A Phase IV, Randomized, Double Blind Study Evaluating the Safety and Efficacy of Apixaban in Subjects with Calf Vein Thrombosis

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Table of Contents

List of Abbreviations

AE	Adverse Event/Adverse Experience
CFR	Code of Federal Regulations
CRF	Case Report Form
DSMB	Data and Safety Monitoring Board
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's Brochure
IND	Investigational New Drug Application
IRB	Institutional Review Board
PHI	Protected Health Information
PI	Principal Investigator
SAE	Serious Adverse Event/Serious Adverse Experience
SOP	Standard Operating Procedure
cDVT	Calf deep vein thrombosis

Study Summary

Title	A Phase IV, Randomized, Double Blind Placebo controlled Study Evaluating the Safety and Efficacy of Apixaban in Subjects with Isolated Calf Vein Thrombosis
Running Title	Golden Calf Trial
Protocol Number	17-009022
Phase	Phase IV
Methodology	Single center, multi-Mayo site randomized, double blind, placebo-controlled, superiority clinical trial.
Overall Study Duration	36 months
Subject Participation Duration	Each individual will be in the study for 3 months
Single or Multi-Site	Single center, multi-Mayo site Trial
Objectives	There are two primary objectives. The first primary objective is to evaluate whether a strategy of active anticoagulation with apixaban is more efficacious than no anticoagulation (i.e., placebo) when monitored with serial ultrasound imaging in the management of patients with isolated calf vein thrombosis (DVT) for the composite endpoint consisting of prevention of thrombus propagation, pulmonary embolism, recurrent venous thromboembolic events, and all cause mortality. The second primary objective, safety, is to assess the combination of major and clinically relevant non-major bleeding for subjects randomized to apixaban vs. placebo control.
Number of Subjects	The number of patients needed is 250, or 125 in each of the two treatment arms.
Diagnosis and Main Inclusion Criteria	Patients will be recruited for study participation if they have a newly diagnosed venous thrombotic event (DVT) limited to the calf veins.
Study Product, Dose, Route, Regimen	Apixaban (10 mg twice daily for 7 days followed by 5 mg twice daily for 3 months) or matching placebo.
Duration of Administration	Total duration of drug administration will be for the duration of study participation 3 months.
Reference therapy	Serial clinical monitoring as is standard of practice with matching placebo. All patients will undergo serial ultrasound imaging at day 7, day 14, and day 90.
Primary Endpoint	Combined endpoint including thrombus propagation, pulmonary embolism, recurrent venous thromboembolism, and all cause mortality over three months.

Sample Size Estimation	An anticipated venous thromboembolic event rate of 10.0 to 12.6% within 3 months for patients randomized to standard medical observation and placebo is expected. We hypothesize the apixaban arm will result in a 3 month event rate of 1.0% to 2.3%. At an interim-analysis alpha level of 0.049 and events rates of 10% and 1.6% for placebo and apixaban, respectively, a sample size of 121/gp is required to achieve 80% power. To account for minor attrition over the course of the study, 125/gp or 250 total is planned for target enrollment.
Statistical Methodology	The primary outcome measure will be tested using a Cochran-Mantel-Haenszel chi-square with clinical site considered as a stratification variable. The pooled estimate of the odds ratio will be used as the primary measure of effect. The study is designed with an interim analysis with an information fraction of 40%. The O'Brien-Fleming alpha spending function will be used to provide control over the type I error rate.

1 Introduction

This document is a protocol for a human research study. This study will be carried out in accordance with the applicable United States government regulations and Mayo Clinic research policies and procedures.

Each year, between 300,000 to 600,000 individuals suffer an acute venous thromboembolic event (1-4). These events primarily involve the deep veins of the lower extremities (deep vein thrombosis, DVT) which may lead to embolization to the pulmonary arteries (pulmonary embolism, PE). Deep vein thrombosis of the lower extremity is divided into two categories depending on the proximal extent of thrombosis. Thrombi involving the popliteal, femoral and iliac veins are categorized together into "proximal DVT" largely due to their increased embolic potential. Indeed, the risk of embolization of proximal DVTs may be as high as 50% (3). Whereas the risk of mortality associated with a PE is high, prompt identification and treatment initiation with anticoagulants is a medical emergency. Both the evaluation and management of proximal DVT and PE has been well established by randomized controlled trial data (5).

In contrast, the management of venous thrombi limited to the calf veins is not well established (6). "Distal" deep vein thrombosis involve either the deep (posterior tibial, peroneal calf, and anterior tibial) or muscular (soleal and gastrocnemius) veins of the calf but do not extend into the popliteal veins. These "calf vein thrombi" (cDVT) are numerous and account for half of the DVT burden in a community setting (150,000 – 300,000 events annually in the United States) (7). While the likelihood of embolization is low, propagation of calf vein thrombi to the popliteal vein greatly augments the PE risk. Prevention of thrombus propagation can be readily accomplished with anticoagulation therapy however this therapy comes with a small risk of major hemorrhage (8). As such, management strategies vary considerably across sites with some investigators advocating conservative ultrasound surveillance without anticoagulation while others recommend full anticoagulant therapy for three months. There are few adequately powered randomized controlled trial data to guide management of these patients. The guidelines recommend serial ultrasound imaging for 2 weeks over anticoagulation therapy unless symptoms are severe or there are risk factors for thrombus extension (5). These guidelines are problematic for several reasons. First, the weight of the recommendation is based on expert opinion only (Grade 2C) and second, validated risk prediction tools for thrombus propagation do not exist (9). Current guidelines also suggest anticoagulation if the thrombus extends but remains confined to the distal veins (Grade 2C). There are little data to support this latter recommendation. Recently, the FDA has approved an oral direct factor Xa inhibitor, apixaban, which has been shown to be a highly effective anticoagulant for VTE (10). This agent has a particular advantage in that it is associated with very low bleeding rates making this anticoagulant particularly attractive for the treatment of cDVT.

We propose a phase IV, randomized, double blind placebo controlled study evaluating the safety and efficacy of apixaban compared to observation with serial ultrasound imaging alone in subjects with acute venous thrombosis limited to the calf veins. The primary objective is to evaluate whether a strategy of anticoagulation with apixaban is more effective than serial ultrasound imaging in the management of patients

with cDVT for the prevention of thrombus propagation, pulmonary embolism and recurrent venous thromboembolic events.

1.1 Background

Venous thromboembolism (VTE) represents a major cause of morbidity and mortality in the USA.(1–3) The incidence of VTE exceeds 1 per 1000 with as many as 600,000 first life-time cases diagnosed annually in this country. The 7 day mortality of patients suffering a thrombotic event is 25% and up to 35% of patients with pulmonary embolism (PE) die suddenly. Venous thromboembolism is therefore the fourth leading cause of death in Western society and the third leading cause of cardiovascular death behind myocardial infarction and stroke. Furthermore, VTE is both a recurrent disease and a morbid disease. Of those individuals surviving the thrombotic event, 30% will develop recurrent venous thromboembolism within 10 years and 20–30% will develop the post-phlebitic syndrome over this time period. VTE is typically a disease of elderly people, with the incidence of thrombotic events increasing significantly beyond age 60. As our population ages, the expected number of VTE annually will increase. Despite advances in radiographic detection, expanded knowledge of risk factors, and anticoagulant development, the incidence of VTE has been relatively constant over the past several decades.

Isolated cDVT accounts for nearly half of all DVTs occurring the United States each year (7). As such, as many as 300,000 cases annually require thoughtful management (1,7). And yet, there is very little high quality data to guide clinicians managing these patients. Indeed, the precise incidence of cDVT in the community is not well established. It is felt that the embolic potential of cDVT left untreated is low and embolization risk only increases with thrombus propagation to the popliteal vein or higher. The risk of proximal propagation if untreated ranges from 2 to 23% and likely varies by the clinical context (6). Cancer, recent surgery, hospital confinement, prior history of VTE and large thrombus size are said to be risk factors for thrombus propagation (5). These factors are derived from different cohorts and do not necessarily deserve the same weighting in a risk assessment strategy. A dedicated risk stratification tool would be immensely helpful to identify those individuals most likely to benefit from anticoagulation therapy however such a tool does not exist.

The RIETE VTE registry identified 1,921 patients with cDVT and compared the risk factors and natural history to 9,165 patients with proximal DVT (16). Of this cohort, 89% received anticoagulant therapy for at least 3 months. Patients with cDVT were significantly younger (65 vs. 70 years), more likely to occur in an inpatient setting (35% vs. 28%), more frequently post-operative (15% vs. 11%), more likely to occur following prolonged travel > 6 hours (3.4% vs. 1.9%) or in the setting of varicose veins (25.7% vs. 20.3%). In contrast, active cancer, pregnancy, and a prior history of VTE were significantly more common in patients with proximal DVT. At 3 months, VTE recurrence rates were similar for cDVT receiving anticoagulation compared to proximal DVT (2.0% vs. 2.7%, $P = 0.07$). Major bleeding (1.0% vs. 2.2%, $P < 0.01$), and mortality rates (2.7% vs. 7.5%; $P < 0.001$) were lower for cDVT patients. Furthermore, these investigators found that patients with isolated cDVT are more often associated with transient or reversible risk factors compared to proximal DVT.

CALTHRO was a natural history study to assess the hypothesis that it is safe to withhold anticoagulation in patients with cDVT (17). A total of 65 patients had cDVT managed without anticoagulants. For these patients, the 3 month event rate was 7.8% including PE, proximal DVT and recurrent cDVT. In summary, isolated cDVT may not be as benign as the guidelines would suggest particularly from the perspective of VTE recurrence (5).

