excluding thrombophlebitis), that is clinically diagnosed by the investigator and confirmed by objective, diagnostic standards of care, tests is defined as TEC.

- **Deep vein thrombosis** will be considered confirmed if there is laboratory confirmation of a positive venographic study, Doppler results or compression ultrasound study. Events documented by clinical diagnosis alone will be rejected. In cases where the event is a recurrent deep vein thrombosis, clear documentation must be provided to demonstrate an interval change from baseline studies.
- The diagnosis of **pulmonary embolism** will be confirmed if a positive angiogram, computed tomographic angiogram, a completed ventilation-perfusion scan or an echocardiogram shows at least two segmental defects without ventilation defects. In cases where the event is a recurrent pulmonary embolism, clear documentation must be provided to demonstrate an interval change from baseline studies.
- **Non-DVT/PE thrombosis** will be considered confirmed if positive on imaging modality.
- The diagnosis of **stroke** will be considered confirmed if the patient has a new focal neurologic deficit and if the signs and symptoms persist for more than 24 hours. All stroke events will be further classified as hemorrhagic or thrombotic based on clinical data.
- The diagnosis of **myocardial infarction** will be considered confirmed if the patient develops symptoms consistent with an event, accompanied by characteristic changes on electrocardiogram and/or elevation of cardiac troponin measured in the serum.
- The diagnosis of **acute arterial insufficiency** will be considered confirmed if the patient develops symptoms or signs consistent with an event, accompanied by the objective determination of arterial insufficiency by pulselessness, arterial Doppler ultrasound or angiogram.

- The diagnosis of **adrenal necrosis** (due to presumptive adrenal vein thrombosis) will be based upon radiologic evidence of unilateral or bilateral adrenal hemorrhage.
- The diagnosis of **skin necrosis** will be considered confirmed if accompanied by symptoms or signs consistent with an event, accompanied by skin biopsy, expert consultation by a dermatologist and/or objective review of a high-resolution photograph of the involved integument by an appropriate specialist.
- The circumstances of any **sudden death** will be reviewed by the DF/HCC Data and Safety Monitoring Committee (DSMC) per Section 12.2.

11.1.2 Safety

Monitoring of adverse events will be conducted throughout the study, and include new or subsequent TEC, major bleeding (in particular fatal, life-threatening, disabling, requiring a surgical intervention), further thrombocytopenia, disseminated intravascular coagulopathy, skin necrosis, allergic reaction or other events which in the opinion of the investigator are related to anticoagulation therapy. New adverse events, including serious adverse events, will be captured on the CRFs including through 30 days after enrollment for isolated HIT and 90 days after enrollment for HITT as well as 30 days after discontinuation of all treatment. New-onset adverse events and serious adverse events should be monitored until they are resolved or are clearly determined to derive from a patient's stable or chronic condition or intercurrent illness(es). Definitions, documentation, and reporting of adverse events are described in section 7.

11.1.3 Definition of Resolution of Thrombocytopenia

Resolution of Thrombocytopenia will be defined as:

- An increase in the platelet count to greater than $100x10^3/\mu L$ in patients with a nadir platelet count less than $100x10^3/\ \mu L$ or
- A stable, non-declining platelet count for more than 72 hours following the initiation of therapy in patients with a nadir platelet count greater than $100x10^3/\ \mu L$.

11.1.4 Definition of Recovery of Thrombocytopenia

Recovery of Thrombocytopenia will be defined as:

- An increase in platelet count to greater than $100x10^3/\ \mu L$ in patients with a pre-apixaban platelet count less than $100x10^3/\ \mu L$ or
- An increase in the platelet count to 1.5 times the pretreatment value in patients with a pre-apixaban platelet count greater than $100x10^3\ \mu L$

12 DATA REPORTING / REGULATORY REQUIREMENTS

Adverse event lists, guidelines, and instructions for AE reporting can be found in Section 7.0

(Adverse Events: List and Reporting Requirements).

