HI-PRO Protocol and Statistical Analyses Plan:

This document contains the following items:

1. Original protocol
2. Final protocol
3. Table summarizing the amendments between the original and final protocols
4. First and final statistical analyses plan (SAP)
   ***Please note: there is only one version of the SAP. No amendments or changes were made.**

Randomized Controlled Trial of Extended-Duration Low-Dose Apixaban to Prevent Recurrence in High-Risk Patients with Provoked Venous Thromboembolism (HI-PRO Trial)

Original protocol

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Protocol Summary

Title: Randomized Controlled Trial of Extended-Duration Low-Dose Apixaban to Prevent Recurrence in High-Risk Patients with Provoked Venous Thromboembolism (HI-PRO Trial)

Design: U.S.-based, single-center, randomized placebo-controlled trial.

Brief Treatment Description: Low-dose apixaban (2.5mg twice daily) for extended-duration secondary prevention of VTE after initial treatment for provoked VTE.

Purpose: To establish the safety and efficacy of low-dose apixaban versus placebo for extended prevention of recurrence after provoked VTE in patients with at least one persistent provoking factor.

Population: Outpatients with provoked VTE with at least one persistent provoking factor.

Enrollment: 600 subjects

Randomization: 1:1

Clinical Site Locations: 1 center (Brigham and Women's Hospital)

Study Duration: 36 months; enrollment period of up to 20 months with 12-month follow-up.

Primary Safety and Efficacy Outcomes:

Primary Safety Outcome: International Society on Thrombosis and Haemostasis (ISTH) major bleeding at 12 months.

Primary Efficacy Outcome: Symptomatic, recurrent VTE, defined as the composite of deep vein thrombosis and/or pulmonary embolism at 12 months.

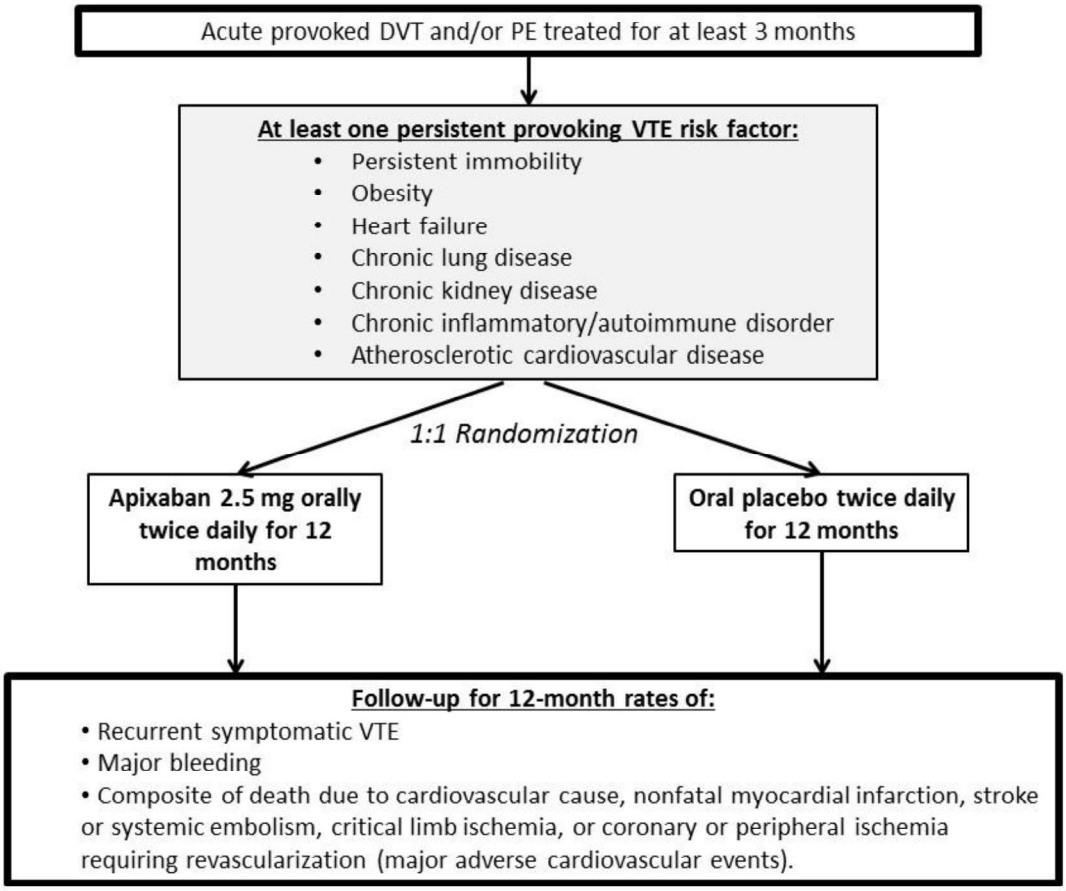
Secondary Safety Outcome: ISTH clinically relevant non-major bleeding at 12 months.