Managing cDVT is therefore particularly challenging for a number of reasons. First, there are few community based epidemiology cohort studies to assess risk factors for cDVT. Second, there is a dearth of information regarding the natural history of this disease. Many studies combine deep veins and muscular veins together under the same category yet these veins are not anatomically similar and likely carry very different embolic and thrombotic propagation propensity. Third, there is a paucity of strong clinical trial data to help guide treatment decisions. Many of the prominent clinical trials excluded cDVT as an entry event. Disparity exists across institutions regarding management protocols. Indeed, many institutions don't mandate calf vein imaging as part of their ultrasound protocol. It is the practice in some clinicians to provide full anticoagulant therapy for patients with cDVT for three months. Other clinicians pursue serial imaging over 2 to 3 weeks and only provide anticoagulant therapy if there is evidence of thrombus propagation to the popliteal vein, embolization to the pulmonary vasculature or symptomatic recurrent venous thrombosis in other locations. Both camps would point to small studies to support their approach. The most appropriate strategy however remains unclear given the lack of strong data.

There have been 6 treatment trials of isolated cDVT (7,11-15). Trial sizes ranged from 32 to 259 patients with a total randomized in all six trials combined of 711 subjects (Table 1). Treatment varied from serial observation to full anticoagulation with warfarin. Treatment duration varied from 10 days to 3 months.

The CACTUS trial is the largest and most recent randomized trial to address this question (15). This was a multinational European trial with 23 participating centers from 3 countries. In this trial, 259 subjects with isolated cDVT were randomized to receive either subcutaneous Nadroparin 171 IU/kg/day or placebo for 42 days. The primary endpoints of the trial included cDVT extension, proximal DVT or PE. The primary safety endpoints were a combination of major plus clinically relevant non-major bleeding. Study endpoints were assessed at 42 and 90 days from enrollment. Venous thrombosis extension was assessed by compression ultrasonography at 3 – 7 days and at 42 days. At 90 days, subjects were contacted by telephone follow up. There was no difference in the primary efficacy outcome at 42 days (3% vs. 5%). At 90 days, the composite outcome was 3.3% in patients receiving LMWH compared to 6.6% for matching placebo (absolute risk difference -2.9%; 95% CI -8.7% to 2.8%; p value 0.28). There were 4% bleeding outcomes in subjects receiving LMWH however only one bleeding event was deemed a major bleed (0.8%). The investigators concluded that LMWH treatment for 42 days was not superior to placebo and resulted in excessive bleeding. There are a number of difficulties with this study which deserve notation (9). First, the slow enrollment of this trial implies strong selection bias. With 22 centers enrolling over 6 years, each center would have enrolled less than 2 patients per year. These investigators met only half of their anticipated enrollment of 572 subjects thus substantially reducing their power for identifying a difference between study arms.

Second, the exclusion criteria were likely too extreme. Patients were excluded from participating if they had a prior history of VTE, cancer, thrombocytopenia, chronic kidney disease, obesity/low body weight or NSAID use. Third, the safety endpoint included major bleeding plus clinically relevant non-major bleeding. The investigators concluded that the bleeding rate of 4% offset any benefits of thrombotic risk reduction however the safety outcome included only 1 patient with major bleeding (0.8%) which is a low and very acceptable rate for VTE treatment. If you compare the bleeding rate of 0.8% to the thrombotic rate of 6.6%, this would seem to be a reasonable tradeoff. In summary, the CACTUS trial provides important data however does not convincingly answer this question.

A trial by Schwarz et al. assessed consecutive patients with symptomatic cDVT limited to the muscular venous segments (soleal or gastrocnemius veins). (14) Exclusion criteria included peroneal or posterior tibial DVT, PE, prior cDVT, heparin induced thrombocytopenia, chronic kidney disease or active bleeding. These investigators assigned 109 patients to receive either Nadroparin 180 IU/kg/day for 10 days with compression hose or compression hose alone. The primary study endpoint was either thrombus propagation assessed by compression ultrasonography (day 3, day 10-12, 4 weeks and 3 months) or symptomatic PE. Two patients in each group were found to have thrombus propagation (3.78%). There were no PEs, major bleeds or deaths in either group. While helpful, these data have major limitations largely related to subject recruitment including low rate of active cancer (4.7%), exclusion of patients with posterior tibial or peroneal DVT, patient immobility (22%), and hospitalization (10.7%) thus limiting the applicability to real world clinical practice.

The ACT trial was a well done pilot, single-center study largely performed to establish study feasibility (7). From 2011 to 2012, these investigators enrolled 70 consecutive patients with calf DVT to receive either LMWH/warfarin or NSAID/paracetamol for 3 months. The primary endpoint of this study was thrombus propagation and PE. Ultrasound was performed at 7 days and 21 days with telephone follow up at 3 months. There were no thrombotic events for subjects randomized to LMWH/warfarin. For subjects randomized to NSAID/paracetamol, the composite event rate was 11.4% including 2.9% rate of PE. Due to small trial size, these differences did not reach statistical significance (p=0.11). There were no major bleeding events. The time in therapeutic range for those randomized to active treatment was 56%. While no firm conclusions can be drawn from this small study, the data is very useful for accrual calculations for a properly powered study. Furthermore, this study establishes feasibility for study recruitment in such a study in contrast to the slowly enrolling CACTUS trial.

Based on these treatment trials, guideline recommendations for patients with cDVT include a preference for serial ultrasound evaluation with observation over anticoagulation therapy in the absence of severe symptoms, active cancer, hospitalized status, prior history of VTE, unprovoked event, multiple venous involvement or large thrombus size (> 7 mm width and or > 5 cm length) or positive fibrin D-Dimer (5). This approach however has **several disadvantages.** **First**, if untreated patients participating in the randomized trials and cohort studies are combined, the anticipated event rate for untreated VTE is relatively high at 11.2% at 3 months (7,12,14,15,17). This includes a DVT propagation rate of 4.8%, PE rate of 1% and VTE recurrence rate of 5.4%. These event rates are high by comparison to patients with unprovoked

proximal DVT or PE. For unprovoked proximal DVT or PE, the event recurrence rate is approximately 8% at one year and 30% at 5 years. For these unprovoked VTE, there is universal agreement that continued anticoagulation therapy is indicated (Grade 1A) (5). If the latter deserves ongoing anticoagulant therapy then cDVT should deserve consideration for anticoagulant therapy as well. **Second**, the reason for avoiding anticoagulant therapy is said to be due to increased rate of major bleeding. In the CACTUS trial, this rate was acceptably low at 0.8% (15). In the trial by Ferarra et al, there were no major bleeding events despite enrollment confined to post-operative patients (13). **Third,** the post thrombotic syndrome following cDVT is said to be low however this has not been adequately studied and no firm conclusion can yet be established. **Fourth**, cDVT was specifically excluded from the recent large randomized trials of DOACs. **Fifth**, serial ultrasound does nothing for VTE prevention. Timing the interval to 7 days between studies may place the patient at considerable risk of thrombotic propagation and embolization which may prove to be a life threatening event. For these combined reasons, a prospective randomized trial of anticoagulant therapy compared to serial ultrasound imaging strategy is necessary and important. Given the vast number of patients suffering calf DVT each year in our society, establishing the most appropriate treatment strategy is paramount.

1.2 Investigational Agent

Apixaban (Eliquis) is an oral direct factor Xa inhibitor which impairs coagulation by inhibiting the conversion of prothrombin to thrombin. It does not require antithrombin for antithrombotic activity and inhibits both free and clot-bound FXa. Apixaban has a half-life of about 12 hours and thus is dosed twice-daily. Bioavailability is approximately 50%, for doses up to 10 mg, after oral dosing with maximum concentrations at 4 hours post ingestion. The pharmacokinetics are linear and plasma protein binding in humans is high at nearly 90% with a volume of distribution of approximately 20 liters. Apixaban is metabolized in the liver mainly via CYP3A4 pathway. Renal excretion accounts for about 27% of total clearance. Approximately 25% of the drug is eliminated in the feces. This drug is not dialyzable due to its high plasma protein binding (the systemic exposure of apixaban is 14% lower for patients on dialysis when compared to not on dialysis). Apixaban is currently FDA approved to reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation, for the treatment of DVT and PE, and for the reduction in the risk of recurrent DVT and PE following initial therapy and for the prophylaxis of deep vein thrombosis (DVT), which may lead to pulmonary embolism (PE), in patients who have undergone hip or knee replacement surgery.

1.3 Clinical Data to Date

The AMPLIFY investigators randomized 5,395 patients with acute VTE to either apixaban (10 mg twice daily for 7 days followed by 5 mg twice daily for 6 months) or enoxaparin/warfarin (10). From an efficacy standpoint, apixaban was deemed non-inferior to standard anticoagulant therapy. Both major bleeding and the composite of major plus non-major yet clinically relevant bleeding were significantly lower for patients receiving apixaban. The Amplify-Ext investigators randomized 2486 patients with VTE who had recently completed 6 – 12 months of anticoagulation to receive one of two

doses of apixaban or placebo for an additional 12 months. Both apixaban doses reduced recurrent VTE without increasing major bleeding compared to placebo (18).

Apixaban is a contender for first line therapy for cDVT for several reasons. **First,** the twice daily dosing of apixaban, although less convenient, may improve efficacy and safety. The peak levels are anticipated to be lower than once daily dosing thus decreasing potential bleeding. The trough levels are anticipated to be higher thus improving efficacy with continued presence of drug relative to once daily dosing. **Second,** the multiple routes of elimination are attractive particularly patients who may have mild renal or hepatic impairment. **Third,** apixaban has been shown to have extremely low rates of major bleeding. In patients with cDVT, the risk reduction of VTE propagation, embolization, or recurrence will more than offset the low bleeding rate.