12.1 Data Reporting

12.1.1 Method

The Office of Data Quality (ODQ) will collect, manage, and perform quality checks on the data for this study.

12.1.2 Responsibility for Data Submission

Investigative sites within DF/HCC or DF/PCC are responsible for submitting data and/or data forms to the Office of Data Quality (ODQ) in accordance with DF/HCC policies.

12.2 Data Safety Monitoring

The DF/HCC Data and Safety Monitoring Committee (DSMC) will review and monitor toxicity and accrual data from this study. The committee is composed of medical oncologists, research nurses, pharmacists, and biostatisticians with direct experience in cancer clinical research. Information that raises any questions about participant safety will be addressed with the Overall PI and study team.

The DSMC will review each protocol up to four times a year or more often if required to review toxicity and accrual data. Information to be provided to the committee may include: up-to-date participant accrual; current dose level information; all grade 2 or higher unexpected adverse events that have been reported; summary of all deaths occurring with 30 days of intervention for Phase I or II protocols; audit results, and a summary provided by the study team. Other information (e.g. scans, laboratory values) will be provided upon request.

13 STATISTICAL CONSIDERATIONS

13.1 Study Design/Endpoints

This is a prospective, open label, single center study designed to evaluate the activity and tolerability of apixaban for the treatment of hospitalized patients with a confirmed diagnosis of isolated heparin induced thrombocytopenia (HIT).

Standard therapy with argatroban in isolated HIT has been associated with an estimated 6-8% incidence of new TEC (approximately 7%). However, the literature also reports mortality rates of up to 20% within 30 days of initiation of argatroban therapy. Furthermore, two recent "real world" analyses revealed a much higher risk of death, limb amputation and new thrombosis than was reported in prior studies.[13,14]

The primary endpoint of this study is to evaluate the activity of the oral factor Xa inhibitor, apixaban as monotherapy in patients with heparin inducted thrombocytopenia (HIT) and heparin

inducted thrombocytopenia with thrombosis (HITT), as defined by the incidence of new symptomatic thromboembolic complications (TEC) within 30 days of the time of initiation of apixaban.

The proportion of patients with confirmed HIT who are alive without new TEC at day 30 will be reported as a binomial proportion. We will also report the rate of new TEC, as estimated in the context of a cumulative incidence model in which death before day 30 in the absence of new TEC is treated as a competing risk.

Based on a recent "real world" analysis, where ¼ patients had HITT and ¾ patients had isolated HIT, the proportion of patients alive and without TEC was 59% in the HITT group and 66% in the isolated HIT group.[14] We calculated the expected proportion of patients alive and without TEC for this present study based on the proportion of patients and event rates in each group from the real world analysis.

A total of 49 patients with a diagnosis or high clinical suspicion for HIT will be enrolled in this study using a one-stage design. We assume a conservative 10% frequency of negative confirmatory testing, thus yielding at least 44 patients with confirmed HIT in whom to assess the efficacy of this treatment at the conclusion of the trial. We anticipate that we will accrue and complete follow up on all patients within 2 years, based on investigators' estimates of incident cases of HIT at MGH.

If at least 34 of 44 confirmed HIT patients are alive without new TEC at day 30, we will consider the study a success. The lower bound of the exact 90% confidence interval associated with this outcome is 0.65, suggesting that if we observe a 77% success rate, the probability that the true but unknown success rate is less than 65% is less than 0.05. We note again that in this calculation, both new TEC or death without TEC by day 30 are considered failures. We will also estimate the rate of new TEC at day 30 using the cumulative incidence model, and provide a 90% confidence interval based on the model estimate of variance.

A descriptive analysis of the secondary efficacy endpoints will be obtained.

Exact binomial 90% confidence intervals will be provided.

Demographic and baseline characteristics will be summarized overall using descriptive statistics (mean, median, standard deviation, minimum, and maximum) for continuous variables (e.g., age) and counts and percents for categorical variables (e.g., gender or race).