Secondary Efficacy Outcome: The composite of death due to cardiovascular cause, nonfatal myocardial infarction, stroke or systemic embolism, critical limb ischemia, or coronary or peripheral ischemia requiring revascularization (major adverse cardiovascular events, including major adverse limb events) at 12 months.

Follow-Up: Follow-up will consist of Electronic Health Record (EHR) review at 12-months from study enrollment.

Interim Analysis: An interim analysis for the primary safety and efficacy outcomes will be performed when 300 subjects have completed 12-month follow-up.

Study Flow Diagram



DVT, deep vein thrombosis; PE, pulmonary embolism; VTE, venous thromboembolism

Figure 1. Study flow-diagram for a single-center, randomized placebo-controlled trial of extended low-intensity apixaban for high-risk provoked VTE.

Study Subject Contact Calendar:

Date	Event	Study Drug
Enrollment (Month 0)	Subject will be consented by study physician and randomized through the Investigational Drug Service computer randomization program.	3 months of study drug (apixaban or placebo) will be given during this visit or sent to subject within 2 business days of the enrollment visit via mail or courier.
Month 3	Study nurse check-in	First 3 months drug containers and unused drug collected via mail and returned to pharmacy for proper disposal, 3 additional months' worth of medication will be given or sent to subject.
Month 6	Study nurse check-in	Drug containers and unused drug collected via mail and returned to pharmacy for proper disposal, 3 additional months' worth of medication will be given or sent to subject.
Month 9	Study nurse check-in	Drug containers and unused drug collected via mail returned to pharmacy for proper disposal, 3 additional months' worth of medication will be given or sent to subject.
Month 12	End-of-treatment visit	All remaining medications, drug containers, and 12-month drug diary will be collected.

Abbreviations and Definitions

Listed in alphabetical order

ACCP, American College of Chest Physicians

ALI, acute limb ischemia

ALT, alanine transaminase

AST, aspartate aminotransferase

BMI, body mass index

BMS, Bristol-Myers Squibb

BWH, Brigham and Women's Hospital

CEC, clinical endpoints committee

CI, confidence interval

CLI, critical limb ischemia

COPD, chronic obstructive pulmonary disease

CrCl, creatinine clearance

CT, computed tomography

cTn, cardiac troponin

DOAC, direct oral anticoagulant

DRVVT, dilute Russell's viper venom

DSMB, Data Safety Monitoring Board

DVT, deep vein thrombosis

eCRF, electronic case report form

FDA, food and drug administration

FSH, follicle stimulating hormone

GPV&E, Global Pharmacovigilance & Epidemiology

HCG, human chorionic gonadotropin

HRT, hormone replacement therapy

IND, investigational new drug

INR, international normalized ratio

IRB, institutional review board

ISTH, International Society on Thrombosis and Haemostasis

IUD, intrauterine device

LMWH, low-molecular weight heparin

MI, myocardial infarction

MR, magnetic resonance

NOACs, non-vitamin K oral anticoagulants

NSAID, nonsteroidal anti-inflammatory drug

PCC, prothrombin complex concentrate

PE, pulmonary embolism

PI, Proteasome inhibitors

REDCap, Research electronic data capture

SAE, significant adverse event

TRG, thrombosis research group

UADE, unanticipated adverse drug effect

UFH, unfractionated heparin

U.S., United States

VTE, venous thromboembolism

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Specific Aims

Provoked VTE is traditionally considered a transient acute disorder requiring a limited duration of anticoagulant therapy. Patients who suffer deep vein thrombosis (DVT) or pulmonary embolism (PE) following major surgery, major trauma, or periods of immobility are generally treated with time-limited anticoagulation for 3 months. However, provoked VTE patients have recently been recognized as a heterogeneous population comprised of those with transient provoking and persistent provoking risk factors (1). Common risk factors in provoked VTE such as obesity, immobility, atherosclerotic cardiovascular disease, heart failure, chronic lung disease, chronic kidney disease, and inflammatory disorders frequently contribute to an enduring rather than transient risk.