1.4 Dose Rationale and Risk/Benefits

The AMPLIFY investigators compared apixaban (10 mg twice daily for 7 days followed by 5 mg twice daily for 6 months) to enoxaparin/warfarin in 5395 patients with acute VTE (10). At the 6 month follow-up, recurrent VTE occurred in 2.3% in the apixaban group compared to 2.7% in the enoxaparin/warfarin group, meeting the criteria for non-inferiority (relative risk 0.84 (95% CI 0.60-1.18; p<0.001). Similar outcomes were noted regardless of whether the initial event was a DVT or PE. Major bleeding occurred in 0.6% of the apixaban compared to 1.8% of the conventional-therapy group. The difference in major bleeding was superior for apixaban (relative risk 0.31 (95% CI, 0.17-0.55; P<0.001). The AMPLIFY-Ext investigators compared continued apixaban (2.5 mg or 5 mg, twice daily) with placebo in 2486 patients who had just completed 6 – 12 months of treatment for an acute VTE (18). Recurrent VTE or death from VTE was significantly lower in those patients assigned to either 2.5 mg (1.7%) or 5 mg (1.7%) twice daily apixaban compared to placebo (8.8%). Major bleeding rates were similarly low for apixaban 2.5 mg (0.2%), apixaban 5 mg (0.1%) and placebo (0.5%). Based on these data from the AMPLIFY trials, apixaban 10 mg twice daily for 7 days followed by 5 mg twice daily will be the dosing prescribed.

2 Study Objectives

Primary Objective: There are two primary objectives. First, the primary efficacy outcome is to evaluate whether a strategy of active anticoagulation with apixaban is more effective than serial ultrasound imaging in the management of patients with isolated calf vein thrombosis (cDVT) for the prevention of the composite outcome including thrombus propagation, pulmonary embolism, recurrent venous thromboembolic events, and all-cause mortality.

Second, the principal safety outcome is to assess the combination of major and clinically relevant non-major bleeding for subjects randomized to apixaban vs. placebo control.

Secondary Objective: There will be two secondary objectives.

The first is to assess the timing of thrombus propagation. The current understanding of thrombus propagation is that if it occurs, it will occur within the first 2 weeks of

diagnosis. This concept of timing of thrombus propagation is the basis for current guideline endorsed approach which limits the requirement for repeated ultrasound up to 2 weeks only. Yet, this guideline recommendation has not been validated. Our study is poised to verify this assumption.

The second is to determine net clinical benefit or harm for the two strategies. The outcome of net clinical benefit or harm will be assessed as the composite of the primary efficacy outcome or the principal safety outcome up to day 90.

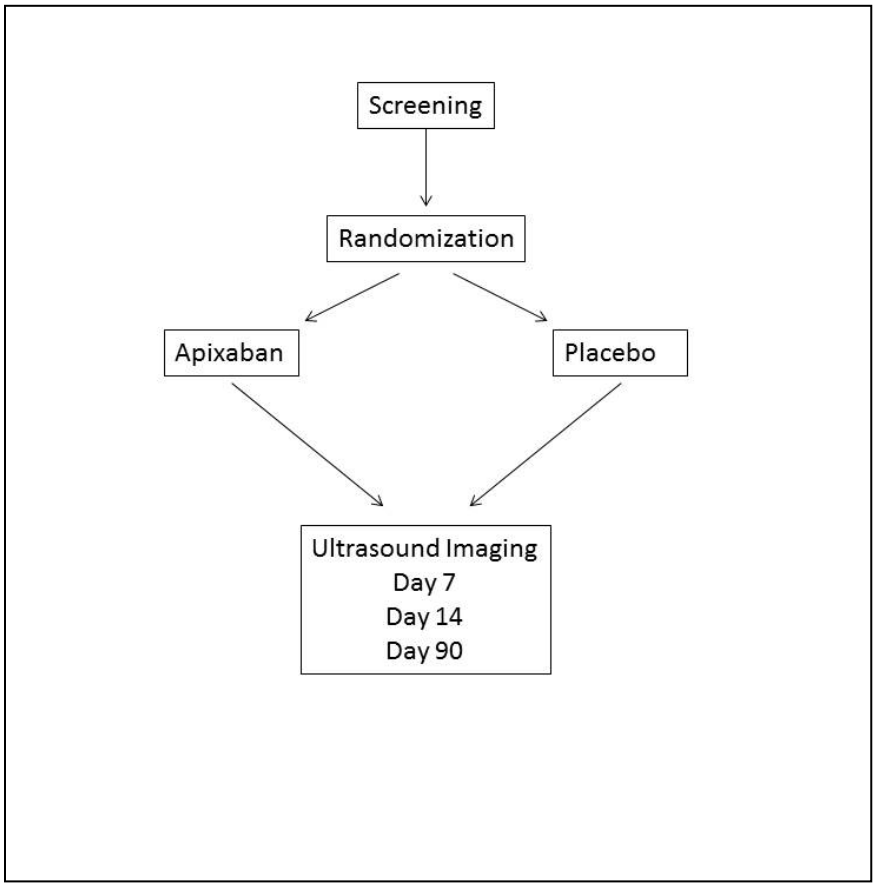
3 Study Design

3.1 General Design

This is a Single center, multi-Mayo site, randomized, double-blind, placebo-controlled, superiority clinical trial. Major bleeding and clinically relevant non-major bleeding will also be evaluated. Subjects will be screened at both outpatient clinic visit appointments or during hospitalization using direct referrals or by daily automated electronic screening of vascular radiology ultrasound and computed tomography reports. The baseline ultrasound will be clinical indicated, obtained for this purpose, and will be carefully reviewed by study personnel. Interested qualified subjects will be consented and offered participation in this trial. Pre-randomization anticoagulation treatment for cDVT is allowed up to a maximum of 72 hours. After randomization, patients allocated to apixaban will receive 10 mg twice daily for 7 days, followed by 5 mg twice daily for 3 months. Patients allocated to placebo control will receive twice daily matching placebo tablets in a similar fashion. All patients will undergo serial ultrasound imaging at 7 days, 14 days and 90 days. Patients developing symptomatic DVT or PE will be evaluated by cross-sectional imaging (ultrasound or computed tomography (CTA)) appropriate for their symptom assessment as part of their standard care. Allocation to treatment will be done centrally. Once consent has been obtained, clinically indicated baseline laboratory values will be confirmed (drawn within past 4 weeks) and subjects will begin treatment and follow-up for 3 months.

The primary composite efficacy endpoint of this study will be a composite of thrombus propagation, pulmonary embolism (PE), symptomatic VTE recurrence including recurrent DVT, PE or all cause fatality. The primary safety outcome will be major bleeding and clinically relevant non-major bleeding (ISTH criteria; 21). All suspected recurrent VTE, deaths, as well as all episodes of bleeding and vascular events will be evaluated by a central, blinded, independent adjudication committee. Adjudication results will be the basis for the final analyses.

There will be two secondary endpoints. The first will assess the timing of thrombus propagation relative to the original date of diagnosis for those individuals who experience a thrombus propagation. The second will be an assessment of net clinical benefit or harm assessed as the composite of the primary efficacy outcome or the principal safety outcome up to day 90.



3.2 Primary Study Endpoints

The primary composite efficacy endpoint of this study will include thrombus propagation either within the calf veins or into proximal deep veins (popliteal, femoral or iliac veins), symptomatic or incidental VTE recurrence or all-cause mortality by day 90. The following criteria will be used to confirm and categorize an outcome VTE event:

1. **Thrombus propagation:** The original calf DVT must be confirmed by either duplex ultrasonography, venography, CT, or MRI. All patients will then undergo serial ultrasound imaging at 7 days, 14 days and 90 days. Propagation is defined by two criteria: (1) when a thrombus previously confined to the calf veins is found to extend into a proximal vein including popliteal, femoral or iliac veins of the ipsilateral limb or (2) if the thrombus extends but remains confined to the calf veins. The thrombus propagation must be confirmed by comparing the new imaging with previous imaging clearly showing extension into a proximal vein not seen on the original imaging study. Thrombus propagation that remains confined to the calf veins must extend beyond 5 cm of the previous thrombus length, extend into a new venous segment (upper, mid, or lower), or involve a new vein (not previously involved) within the calf (example, the original involvement was

confined to the posterior tibial vein and now there is new involvement of the gastrocnemius vein.)

2. **Recurrent DVT:** A recurrent DVT must be distinguished from the original thrombus by comparing serial imaging modalities. In order to be classified as a recurrent event, there must be new filling defects evident on the second study not appreciated on the original images or an interval study clearly showing thrombus resolution.
3. **PE:** Symptomatic pulmonary emboli must be confirmed by either CT, MR or conventional pulmonary angiography or VQ perfusion imaging.
4. **Incidental VTE recurrence:** It is anticipated that recurrent venous thrombosis or thrombus propagation may be identified incidentally (without new or changing symptoms). In order to be classified as an event, the thrombus in question must be confirmed by cross sectional imaging (duplex ultrasonography, venography, CT, MRI or VQ).
5. **All-cause mortality**

3.3 Safety Endpoints

The primary safety endpoints will include the major bleeding and clinically relevant non-major bleeding. This will include any episode of major bleeding including fatal bleeding or any episode of clinically relevant non-major bleeding. The following criteria will be used to confirm and categorize a bleeding episode:

1. **Major bleeding:** Major bleeding is defined as overt bleeding plus a hemoglobin decrease of ≥ 2 g/dL or transfusion of ≥ 2 units of packed red blood cells, or bleeding at a critical site: intracranial, intraspinal, intraocular, retroperitoneal, pericardial intra-articular, intramuscular with compartment syndrome, or fatal bleeding.
2. **Clinically relevant non-major bleeding:** Clinically relevant non-major bleeding is defined as any overt, actionable sign of hemorrhage meeting at least one of the following criteria: (i) requiring nonsurgical, medical intervention by a healthcare professional, (ii) leading to hospitalization or increased level of care, or (iii) prompting evaluation.
3. **Minor bleeding:** Minor bleeding is defined as overt bleeding that did not meet criteria for major bleeding.