90% EXACT BINOMIAL CONFIDENCE INTERVALS FOR VARIOUS OBSERVED PROPORTIONS OF PATIENTS ALIVE WITHOUT NEW TEC AT DAY 30

Observed Response Rate	90% CI

32/44 (73%)	**(60% to 83%)**
34/44 (77%)	**(65% to 87%)**
36/44 (82%)	**(70% to 91%)**

13.2 Sample Size, Accrual Rate and Study Duration:

See Section 13.1 above.

Both men and women of all races and ethnic groups are eligible for this trial. It is hoped that the accrual targets will resemble the gender, ethnic, and racial composition of the U.S. population as closely as possible.

13.3 Interim Monitoring Plan:

The study will be suspended for toxicity review if 5 or more patients out of the first 15 experience major hemorrhagic or thrombotic complications. The following table summarizes the probability of suspension given various probabilities of major hemorrhagic or thrombotic complications.

Probability of major hemorrhagic or thrombotic complications	0.13	0.20	0.33	0.40
Probability of suspension	0.04	0.16	0.60	0.78

Suspension will also be warranted if death without new TEC occurs in 2 or more of the first 15 patients. The following table summarizes the probability of suspension given various probabilities of death without new TEC.

Probability of death without new TEC	0.10	0.13	0.20	0.25
Probability of suspension	0.45	0.61	0.83	0.92

13.4 Analysis of Primary Endpoints:

See section 13.1

13.5 Analysis of Secondary Endpoints:

See section 13.1

13.6 Reporting and Exclusions

13.6.1 Evaluation of Toxicity

All participants will be evaluable for toxicity from the time of their first treatment.

13.6.2 Evaluation of the Primary Efficacy Endpoint

The full analysis (FA) dataset will include all patients that receive at least one dose of study drug. The per protocol (PP) dataset is a subset of the FA dataset, excluding patients that are subsequently ruled out for this diagnosis by negative confirmatory laboratory testing. The primary efficacy analysis will be conducted in the PP data set. All safety analyses will be performed on the FA dataset. The incidence of new TEC following the initiation of apixaban therapy for HIT is the primary efficacy endpoint of this study, however the tolerability and side effects will be monitored as well.

14 PUBLICATION PLAN

The results should be made public within 24 months of reaching the end of the study. The end of the study is the time point at which the last data items are to be reported, or after the outcome data are sufficiently mature for analysis, as defined in the section on Sample Size, Accrual Rate and Study Duration. If a report is planned to be published in a peer-reviewed journal, then that initial release may be an abstract that meets the requirements of the International Committee of Medical Journal Editors. A full report of the outcomes should be made public no later than three (3) years after the end of the study.