Data from 4,553 patients in the EINSTEIN CHOICE trial and the EINSTEIN VTE Continued Treatment Study demonstrate that provoked VTE patients with persistent provoking factors have a reduction in recurrence with extended duration anticoagulation compared with low-dose aspirin or placebo (1.5% vs. 4.9%) (2,3). Common persistent provoking factors included immobility, obesity, heart failure, and chronic inflammatory disorders, such as Crohn's Disease. Despite being highly prevalent, persistent provoking factors are rarely considered when stopping anticoagulation in patients with provoked VTE who have completed the typical 3- to 6-month duration of therapy. The 2016 American College of Chest Physicians (ACCP) Guidelines on Antithrombotic Therapy for VTE do not distinguish between transient and persistent provoking risk factors and recommend limited-duration anticoagulation for provoked events (4).

However, an emerging opinion is that optimal duration of anticoagulation in provoked VTE patients should be determined based on data from the extended duration rivaroxaban trials (5). Such a strategy breaks from the tradition of dichotomizing VTE as provoked or unprovoked. Rather, persisting risk factors such as heart failure, obesity, family history of VTE, acquired or hereditary thrombophilia, and immobilization are incorporated into the decision-making process for pathways focused on secondary prevention. A suitable long-term strategy for secondary prevention has been recommended in evidence-based clinical practice guidelines for patients with unprovoked VTE (4). Extended-duration anticoagulation with warfarin or the direct oral anticoagulants (DOACs) is validated and recommended for prevention of recurrent unprovoked VTE in patients with a low-risk of bleeding (6). In a landmark extension trial of patients with unprovoked VTE, the AMPLIFY-EXT trial compared two doses of apixaban (2.5 mg and 5 mg, twice daily) with placebo in 2486 patients with VTE who had completed 6 to 12 months of anticoagulation therapy and for whom there was clinical equipoise regarding the need for extended-duration anticoagulant therapy for secondary prevention (7). Symptomatic recurrent VTE or death from VTE occurred in 73 of the 829 patients (8.8%) who were receiving placebo versus 14 of the 840 patients (1.7%) who were receiving 2.5 mg of apixaban and 14 of the 813 patients (1.7%) who were receiving 5 mg of apixaban ($p<0.001$ for both comparisons). In Kaplan-Meier analysis, the apixaban 2.5 mg twice daily

regimen demonstrated a major and clinically-relevant nonmajor bleeding rate similar to that of placebo.

Based on the emerging evidence that provoked VTE patients may require extended-duration anticoagulation for secondary prevention, the apixaban 2.5 mg twice daily dose could be a critical addition to our armamentarium in those at high risk for recurrence at the transition of care from the acute to the chronic treatment phase. However, this hypothesis needs to be tested in a randomized clinical trial. We propose a single-center, randomized placebo-controlled trial conducted at Brigham and Women's Hospital (BWH) to evaluate the impact of low-dose apixaban (2.5 mg twice daily) in a study population exclusively comprised of provoked VTE patients with at least one persistent provoking factor. We have the following study aims:

Specific Aim #1: To compare the 12-month rate of recurrent symptomatic VTE in patients with provoked VTE and at least one persistent provoking factor who are randomized to either apixaban (2.5 mg orally twice daily) as monotherapy or placebo after completing at least 3 months of therapeutic anticoagulation and who have a low risk of bleeding.

Hypothesis #1: Compared with placebo, oral apixaban (2.5 mg twice daily) will reduce the 12-month rate of symptomatic VTE in patients with provoked VTE and at least one persistent provoking factor who have completed at least 3 months of therapeutic anticoagulation and who have a low risk of bleeding.