All suspected recurrent VTE, deaths, as well as all episodes of bleeding and vascular events will be evaluated by a central, blinded, independent adjudication committee. Adjudication results will be the basis for the final analyses.

3.4 Secondary Endpoints

The first secondary endpoint will be to establish the timing of thrombus propagation for those individuals who have suffered such an event. The date of thrombus propagation confirmation will be compared to the date of the original DVT diagnosis for this purpose.

The second secondary outcome will include an assessment of net clinical benefit or harm as the composite of the primary efficacy outcome or the principal safety outcome up to day 90.

4 Subject Selection Enrollment and Withdrawal

4.1 Inclusion Criteria

1. Age range: ≥ 18 years
2. Both males and females
3. Confirmed acute calf vein thrombosis confined to either the deep (posterior tibial, anterior tibial, or peroneal) or muscular (gastrocnemius or soleal) veins.
4. Negative serum or urine pregnancy test done (within 2 weeks) prior to randomization, for women of childbearing potential only. Note: A Women of childbearing potential (WOCBP) is defined as any female who has experienced menarche and who has not undergone surgical sterilization (hysterectomy or bilateral oophorectomy) and is not postmenopausal. Menopause is defined as 12 months of amenorrhea in a woman over age 45 years in the absence of other biological or physiological causes.
5. Ability to provide written informed consent.

4.2 Exclusion Criteria

1. Any of the following because this study involves an investigational agent whose genotoxic, mutagenic and teratogenic effects on the developing fetus and newborn are unknown:
   - Pregnant women
   - Nursing women
   - Men or women of childbearing potential who are unwilling to employ adequate contraception

   Note: Women of child bearing potential must agree to follow instructions for method(s) of contraception for the duration of treatment with study drug(s) plus 33 days after finishing the last dose.

   Males who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception for the duration of treatment with study drug(s) plus 93 days after finishing the last dose.

   Azoospermic males and WOCBP who are continuously not heterosexually active are exempt from contraceptive requirements. However they must still undergo pregnancy testing as described in this section.

   Note: Investigators shall counsel WOCBP and male subjects who are sexually active with WOCBP on the importance of pregnancy prevention and the implications of an unexpected pregnancy Investigators shall advise WOCBP and male subjects who are sexually active with WOCBP on the use of highly effective

methods of contraception. Highly effective methods of contraception have a failure rate of < 1% when used consistently and correctly.

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

HIGHLY EFFECTIVE METHODS OF CONTRACEPTION

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

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

2. Acute co-existing proximal DVT (popliteal, femoral, iliac veins or IVC), pulmonary embolism, splanchnic vein thrombosis, cerebral venous sinus thrombosis within the past 3 months for whom anticoagulation therapy is indicated.
3. Age < 18 years.
4. Continuous treatment with therapeutic anticoagulant for more than 72 hours pre-randomization.
5. Contraindication to anticoagulant therapy
6. Significant kidney disease. Creatinine clearance < 25 ml/min using the Cockcroft-Gault equation: GFR = (140-age) * (Wt in kg) * (0.85 if female) / (72 * Cr). (within last four weeks)
7. Significant liver disease (e.g. acute hepatitis, chronic active hepatitis, cirrhosis) or ALT (or AST) > 3 x ULN. (within last four weeks)
8. Platelet count < 50 $x10^9$/L.(within last four weeks)
9. Life expectancy < 12 months.
10. Current active bleeding.
11. Concomitant use of strong CYP3A4 inhibitors (e.g., HIV protease inhibitors, systemic ketoconazole) or strong CYP 3A4 inducers like rifampicin.
12. Active cancer defined as any evidence of cancer on cross-sectional imaging or cancer treatments within the past 6 months (chemotherapy, radiation therapy or cancer related surgery).
13. Anticipated need for urgent/emergent surgery or major invasive procedure.

14. Dual antiplatelet therapy (thienopyridine plus aspirin) and/or aspirin greater than 165 mg while on study medication.

4.3 Subject Recruitment, Enrollment and Screening

This is a multi-Mayo center, randomized, double blind, placebo controlled, superiority trial for efficacy. Experienced data management personnel enroll patients, collect clinical trial data and ensure quality control. Patient registration occurs using centralized registration and randomization systems to ensure patient eligibility. The Research Radiology Core provides radiological image management including a centralized system of image collection, archiving and review for clinical studies. The Research Pharmacy Core offers a central pharmacy service, along with quality-control systems for medication order fulfillment, shipment and reconciliation.

Patients will be recruited from two potential sources, hospital in-patients and out-patients attending anticoagulation clinics at one of three sites: Mayo Clinic Rochester, Mayo Clinic Eau Claire, or Mayo Clinic La Crosse. Upon subject identification, the study will be explained in detail by the investigators or study coordinator, the consent form reviewed, questions answered, and the consent form signed.

4.3.1 Recruitment of Patients

We anticipate that a sizable percentage of patients will be recruited from Mayo Clinic Rochester. Patients will be recruited from Mayo Clinic Rochester, Mayo Clinic Eau Claire, or Mayo Clinic La Crosse.

4.4 Early Withdrawal of Subjects

4.4.1 Study Endpoint Achieved

A small percentage of patients will meet either a thrombotic or bleeding outcome event as part of trial participation. These outcomes may be clinically symptomatic or may be identified as part of either the serial ultrasound imaging protocol or cross-sectional imaging obtained for other clinically indicated conditions.

1. **Thrombotic endpoint:**

a. If the patient suffers a symptomatic or asymptomatic thrombotic recurrence which is confirmed by cross-sectional imaging, then the study medication should be discontinued and the patient should be initiated on an alternate therapeutic anticoagulant based on guideline recommendations. Alternate anticoagulants could include enoxaparin/warfarin, rivaroxaban, edoxaban or dabigratran.

b. If the serial ultrasound imaging clearly identifies thrombus propagation which remains confined to the calf veins, then the study medication should be discontinued and the patient should be initiated on an alternate therapeutic anticoagulant based on guideline recommendations.

c. During normal business hours, the patient may be unblinded by contacting the Central Office (see page 1 of protocol). The Central Office will seek approval from the PI or a delegated Investigator prior to unblinding. During emergency circumstances where patient safety is felt to be compromised, study allocation can

be rapidly determined by drawing a heparin antiXa activity measure. If the patient is allocated to apixaban, the level will be elevated, unless they are not taking their medication. For patients allocated to placebo the levels will be undetectable. The unblinding site must notify the central office of the unblinding event within 72 hours of becoming aware.

2. **Hemorrhagic endpoint:**

a. Non-major Clinically Relevant Bleed: If the patient suffers a non-major clinically relevant bleed, then the study medication should be temporarily discontinued until the site and circumstances of the bleeding event have been evaluated. If these circumstances can be rectified, then the patient can remain on the study medication which will be restarted as soon as clinically indicated.

b. Major Bleed: If the patient suffers a major bleed, then the study medication should be discontinued and the patient cared for as clinically appropriate. Under these circumstances, the patient will be unblinded to determine the specific study medication (apixaban or matching placebo) by contacting the Central Office (see page 1 of protocol). During emergency circumstances where patient safety is felt to be compromised, study allocation can be rapidly determined by drawing a heparin antiXa activity measure. If the patient is allocated to apixaban, the level will be elevated, unless they are not taking their medication. For patients allocated to placebo the levels will be undetectable. The unblinding site must notify the central office of the unblinding event within 72 hours of becoming aware. Whether to restart an alternative anticoagulant will be left at the discretion of the medical care provider attending the patient.

c. Life-threatening Bleed: If the patient suffers a life-threatening bleed, then the study medication should be discontinued and the patient cared for as clinically appropriate. During emergency circumstances where patient safety is felt to be compromised, study allocation can be rapidly determined by drawing a heparin antiXa activity measure. If the patient is allocated to apixaban, the level will be elevated, unless they are not taking their medication. For patients allocated to placebo the levels will be undetectable. The unblinding site must notify the central office of the unblinding event within 72 hours of becoming aware. During normal business hours, the patient may be unblinded by contacting the Central Office (see page 1 of protocol).Treatment may include the use of prothrombin complex concentrates (K-Centra) depending on which study medication the subject was receiving (apixaban or placebo). Once the specific antidote for direct oral factor Xa inhibitors, andexanet alpha, has been FDA approved, the use of this medicine would also be appropriate.