REFERENCES

1. Kelton JG, Warkentin TE. Heparin-induced thrombocytopenia: a historical perspective. Blood 2008;112:2607-16.
2. Martel N, Lee J, Wells PS. Risk for heparin-induced thrombocytopenia with unfractionated and low-molecular-weight heparin thromboprophylaxis: a meta-analysis. Blood 2005;106:2710-5.
3. Warkentin TE. Heparin-induced thrombocytopenia: pathogenesis and management. Br J Haematol 2003;121:535-55.
4. Warkentin TE, Kelton JG. A 14-year study of heparin-induced thrombocytopenia. Am J Med 1996;101:502-7.
5. Amiral J, Bridey F, Dreyfus M, et al. Platelet factor 4 complexed to heparin is the target for antibodies generated in heparin-induced thrombocytopenia. Thromb Haemost 1992;68:95-6.
6. Warkentin TE, Greinacher A. Heparin-induced anaphylactic and anaphylactoid reactions: two distinct but overlapping syndromes. Expert Opin Drug Saf 2009;8:129-44.
7. Warkentin TE, Kelton JG. Temporal aspects of heparin-induced thrombocytopenia. N Engl J Med 2001;344:1286-92.
8. Sheridan D, Carter C, Kelton JG. A diagnostic test for heparin-induced thrombocytopenia. Blood 1986;67:27-30.
9. Warkentin TE. Heparin Induced Thrombocytopenia. In: Warkentin TE, ed. Laboratory Testing for Heparin-Induced Thrombocytopenia. 3rd ed. New York: Marcel Dekker, Inc; 2004:271-311.
10. Linkins LA, Dans AL, Moores LK, et al. Treatment and prevention of heparin-induced thrombocytopenia: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest 2012;141:e495S-530S.
11. Lewis BE, Wallis DE, Berkowitz SD, et al. Argatroban anticoagulant therapy in patients with heparin-induced thrombocytopenia. Circulation 2001;103:1838-43.
12. Lewis BE, Wallis DE, Leya F, Hursting MJ, Kelton JG. Argatroban anticoagulation in patients with heparin-induced thrombocytopenia. Arch Intern Med 2003;163:1849-56.
13. Bolbrinker J, Garbe E, Douros A, et al. Immobilization and high platelet count are associated with thromboembolic complications in heparin-induced thrombocytopenia. Pharmacoepidemiol Drug Saf 2017.
14. Kuter DJ, Konkle BA, Hamza TH, et al. Clinical outcomes in a cohort of patients with heparin-induced thrombocytopenia. Am J Hematol 2017;92:730-8.
15. Warkentin TE, Elavathil LJ, Hayward CP, Johnston MA, Russett JI, Kelton JG. The pathogenesis of venous limb gangrene associated with heparin-induced thrombocytopenia. Ann Intern Med 1997;127:804-12.
16. Warkentin TE, Sikov WM, Lillicrap DP. Multicentric warfarin-induced skin necrosis complicating heparin-induced thrombocytopenia. Am J Hematol 1999;62:44-8.
17. Salter BS, Weiner MM, Trinh MA, et al. Heparin-Induced Thrombocytopenia: A Comprehensive Clinical Review. J Am Coll Cardiol 2016;67:2519-32.
18. Agnelli G, Buller HR, Cohen A, et al. Oral apixaban for the treatment of acute venous thromboembolism. N Engl J Med 2013;369:799-808.
19. Agnelli G, Buller HR, Cohen A, et al. Apixaban for extended treatment of venous thromboembolism. N Engl J Med 2013;368:699-708.
20. Walenga JM, Prechel M, Hoppensteadt D, et al. Apixaban as an alternate oral anticoagulant for the management of patients with heparin-induced thrombocytopenia. Clin Appl Thromb Hemost 2013;19:482-7.

21. Sharifi M, Bay C, Vajo Z, Freeman W, Sharifi M, Schwartz F. New oral anticoagulants in the treatment of heparin-induced thrombocytopenia. Thromb Res 2015;135:607-9.
22. Larsen PB, Jorgensen M, Friis-Hansen L, Ingeberg S. Apixaban used for the management of heparin-induced thrombocytopenia in a 72-year-old woman with lung cancer. Clin Case Rep 2015;3:987-9.
23. Frost C, Wang J, Nepal S, et al. Apixaban, an oral, direct factor Xa inhibitor: single dose safety, pharmacokinetics, pharmacodynamics and food effect in healthy subjects. Br J Clin Pharmacol 2013;75:476-87.
24. Kearon C, Akl EA, Comerota AJ, et al. 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.

APPENDIX A PERFORMANCE STATUS CRITERIA

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

APPENDIX B INFORMATION ON POSSIBLE DRUG INTERACTIONS

Information on Possible Interactions with Other Agents for Patients and Their Caregivers and Non-Study Healthcare Team

The participant _____ is enrolled on a clinical trial using the agent **APIXABAN**. This clinical trial is a Principal Investigator initiated study. This form is addressed to the participant, but includes important information for others who care for this participant.