Specific Aim #2: To compare the 12-month rate of ISTH major bleeding in patients with provoked VTE and at least one persistent provoking factor who are randomized to either apixaban (2.5 mg orally twice daily) as monotherapy or placebo after completing at least 3 months of therapeutic anticoagulation and who have a low risk of bleeding.

Hypothesis #2: Compared with placebo, oral apixaban (2.5 mg twice daily) will be associated with a similar rate of ISTH major bleeding at 12 months in patients with provoked VTE and at least one persistent provoking factor who are randomized to either apixaban (2.5 mg orally twice daily) as monotherapy or placebo after completing at least 3 months of therapeutic anticoagulation and who have a low risk of bleeding.

Introduction and Background

Provoked venous thromboembolism (VTE) is traditionally considered a transient acute disorder requiring a limited duration of anticoagulant therapy. Patients who suffer deep vein thrombosis (DVT) or pulmonary embolism (PE) following major surgery, major trauma, or periods of immobility are generally treated with time-limited anticoagulation for 3 months. However, provoked VTE patients have recently been recognized as a heterogeneous population comprised of those with transient provoking and persistent provoking risk factors (1). Common risk factors in provoked VTE such as obesity, immobility, atherosclerotic cardiovascular disease, heart failure, chronic lung disease, chronic kidney disease, and inflammatory disorders frequently contribute to an enduring rather than transient risk. Furthermore, epidemiological studies (8,9) and the randomized clinical trial EINSTEIN CHOICE (3) suggest that VTE is best characterized as a chronic disorder with periodic relapses. A landmark Danish National Registry analysis demonstrated that patients who suffer provoked or unprovoked VTE have an increased risk of recurrence over the ensuing 30 years and that recurrent PE causes increased mortality (10). While the rate of VTE recurrence ranges 30-50% over 10 years for unprovoked VTE (also termed idiopathic; unprovoked implies that an immediate trigger for the VTE cannot be identified), recurrent events occur in about 20% of patients over 10 years after a provoked event (provoked VTE is defined as post-operative, post-major trauma, post-hospitalization, or related to pregnancy, hormonal contraception/replacement therapy, or immobility) (11–13). Based on these data, provoked VTE patients represent a population vulnerable to VTE recurrence, especially at the transition of care from the initial (acute) treatment phase to the chronic treatment phase, at which point anticoagulation is discontinued in most of these patients.

The EINSTEIN CHOICE trial recently evaluated the safety and efficacy of regimens of full- or lower-intensity anticoagulant therapy versus low-dose aspirin for secondary prevention of VTE after an initial provoked or unprovoked event (2). The EINSTEIN CHOICE Investigators randomly assigned 3396 patients with VTE to receive either once-daily rivaroxaban (at doses of 20 mg or 10 mg) or 100 mg of aspirin. Prior to enrollment in EINSTEIN CHOICE, all study patients completed 6 to 12 months of anticoagulation therapy, and their providers were in equipoise regarding the need for extended anticoagulation. Approximately 60% of patients in EINSTEIN CHOICE had suffered provoked VTE. Symptomatic recurrent VTE occurred in 17 of 1107 patients (1.5%) receiving 20 mg of rivaroxaban and in 13 of 1127 patients (1.2%) receiving 10 mg of rivaroxaban, and in 50 of 1131 patients (4.4%) receiving low-dose aspirin (hazard ratio for 20 mg of rivaroxaban vs. aspirin, 0.34; 95% confidence interval [CI], 0.20 to 0.59; hazard ratio for 10 mg of rivaroxaban vs. aspirin, 0.26; 95% CI, 0.14 to 0.47; $P<0.001$ for both comparisons). Rates of major bleeding were similar (0.5% in the group receiving 20 mg of rivaroxaban, 0.4% in the group receiving 10 mg of rivaroxaban, and 0.3% in the low-dose aspirin group) (2).

Data from 4,553 patients in EINSTEIN CHOICE and the EINSTEIN VTE Continued Treatment Study demonstrate that provoked VTE patients with persistent provoking

factors have a reduction in recurrence with extended duration anticoagulation compared with low-dose aspirin or placebo (1.5% vs. 4.9%) (2,3). Common persistent provoking factors included immobility, obesity, heart failure, and chronic inflammatory disorders, such as Crohn's Disease and rheumatoid arthritis. Despite being highly prevalent, persistent provoking factors are rarely considered when stopping anticoagulation in patients with provoked VTE who have completed the typical 3- to 6-month duration of therapy. The 2016 American College of Chest Physicians (ACCP) Guidelines on Antithrombotic Therapy for VTE do not distinguish between transient and persistent provoking risk factors and recommend limited-duration anticoagulation for provoked events (4).