4.4.2 When and How to Withdraw Subjects

Conditions under which a subject may be withdrawn from the study prior to that subject completing all of the study related procedures may include:

1. Subject safety issues:
    a. Major bleeding including life threatening bleeding. For patients suffering a major bleed, the clinical scenario will be reviewed by the primary care provider caring for the patient to determine study drug termination. The site or overall investigators can also assist with this decision making.
    b. Thromboembolic Event. For patients suffering a thromboembolic event, study drug should be discontinued and an alternative anticoagulant initiated by the health care provider caring for the patient.
2. Failure of subject to adhere to protocol requirements.
3. Thrombocytopenia. For platelet counts below 50 $x10^9$/L, the patient will be excluded from continued participation.
4. Development of severe renal impairment (creatinine clearance < 25 ml/min). Renal function assessment will not be followed for the purposes of this study but only if clinically indicated.
5. Development of severe hepatic impairment (LFTs > 3x ULN). Liver function assessment will not be followed for the purposes of this study but only if clinically indicated.
6. Subject decision to withdraw from the study (withdrawal of consent)

4.4.3 Data Collection and Follow-up for Withdrawn Subjects

For subjects withdrawn from the study, follow-up data will be collected throughout the protocol defined follow-up period. This is regardless of compliance or tolerance with study medication, provided participants are willing to provide follow up examinations. This data is important to the integrity of the final study analysis since early withdrawal could be related to the safety profile of apixaban. If a subject withdraws consent to participate in the study, for subject safety reasons, attempts will be made to obtain permission to collect follow up information, whenever possible.

5 Study Drug

5.1 Description

Apixaban, an oral factor Xa inhibitor, will be provided as a 5 mg tablet or matching placebo.

5.2 Treatment Regimen

Patients randomized to apixaban will be treated with 10 mg twice daily for 7 days followed by 5 mg twice daily for 3 months. Patients assigned to matching placebo will take their tablets in a similar fashion.

5.3 Ultrasound surveillance

Following the initial diagnostic duplex ultrasound establishing the presence of a calf vein thrombosis, all subjects, regardless of randomization, will undergo serial follow

up venous ultrasound imaging of the original involved lower extremity at 7 days, 14 days and 3 months. All images will be compared to the original study by a radiologist dedicated to the ultrasound practice but blinded to treatment allocation. The standard ultrasound imaging protocol used for clinical DVT assessment will be used for this study without modification. The patient will be positioned supine with slight reversed Trendelenburg (10°) on the examination table with the hip externally rotated and the knee slightly flexed in an outward position ("Frog leg" posture). A linear ultrasound probe adjusted to the LEV setting at 9MHz will be optimized to depth, gain and focal zone. Venous imaging will begin at the common femoral vein and continued throughout the leg and foreleg to the calf veins carefully assessing each deep venous segment. The great saphenous vein is also imaged in this manner however an extension of thrombus into this superficial vein will not be included as an efficacy endpoint. Image acquisition will include grey scale cross-sectional imaging of each venous segment with and without compression. Color imaging will be included for each venous segment to confirm patency. Once the calf DVT is identified, both the distal and proximal most extent of the thrombus will be marked on the skin using a skin pen. The thrombus length will then be measured and recorded by measuring the distance from the distal to the proximal skin mark. For those patients with multiple calf vein involvement, the length of each thrombus should be measured and recorded. Images will be compared side by side with the archived original study to determine whether thrombus propagation has occurred. All images will be interpreted by a radiologist with expertise and dedication to vascular ultrasound but blinded to treatment allocation. All images will be archived in our PACs system.

5.4 Method for Assigning Subjects to Treatment Groups

In general, the patient should be randomized as soon as possible after the baseline evaluation is completed. Randomization should be completed and study drug started on the day of evaluation.

5.4.1 Stratification

Prior to randomization, subjects will be stratified on thrombotic risk based on the presence of one or more of the following characteristics: deep vs. muscular venous thrombosis, postoperative status, and single vs. multiple venous segment involvement.

5.4.2 Central Automated Randomization

Subjects will be randomized in 1:1 ratio to either apixaban group or placebo group. The randomization scheme will be generated by the study statistician.

5.5 Preparation and Administration of Study Drug

Drug (apixaban or matching placebo) will be stored and distributed from McKesson to each of the 3 study sites. This study uses a double blind design. Specifically, McKesson will pre-package the doses of either apixaban or matching placebo into bottles labeled with assigned bottle numbers, and then dispense a three month supply of the drug to the Mayo Clinic Pharmacy at each study site.

Upon randomization, the Mayo Clinic Pharmacy (MCP) at each site will be informed of the subject's allocation. The MCP pharmacist will then dispense the drug (apixaban or matching placebo) according to randomized assigned bottle number in a three month's supply (200 tablets/bottle). The study coordinator will then go to MCP, retrieve the drug and hand it to the patient. The first dose will be given to the patient immediately upon receiving the medication. Three month's supply will be provided to the patient.

For the initial 7 days, subjects will take 2 tablets (apixaban or matching placebo) twice daily (total of 4 tablets per day). Thereafter patients will take one tablet twice daily (apixaban 5 mg or matching placebo). Drug labeling will be according to national law and GMP ruling Annex 13.19. Active study drug and placebo will be stored at 15-25°C (59-77°F).

Subject Compliance Monitoring

Study medication should be used in accordance with the protocol, under the responsibility of the investigator. The research pharmacist or any authorized person should maintain a complete and accurate record of the receipt of all study medication supplied to the site by McKesson. These records should include dates of receipt, batches and quantities received. The sponsor will provide bulk drug supply to McKesson. McKesson will then package "open label" stock drug in bottles containing 200 tablets of either apixaban or matching placebo. Upon request, each site will then be supplied with open label drug in bottles. Upon receipt of drug from McKesson, each Mayo Clinic Pharmacy site will coordinate the randomization received by the statistician and label the bottle and dispense blinded prescription bottle to study coordinator. The study coordinator will then disperse drug to the subject.

Sites will be supplied enough study drug to complete half of their assigned recruitment target. Recruitment targets are as follows: Rochester (150 patients), La Crosse (50 patients), Eau Claire (50 patients). Once each site is nearing half of their recruitment target, then they will request additional drug from McKesson. This shipment plan will help to redistribute available drug to the sites most actively recruiting.

Record keeping at each site MCP will include subject number, the date, quantity and batch numbers of the dispensed and returned medication and the dispenser. All non-dispensed medication supplied to the site by McKesson should be kept securely in the original containers in a designated locked container until retrieved/dispensed.

Subjects should be instructed to return all used, partially used, or unused medication packaging to the site.

A log should be kept by subject number, of the date, quantity, and batch numbers returned (the dispensing and the return log may be combined). For medication supplied to the site by McKesson, the total amount of medication used and unused should equal the amount received, any discrepancies should be explained in writing. All unused medication will be destroyed and records of shipment/receipt and or destruction will be maintained.

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

5.6 Prior and Concomitant Therapy

Non-steroid anti-inflammatory drugs (NSAIDs) and antiplatelet agents are discouraged. However, if indicated, aspirin up to a dosage of 165 mg/day will be allowed. Dual antiplatelet therapy (P2Y12 inhibitor plus aspirin) and/or aspirin greater than 165 mg are not permitted.

5.7 Packaging

Apixaban (5 mg tablet strength or matching placebo control) will be provided in a HDPE-bottle containing 200 tablets to complete a total of 3 months of therapy.

5.8 Blinding of Study

This is a double blind placebo controlled study.

5.8.1 Receipt of Drug Supplies

The BMS/Pfizer will provide bulk drug supply to McKesson. McKesson will then package drug pre-labeled by assigned randomization bottle numbers in bottles containing 200 tablets of either apixaban or matching placebo to each site. Upon request, each site will then be supplied with drug in bottles, along with a shipment manifest of the total bottle numbers dispensed. Upon receipt of drug from McKesson, each Mayo Clinic Pharmacy site will coordinate the dispensing of the blinded randomized treatment to study coordinator. Upon receipt of the study treatment supplies, an inventory must be performed and a drug receipt log filled out by the person accepting the shipment at MCP. The designated study staff will count and verify that the shipment contains all the items noted in the shipping invoice. Any discrepancies, damaged or unusable study drug in a given shipment (active drug or comparator) will be documented in the study files. The sponsor-investigator will be notified immediately of any discrepancies, damaged or unusable products that are received. Delegated unblinded study staff will have access to the randomization key. Through use of a Mayo licensed randomization software, the bottle numbers will be assigned to the designated site at the time of randomization using the stratification outlined in 5.4.1.

5.8.2 Storage

Apixaban (and matching placebo control) will be stored at MCRP 15-25°C (59-77°F).

5.8.3 Dispensing of Study Drug

Upon randomization, the MCP will be informed of the subject's allocation. The MCP research pharmacist will then assemble the drug in a three month's supply. The study coordinator will then go to MCP, retrieve the drug and hand it to the patient. The first dose will be given to the patient immediately upon receiving the medication. Apixaban 5 mg (or matching placebo) will be provided in a HDPE-bottle containing 200 tablets.

Regular study drug reconciliation should be performed to document drug assigned, drug dispensed, drug returns, and drug remaining. This reconciliation should be logged on the drug reconciliation form, and signed and dated by the study team.

5.8.4 Return or Destruction of Study Drug

At the completion of the study, there will be a final reconciliation of drug shipped, drug dispensed, drug returns, and drug remaining. This reconciliation will be logged on the drug reconciliation form, signed and dated. Any discrepancies noted will be documented and investigated, prior to return or destruction of unused study drug. Drug destroyed on site will be documented in the study files.

6 Study Procedures

6.1 Visit 1 (day 0)

At the time of the initial assessment (Randomization visit, day 0 on the flow chart), the complete history and physical examination performed by the health care provider attending the patient will be recorded by the enrolling study personnel. Recent baseline laboratory data (collected within 4 weeks) will include complete blood counts (CBC), creatinine, and ALT (or AST). The creatinine clearance will be calculated using the method of Cockcroft and Gault:

Cockcroft-Gault GFR = (140-age) * (Wt in kg) * (0.85 if female) / (72 * Cr)

These laboratory values must be current within 4 weeks of this initial encounter.