Apixaban may interact with other drugs. Because of this, it is very important to tell your study doctors about all of your medicine before you start this study. It is also very important to tell them if you stop taking any regular medicine, or if you start taking a new medicine while you take part in this study. When you talk about your medicine with your study doctor, include medicine you buy without a prescription at the drug store (over-the-counter remedy), or herbal supplements such as St. John's wort.

Many health care prescribers can write prescriptions. You must also tell your other prescribers (doctors, physicians' assistants or nurse practitioners) that you are taking part in a clinical trial. These are the things that you and they need to know:

Apixaban interacts with drugs that work certain specific enzyme(s) in your liver.

- The enzymes in question are CYP3A4 and P-glycoprotein. Inhibitors of CYP3A4 and P-gp increase exposure to apixaban and could result in high levels of the active drug, increasing the chance of harmful side effects such as the risk of bleeding. Inducers of CYP3A4 and P-gp decrease exposure to apixaban and could reduce the effectiveness of the drug which could thereby increase the risk of stroke and other thromboembolic events.
- Therefore, if you are on any medication that involves CYP3A4 and P-glycoprotein, apixaban must be discontinued.
- You and healthcare providers who prescribe drugs for you must be careful about adding or removing any drug in this category.
- Before you start the study, your study doctor will work with your regular prescriber to switch any medicines that are considered "strong inducers/inhibitors or substrates of CYP3A4 and P-glycoprotein
- Your prescribers should look at this web site http://medicine.iupui.edu/clinpharm/ddis/table.aspx or consult a medical reference to see if any medicine they want to prescribe is on a list of drugs to avoid.
- Please be very careful! Over-the-counter drugs have a brand name on the label—it's usually big and catches your eye. They also have a generic name—it's usually small and located above or below the brand name, and printed in the ingredient list. Find the generic name and determine, with the pharmacist's help, whether there could be an adverse interaction.
- Be careful:

- If you take acetaminophen regularly: You should not take more than 4 grams a day if you are an adult or 2.4 grams a day if you are older than 65 years of age. Read labels carefully! Acetaminophen is an ingredient in many medicines for pain, flu, and cold.
- If you take herbal medicine regularly: You should not take St. John's wort while you are taking Apixaban.

Other medicines can be a problem with your study drugs.

- You should check with your doctor or pharmacist whenever you need to use an over-the-counter medicine or herbal supplement.

- Your regular prescriber should check a medical reference or call your study doctor before prescribing any new medicine for you. Your study doctor's name is

Dr. Rachel Rosovsky and she can be contacted at 617-726-2000.

APPENDIX C APIXABAN PACKAGE INSERT

https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/202155s000lbl.pdf

APPENDIX D

Transition to apixaban from other anticoagulants: taken from package insert

2.4 Converting from or to ELIQUIS

Switching from warfarin to ELIQUIS: Warfarin should be discontinued and ELIQUIS started when the international normalized ratio (INR) is below 2.0.

Switching from anticoagulants other than warfarin (oral or parenteral) to ELIQUIS: Discontinue the anticoagulant other than warfarin and begin taking ELIQUIS at the usual time of the next dose of the anticoagulant other than warfarin.

APPENDIX E

Child-Pugh B and C) Definition

Five clinical features are used to assess the severity of liver disease: 1) grade of hepatic encephalopathy, 2) degree of ascites 3) total bilirubin level, 4) serum albumin, and 5) prothrombin time prolongation (measured as INR). The total point score is then used to determine each patient's Child-Pugh class.

Factor	1 point	2 points	3 points
Encephalopathy	None	Altered mood/confusion or inappropriate behavior, impending stupor, somnolence	Markedly confused, stuporous but arousable or Comatose/unresponsive
Ascites	Absent	Slight	Moderate
Bilirubin (mg/dL)	<2	2-3	>3
Albumin (g/dL)	>3.5	2.8-3.5	<2.8
Prothrombin time prolongation (INR)	<1.7	1.7-2.3	>2.3

Child Pugh Interpretation

5-6 points	Child class A
7-9 points	Child class B
10-15 points	Child class C