6.2 Surveillance and Follow up.

Following randomization, subjects will be assigned to either active treatment with apixaban or placebo control for a total of 90 days. Each subject will then undergo follow up ultrasound imaging at 7 days (+/- 2 days), 14 days (+/- 2 days) and 90 days (+/- 7 days). This ultrasound imaging study will focus on venous thrombus propagation into the proximal venous segments. At each follow up, all venous segments of the involved lower extremity will be imaged. This imaging should be performed at a site participating in this research project. Patients will be called at Days 30 & 60 (+/- 7 days) to check their health status, adverse reactions and medication compliance.

Patients will be instructed to report to the clinic immediately if they had any bleeding or symptoms of recurrent deep-vein thrombosis, pulmonary embolism, or both. All suspected episodes of recurrent thrombosis will be investigated with the use of objective tests, according to prespecified diagnostic algorithms. At 3 months (+/- 7 days), patients will return for a routine clinically indicated ultrasound and clinical assessment.

Study Activity	Day 0	Day 7 (± 2 days)	Day 14 (± 2 days)	Day 30 (± 7 days)	Day 60 (± 7 days)	Day 90 (± 7 days)
Informed consent	X					
History	X					
Concurrent meds	X	X	X	X	X	X

Collect data from clinical physical exam (Ht, Wt, BSA, VS)	X					
Collect Lab Values (CBC, creatinine, ALT/AST)[a]	X[a]					
Adverse event evaluation		X	X	X	X	X
B-HCG	X[b]					
Drug dispensing and collection of any unused drug	X					X
Ultrasound[c]	X	X	X			X
Telephone survey (appendix A)				X	X	

a = Collect data from clinical testing in the last 4 weeks.
b = Women of child bearing potential only. If not done clinically in the last 2 weeks.
c = The baseline ultrasound will be requested and performed by the provider caring for the patient. This will be a clinically indicated study and will not be repeated for study purposes. This US will serve as the baseline imaging study for trial purposes.

7 Statistical Considerations

7.1 Sample Size Determination

An anticipated venous thromboembolic event rate of 12.6% within 3 months for patients randomized to standard medical observation and placeo is expected (Table Below). The composite venous thrombosis event rate of 12.6% includes a thrombus propagation rate of 5.4%, pulmonary embolism rate of 0.5% and recurrent venous thrombosis rate of 6.7% over this time interval. Specifically, for sample size calculations, we consider an ***event rate of 10% for the placebo arm***. By comparison, thromboembolic outcomes in the AMPLIFY trial for those subjects randomized to apixaban was 2.3% at 6 months. We hypothesize the apixaban arm in this study will result in a 3 month event rate in the range of 1.0% to 2.3%. Specifically, for sample size calculations, we consider an ***event rate of 1.6% for the apixaban arm***.

Trial	n	Population	Treatment	Follow up Duration	Propagation	PE	VTE Recurrence	Major Bleed
Hull[11]	32	All comers	Warfarin UFH 5000 BID	3 mo		0 0	0 0	
Lagerstedt[12]	51	Inpatient	Warfarin Placebo	3 mo		0 3.6%	0 29%	8.7% 0
Ferrara[13]	192	Post op	LMWH/Warf Single vein multiple vein	 6 wk 3 mo 6 wk 3 mo	 14% 9% 35% 10%	 0 0 1.6% 1.6%		 0 0 0 0
Schwarz[14]	107	All comers	LMWH x 10d Placebo	3 mo	3.8% 3.8%	0 0		0 0
Horner[7]	70	All comers	LMH/Warf NSAIDs	3 mo	0 8.6%	0 2.9%		0 0
Righini[15]	259	All comers	LMH x 42d Placebo	3 mo	1.6% 5.3%	1.6% 0	0 4%	0.8% 0

The detailed listing of assumptions used to estimate the sample size are as follows:

- 3 month thromboembolic outcomes for the placebo arm = 10.0%
- 3 month thromboembolic outcomes for the apixaban arm = 1.6%
- Equal allocation to both treatment groups

- One interim analysis using O'Brien-Flemming-like alpha spending function conducted after 40% of the enrolled participants have their 90 day outcome assessed (40% information fraction)
- An overall two-sided significance level of 0.05 with a final adjusted alpha of 0.0492 (after interim analysis correction)
- Target power = 80%
- Normal approximation to the proportions, two independent groups, no continuity correction

Based on the assumptions above, a sample size of 121 per arm would be required. We round this estimate to 125/group (250 total) to account for minor attrition to the intention to treat analysis set including subject dropout and missing data.

7.2 Statistical Methods

7.2.1 Primary Hypothesis:

We hypothesize that apixaban 5 mg twice daily is associated with a significantly lower rate of the primary composite efficacy outcome compared to matched placebo in patients with calf DVT.

7.2.1.2 Primary Efficacy Analysis: All patients randomized to receive at least one dose of apixaban 5 mg or matching placebo control will be included in the primary analysis under intention to treat (see analysis sets below). The analysis of the primary composite endpoint will only include events occurring during the 3 months of study medication use.

Frequency of the primary composite efficacy endpoint will be tabulated by treatment arm without regard to the time the event was observed within the 3 month study period. The Cochran-Mantel-Haenszel test will be used to compare the event rates by treatment group. The pooled estimate of the odds ratio will be used as the primary measure of association for the study.

An exploratory analysis will investigate the time to event is defined as the time from randomization to the first occurrence of a primary composite efficacy outcome event. Patients who were lost to follow-up or who withdrew consent before the end of the three month treatment period will be censored at the last day the patient had a complete assessment for study outcomes within the 3 month study period. The incidence curves of VTE events will be plotted using the Kaplan-Meier estimator by treatment group. The difference in the incidences of the primary composite outcome at 3 months between treatment arms will be estimated and tested using a normal approximation of the binomial distribution.

7.2.1.3 Safety Analysis: All patients who received at least one dose of study medication will be included in the safety analysis. The analysis of major bleeding and clinically relevant non-major bleeding events will include those events which occurred during the 3 month study period. Major bleeding events observed later will be described separately.

Frequency of major bleeding and clinically relevant non-major bleeding will be tabulated by treatment arm. The incidence of major bleeding and clinically relevant non-major bleeding will be summarized as a combined endpoint and separate endpoints by treatment arm. The difference in the incidences of the combined endpoint at 3 months between treatment arms will be estimated and tested using a normal approximation of the binomial distribution.

The outcome of net clinical benefit or harm will be assessed as the composite of the primary efficacy outcome or the principal safety outcome up to day 90. The difference in the incidences of the combined endpoint at 3 months between treatment arms will be estimated and tested using a normal approximation of the binomial distribution. All tests will be conducted at the two-sided 0.05 significance level.

Multiplicity

No correction to the type I error rate will be applied to account for the primary and secondary endpoints. Accordingly, all analyses will utilize a two-sided alpha=0.05 level of significance with exception of the primary analysis. For the primary analysis, the final alpha level will be determined by the alpha spending function as defined in the following section.

Interim Analysis

A partially blinded interim analysis will be conducted when 40% of the planned participants complete the 90 day outcome assessment (i.e., after the 100th participant completes the 90 day outcome). The O'Brien-Fleming-like alpha spending function will be used to determine the final alpha level. At time of study planning, 40% information fraction results in an interim stopping p-value of <0.00079. This value may vary slightly depending on the final data included in interim analysis. For partial blinding, the actual treatment codes will be replaced by generic "Treatment A" and "Treatment B" labels by the unblinded statistician for the DSMB's review. In the event a full unblinding of the study is desired, the DSMB will be able to request the actual treatment assignments from the unblinded study statistician.

7.3 Subject Population(s) for Analysis

The subject populations whose data will be subjected to the study analysis both for the primary efficacy and safety analyses will include all randomized population under the intention to treat principle. Any subject randomized into the study, regardless of whether they received study drug will be included in the primary efficacy analysis provided the participant does not withdraw consent for use of any data collected in the course of the study or as otherwise required by institutional review board determination.

The per protocol analysis set will also be utilized for exploratory analyses. For this analysis, the participant will be expected to have obtained all outcome measurements over the 90 days along with >80% compliance with medication. Furthermore, the participant will need to not have a three day period (6 half-lives of apixaban) with no study medication. We will also perform a “full analysis set” and an “on-treatment” analysis for the study outcomes. For the purpose of this study, the full analysis set will be determined in accordance with ICH E9 guidelines. The on-treatment analysis data set will include subjects who are randomized to study and take at least one dose of study medication.

8 Safety and Adverse Events

8.1 Definitions

1. Adverse Events. 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). The casual relationship can be one of the following:

Related: There is a reasonable causal relationship between study drug administration and the AE.

Not related: There is not a reasonable causal relationship between study drug administration and the AE.

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

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.)

2. Serious Adverse Events. Serious Adverse Event (SAE) is any untoward medical occurrence; 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, adverse events of special interest, 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 (eg, death is an endpoint, if death occurred due to anaphylaxis, anaphylaxis must be reported).

The following hospitalizations are not considered SAEs in BMS clinical studies: 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).

3. Adverse Events of Special Interest. In this study, the following adverse events are to be reported to BMS as serious events, 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.

4. 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 Worldwide.Safety@bms.com of this event via, MedWatch or appropriate Pregnancy Surveillance Form in accordance with SAE

reporting procedures. Protocol-required procedures for study discontinuation and follow-up must be performed on the participant. Follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome and, where applicable, offspring information must be reported on the, MedWatch or appropriate Pregnancy Surveillance Form. Any pregnancy that occurs in a female partner of a male study participant should be reported to BMS. Information on this pregnancy 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.

5. 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 an SAE.

6. Non-serious Adverse Event. Non-serious Adverse Events (AE) are to be provided to BMS in aggregate via interim or final study reports as specified in the agreement or, if a regulatory requirement [eg, IND US trial] as part of an annual reporting requirement.

Non-serious AE information should also be collected from the start of a placebo lead-in period or other observational period intended to establish a baseline status for the subjects. A non-serious adverse event is an AE not classified as serious.

7. Serious Adverse Event Collection and Reporting. Following the subject's written consent to participate in the study, all SAEs, whether or not related to the BMS product under study, must be collected, including those thought to be associated with protocol-specified procedures. SAEs must be recorded on CIOMS or FDA MedWatch 3500A Form and reported to BMS (or designee) within 1 business day to comply with regulatory requirements. A form should be completed for any event where doubt exists regarding its status of seriousness. Although overdose and cancer are not always serious by regulatory definition, these events should be recorded on a form and reported to BMS within 1 business day.

All SAEs must be reported by confirmed facsimile (fax) transmission or reported via electronic mail to:

SAE Email Address: Worldwide.Safety@BMS.com
SAE Facsimile Number: 1-609-818-3804

If only limited information is initially available, follow-up reports may be required. For studies capturing SAEs through electronic data capture (EDC), electronic submission is the required method for reporting. The paper forms should be used and submitted immediately, only in the event the electronic system is unavailable for transmission. When paper forms are used, the original paper forms are to remain on site.
If it is discovered a patient is pregnant or may have been pregnant at the time of exposure to the BMS product under study, the pregnancy, AEs associated with maternal exposure and pregnancy outcomes must be recorded on a Pregnancy

Surveillance Form and reported to BMS (or designee) within 1 business day by confirmed fax or reported via electronic mail to Worldwide.Safety@BMS.com. If only limited information is initially available, follow-up reports may be required. The original BMS forms are to remain on site. Follow-up information should be obtained on pregnancy outcomes for one year following the birth of the offspring.
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.

8. Non-serious Adverse Event Collection and Reporting. The collection of non-serious AE information should begin at initiation of study drug. All non-serious 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.

Non-serious AEs should be followed to resolution or stabilization, or reported as SAEs if they become serious. Follow-up is also required for non-serious 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.

9. SAE Reconciliation. The investigator will reconcile the clinical database SAE cases transmitted to BMS Global Pharmacovigilance (GPV&E). Frequency of reconciliation will be done every three months and once prior to study database lock. BMS GPV&E will e-mail upon request from the investigator, the GPV&E reconciliation report. Requests for reconciliation should be sent to aepbusinessprocess@bms.com. The data elements listed on the GPV&E reconciliation report will be used for case identification purposes. If the investigator determines a case was not transmitted to BMS GPV&E, the case will be sent immediately.

Non-serious Adverse Event Collection and Reporting

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 to BMS 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).

10. Other Safety Considerations. Any significant worsening noted during interim or final physical examinations, electrocardiograms, X-rays, and any other potential safety assessments, whether or not these procedures are required by the protocol, should also be recorded as a non-serious or serious AE, as appropriate, and reported accordingly.

8.2 Recording of Adverse Events

At each contact with the subject, the study team must seek information on adverse events by specific questioning. Information on all adverse events should be recorded immediately in the source document, and also in the appropriate adverse event section of the case report form (CRF). All clearly related signs, symptoms, and abnormal diagnostic, laboratory or procedure results should recorded in the source document.

All adverse events occurring during the study period must be recorded. The clinical course of each event should be followed until resolution, stabilization, or until it has been ultimately determined that the study treatment or participation is not the probable cause. Serious adverse events that are still ongoing at the end of the study period must be followed up, to determine the final outcome. Any serious adverse event that occurs after the study period and is considered to be at least possibly related to the study treatment or study participation should be recorded and reported immediately.

8.3 Reporting of Serious Adverse Events and Unanticipated Problems

When an adverse event has been identified, the study team will take appropriated action necessary to protect the study participant and then complete the Study Adverse Event Worksheet and log. The sponsor-investigator will evaluate the event and determine the necessary follow-up and reporting required.

8.3.1 Sponsor-Investigator reporting: notifying the Mayo IRB

The sponsor-investigator will report to the Mayo IRB any UPIRTSOs and Non-UPIRTSOs according to the Mayo IRB Policy and Procedures. Any serious adverse event (SAE) which the Principal Investigator has determined to be a UPIRTSO will be reported to the Mayo IRB as soon as possible but no later than 5 working days after the investigator first learns of the problem/event.

Information collected on the adverse event worksheet (*and entered in the research database)*:

- Subject's name:
- Medical record number:

- Disease/histology (if applicable):
- The date the adverse event occurred:
- Description of the adverse event:
- Relationship of the adverse event to the research (drug, procedure, or intervention):
- If the adverse event was expected:
- The severity of the adverse event: (use a table to define severity scale 1-5)
- If any intervention was necessary:
- Resolution: (was the incident resolved spontaneously, or after discontinuing treatment)
- Date of Resolution:

The sponsor-investigator will review all adverse event reports to determine if specific reports need to be made to the IRB and FDA. The sponsor-investigator will sign and date the adverse event report when it is reviewed. For this protocol, only directly related SAEs/UPIRTSOs will be reported to the IRB.

8.3.2 Sponsor-Investigator reporting: Notifying the FDA

The sponsor-investigator will report to the FDA all unexpected, serious suspected adverse reactions according to the required timelines, formats and requirements.

Unexpected fatal or life threatening suspected adverse reactions where there is evidence to suggest a causal relationship between the study drug/placebo and the adverse event, will be reported as a serious suspected adverse reaction. This will be reported to the FDA on FDA Form 3500A, no later than 5 business days after the sponsor-investigator's initial receipt of the information about the event.

Other unexpected serious suspected adverse reactions where there is evidence to suggest a causal relationship between the study drug/placebo and the adverse event, will be reported as a serious suspected adverse reaction. This will be reported to the FDA on FDA Form 3500A, no later than 15 business days after the sponsor-investigator's initial receipt of the information about the event.

Any clinically important increase in the rate of serious suspected adverse reactions over those listed in the protocol or product insert will be reported as a serious suspected adverse reaction. This will be reported to the FDA on FDA Form 3500A no later than 15 business days after the sponsor-investigator's initial receipt of the information about the event.

Findings from other studies in human or animals that suggest a significant risk in humans exposed to the drug will be reported. This will be reported to the FDA on FDA Form 3500A, no later than 15 business days after the sponsor-investigators initial receipt of the information about the event.

8.4 Medical Monitoring

The Principal Investigators will oversee the safety of the study. This safety monitoring will include careful assessment and appropriate reporting of adverse events as noted above, as well as the construction and implementation of a site data and

safety-monitoring plan (see section 10 “Study Monitoring, Auditing, and Inspecting”). Medical monitoring will include a regular assessment of the number and type of serious adverse events.

9 Data Handling and Record Keeping

9.1 Confidentiality

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

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

9.2 Source Documents

Source data is all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. Examples of these original documents, and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, subjects’ diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial.

9.3 Case Report Forms

The study case report form (CRF) is the primary data collection instrument for the study. All data requested on the CRF must be recorded. All missing data must be explained. If a space on the CRF is left blank because the procedure was not done or the question was not asked, write “N/D”. If the item is not applicable to the individual case, write “N/A”. All entries should be printed legibly in black ink. If any entry error has been made, to correct such an error, draw a single straight line through the incorrect entry and enter the correct data above it. All such changes must be initialed and dated. Do not erase or use “white-out” for errors. For clarification of illegible or uncertain entries, print the clarification above the item, then initial and date it. If the reason for the correction is not clear or needs additional explanation, neatly include the details to justify the correction.

Data Management

A RedCap database system (DMS) for the collection, storage and management of all study data will be developed at Mayo Clinic Rochester. The RedCap database will provide for data entry (including data entry at the trial sites using a web portal and immediate storage of the data in the central database), data security, and reporting. The data management team will develop a data validation plan, rule set specifications, and programming logic to implement data validation rules. The rule set will include checks for missing fields, range checks, skip pattern-logic, and inter and intra form checks.

9.4 Records Retention

The sponsor-investigator will maintain records and essential documents related to the conduct of the study. These will include subject case histories and regulatory documents.

The sponsor-investigator will retain the specified records and reports for;

1. Up to 2 years after shipment and delivery of the drug for investigational use is discontinued and the FDA has been so notified. OR
2. As outlined in the Mayo Clinic Research Policy Manual –"Access to and Retention of Research Data Policy" [redacted]

Whichever is longer.

10 Study Monitoring, Auditing, and Inspecting

10.1 Study Monitoring Plan

This study will be internally monitored on a routine basis during the conduct of the trial. Clinical trial monitoring requires review of the study data generated throughout the duration of the study to ensure the validity and integrity of the data along with the protection of human research subjects. This will assist sponsor-investigators in complying with Food and Drug Administration regulations.

The investigator will allocate adequate time for such monitoring activities. The Investigator will also ensure that the monitor or other compliance or quality assurance reviewer is given access to all the study-related documents and study related facilities (e.g. pharmacy, diagnostic laboratory, etc.), and has adequate space to conduct the monitoring visit.

10.2 Auditing and Inspecting

The investigator will permit study-related monitoring, audits, and inspections by the IRB, the sponsor, and government regulatory agencies, of all study related documents (e.g. source documents, regulatory documents, data collection instruments,

study data etc.). The investigator will ensure the capability for inspections of applicable study-related facilities (e.g. pharmacy, diagnostic laboratory, etc.).

Participation as an investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable compliance offices.

11 Ethical Considerations

This study is to be conducted according to United States government regulations and Institutional research policies and procedures. This protocol and any amendments will be submitted to a properly constituted local Institutional Review Board (IRB), in agreement with local legal prescriptions, for formal approval of the study. The decision of the IRB concerning the conduct of the study will be made in writing to the sponsor-investigator before commencement of this study.

All subjects for this study will be provided a consent form describing this study and providing sufficient information for subjects to make an informed decision about their participation in this study. This consent form will be submitted with the protocol for review and approval by the IRB for the study. The formal consent of a subject, using the Approved IRB consent form, must be obtained before that subject undergoes any study procedure. The consent form must be signed by the subject and the individual obtaining the informed consent.

12 Study Finances

12.1 Funding Source

The (BMS/Pfizer American Thrombosis Investigator Initiated Research Program (ARISTA-USA) is established to fund innovative medical research from investigators in the United States. This study is funded through the competitive request for application (RFA) through this Bristol Myers Squibb/Pfizer Alliance funding program.

13 Publication Plan

The success of this trial will depend largely on the number and quality of its scientific publications and presentations. The purpose of the policy established is to encourage and facilitate the presentation of trial analyses while providing guidelines that ensure appropriate use of the data, timely completion of manuscripts and presentations, equitable access to authorship, and adherence to established principles of authorship using the ICMJE criteria.

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Appendix A. Telephone Script:

Protocol Title: A Phase IV, Randomized, Double Blind Study Evaluating the Safety and Efficacy of Apixaban in Subjects with Calf Vein Thrombosis
Principal Investigator: Robert McBane, MD

Completed By: _____

Date: _____

Circle One: Day 7 Day 14 Day 30 Day 60 Day 90

"Good morning/afternoon. This is _____ calling from Mayo Clinic Rochester/Eau Claire/La Cross. May I speak to_____?" **(If participant is there proceed to the following)**

"I would like to ask you a few questions regarding your blood thinner medication**,** you are taking for the clinical trial in which you have been enrolled. This will allow us to gather very important information about the safety and benefit of using this medication in treating and preventing blood clots."

I would like to ask these questions related to our study after confirming your name:

_____

1. Since your last visit, have you missed any doses of your blood thinner medication?
   ____ Yes,
   If yes, approximately how many doses do you estimate that you have missed? __
   ____ No, I have not missed any doses of medication

2. Since your last visit, have you had another blood clot problem?
   ____ Yes, a DVT
   ____ Yes, a PE
   ____ Both a DVT and a PE
   ____ Yes, something else (e.g. an arterial clot)
   ____ No, I have not had any more clots.

3. While you have been taking this medication as recommended, have you experienced any major bleeding which required hospitalization or blood transfusion?
   ____ Yes
   If yes, please describe: _____
   ____ No

4. While you have been taking this medication as recommended, have you experienced any bleeding other than from injury?
   ____ Yes,
   If yes, please describe_____
   ____ No

5. Which of the following best applies to your current activity rating:
   A. ____ Fully active, able to carry on all pre-disease performance without restriction.
   B. ____ Restricted in physically strenuous activity, but able to walk and to carry out work of a light or sedentary nature (for example, light house work, or office work).
   C. ____ Able to walk and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
   D. ____ Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
   E. ____ Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.

6. Have you started any new medications?
   ____ Yes
   If yes, please list: _____
   ____ No

7. Have you had any new leg swelling?
   ____ Yes,
   If yes, suggest that the patient see their medical provider
   ____ No

8. Have you had any new chest pain or shortness of breath?
   ____ Yes,
   If yes, suggest that the patient see their medical provider
   ____ No

9. On a scale of 0 – 10, what is your current pain level for the involved leg with the blood clot? (circle one)

   0 1 2 3 4 5 6 7 8 9 10

Do you have any questions for me?

Thank you for participating in our study.

Appendix B1. Case Report Form; Initial data

Date Completed: _____ Completed By: _____

Name: _____

Birth date: _____ **Gender:** 1☐Female 2☐Male

Height (cm): _____

Weight (kg): _____

Qualifying Event: Has the patient had a documented calf DVT confirmed by imaging? *(check one)*

1☐Yes 2☐No If yes: Date diagnosed: *(mm/dd/yyyy)* __ __/__ __/__ __ __ __

Location of the DVT

Leg involved *(check one)* 1☐Right 2☐Left 3☐Bilateral

Lower extremity deep vein involved *(check all that apply and provide length of thrombus in cm)*

1☐Posterior Tibial Length _____ cm

2☐Peroneal Length _____ cm

3☐Anterior Tibial Length _____ cm

4☐Gastrocnemius Length _____ cm

5☐Soleal Length _____ cm

Was there evidence of proximal vein involvement (popliteal, femoral, ilial vein*)* 1☐Yes 2☐No
How was the thrombus confirmed? 1☐Utrasound 2☐ CT 3☐MRI

Pain assessment

On a scale of 0 – 10, what is your current pain level for the involved leg with the blood clot? (circle one)

0 1 2 3 4 5 6 7 8 9 10

Clinical Characteristics

No identified risk factors *(unprovoked, check one)* 1☐Yes 2☐No

Surgery (within past 3 months) *(check one)* 1☐Yes 2☐No

Trauma (within past 3 months) *(check one)* 1☐Yes 2☐No

Travel > 6 hrs (within past 3 months) *(check one)* 1☐Yes 2☐No

Prior personal history of VTE *(check one)* 1☐Yes 2☐No

Family history of VTE *(check one)* 1☐Yes 2☐No

Estrogen therapy*(check one)* 1☐Yes 2☐No

Postpartum (within 6 weeks of delivery) *(check one)* 1☐Yes 2☐No

Hospitalization (within past 3 months) *(check one)* 1☐Yes 2☐No

Past Cancer history *(check one)* 1☐Yes 2☐No

Known thrombophilia *(check one)* 1☐Yes 2☐No

Describe _____

Inflammatory bowel disease (*check one)* 1☐Yes 2☐No

Laboratory Data

Date collected (mm-dd-yr): ___ ___-___ ___-___ ____

CBC: Hgb_____ WBC_____ Platelet_____
Creatinine: _____ ALT: _____ AST:_____

Smoking status *(check one)* 1☐active smoker 2☐former smoker 3☐never smoker

Appendix B2. Case Report Form; Follow up data

Date Completed: _____

Completed By: _____

Circle One: Day 7 Day 14 Day 30 Day 60 Day 90 Day 365

Lower extremity deep vein involved *(check all that apply and provide length of thrombus in cm)*

1☐Posterior Tibial Length _____ cm

2☐Peroneal Length _____ cm

3☐Anterior Tibial Length _____ cm

4☐Gastrocnemius Length _____ cm

5☐Soleal Length _____ cm

Was there evidence of DVT propagation confirmed by imaging? *(check one)* 1☐Yes 2☐No

If yes, which veins were involved (check all that apply)?

1☐Popliteal

2☐Femoral

3☐Iliac

4☐IVC

Pain assessment

On a scale of 0 – 10, what is your current pain level for the involved leg with the blood clot? (circle one)

0 1 2 3 4 5 6 7 8 9 10

Has patient had a documented recurrent venous thrombosis confirmed by imaging? *(check one)*

1☐Yes 2☐No

If yes: Date diagnosed: *(mm/dd/yyyy)* __ __/__ __/__ __ __ __

Pulmonary Embolism *(check one)* 1☐Yes 2☐No

Lower extremity deep vein thrombosis *(check one)* 1☐Yes 2☐No

Upper extremity deep vein thrombosis *(check one)* 1☐Yes 2☐No
(jugular, innominate, subclavian, axillary, brachial)

Splanchnic vein thrombosis *(check one)* 1☐Yes 2☐No
(hepatic, portal, splenic, mesenteric, renal, gonadal)

Cerebral vein thrombosis 1☐Yes 2☐No

Fatal PE: *(check one)* 1☐Yes 2☐No

Was the VTE recurrence: *(check one)* 1☐Symptomatic 2☐ Incidental

How was the thrombus confirmed?

1☐Utrasound 2☐ CT 3☐MRI 4☐ VQ scan 5☐Surgery 6☐ Autopsy

Arterial clot: *(check one)* 1☐Yes 2☐No

If Yes, *(check all that apply)* ☐MI
☐TIA/Stroke
☐Peripheral embolism

Has patient had a major bleed? *(check one)* 1☐Yes 2☐No

If Yes, date of major bleed: *(mm/dd/yyyy)* __ __/__ __/__ __ __ __

If Yes *(check all that apply)*

☐Intracranial (intracerebral (hemorrhagic stroke), subarachnoid, subdural)
☐Intraspinal/epidural
☐Intraocular
☐Intraarticular
☐Intramuscular with compartment syndrome
☐Retroperitoneal
☐Pericardial
☐Fatal bleeding
☐GI
☐GU
☐Pulmonary
☐Other Specify: _____

Has patient had a clinically relevant non-major bleed? *(check one)* 1☐Yes 2☐No

If Yes, date of clinically relevant non-major bleed: *(mm/dd/yyyy)* __ __/__ __/__ __ __ __

If Yes, what were the consequences *(check all that apply)*

☐ Required medical intervention
☐ Unscheduled contact with health care team
☐ Temporary cessation of study treatment

Has patient had a minor bleed? *(check one)* 1☐Yes 2☐No

If Yes, date of minor bleed: *(mm/dd/yyyy)* __ __/__ __/__ __ __ __

Last Date (any modality of) protocol therapy was given: *(mm/dd/yyyy)* __ __/__ __/__ __ __ __
(date of last treatment dose on this study or date decision made to stop protocol treatment)