However, an emerging opinion is that optimal duration of anticoagulation in provoked VTE patients should be determined based on data from the extended duration rivaroxaban trials (5). Such a strategy breaks from the tradition of dichotomizing VTE as provoked or unprovoked. Rather, persisting risk factors such as heart failure, obesity, family history of VTE, acquired or hereditary thrombophilia, and immobilization are incorporated into the decision-making process for pathways focused on secondary prevention.

A suitable long-term strategy for secondary prevention has been recommended in evidence-based clinical practice guidelines for patients with unprovoked VTE (4). Extended-duration anticoagulation with warfarin or the direct oral anticoagulants (DOACs) is validated and recommended for prevention of recurrent unprovoked VTE in patients with a low-risk of bleeding (6). However, current evidence-based clinical practice guidelines are inadequate for secondary prevention in patients with provoked VTE based on several extended-duration anticoagulation trials that included patients with provoked and unprovoked VTE. In a randomized controlled trial of rivaroxaban for extended-duration secondary prevention in patients with either provoked (26%) or unprovoked (74%) DVT, recurrent VTE occurred in 8 patients (1.3%) in the rivaroxaban group compared with 42 patients (7.1%) in the placebo group (hazard ratio, 0.18; 95% CI, 0.09 to 0.39; P<0.001, relative risk reduction, 82%) (3).

In a landmark extension trial of patients with unprovoked VTE, the AMPLIFY-EXT trial compared two doses of apixaban (2.5 mg and 5 mg, twice daily) with placebo in 2486 patients with VTE who had completed 6 to 12 months of anticoagulation therapy and for whom there was clinical equipoise regarding the need for extended-duration anticoagulant therapy for secondary prevention (7). Symptomatic recurrent VTE or death from VTE occurred in 73 of the 829 patients (8.8%) who were receiving placebo versus 14 of the 840 patients (1.7%) who were receiving 2.5 mg of apixaban and 14 of the 813 patients (1.7%) who were receiving 5 mg of apixaban (p<0.001 for both comparisons). In Kaplan-Meier analysis, the apixaban 2.5 mg twice daily regimen demonstrated a major and clinically-relevant nonmajor bleeding rate similar to that of placebo. While approximately 9% of the patients in the AMPLIFY-EXT trial had transient or reversible risk factors for VTE, the provoked VTE population only accounted for approximately 200 patients and precluded a well-powered analysis. Furthermore, the intent of the AMPLIFY-EXT trial was to study unprovoked VTE (7).

Finally, the HI-PRO trial is evaluating a more complex aspect of VTE secondary prevention. Rather than using the simple dichotomized view of VTE as provoked or unprovoked, HI-PRO is focusing on how the risk of recurrence in patients with persisting provoking factors may be modulated by low-dose apixaban. The foundation of this question is based on the current direction in which the field of VTE is moving (5) and supported by the more pathophysiologically-sound ISTH classification of risk factors (1).

Apixaban 2.5 mg twice daily may have additional advantages for extended-duration secondary prevention of VTE compared with rivaroxaban 10 mg daily (which has U.S. FDA approval for extended-duration therapy). Apixaban is a more pharmacokinetically rational regimen, given the half-life of these two DOACs. In trials of stroke prevention of atrial fibrillation, apixaban demonstrated a relatively lower frequency of gastrointestinal bleeding compared with warfarin (14–17). Apixaban has fewer off-target side effects than rivaroxaban, which can cause severe headache (necessitating urgent head CT) and severe rash.

Based on the emerging evidence that provoked VTE patients may require extended-duration anticoagulation for secondary prevention, the apixaban 2.5 mg twice daily dose could be a critical addition to our armamentarium in those at high risk for recurrence at the transition of care from the acute to the chronic treatment phase. However, this hypothesis needs to be tested in a clinical trial. We propose a single-center, randomized controlled trial conducted at Brigham and Women's Hospital (BWH) to evaluate the feasibility of low-dose apixaban (2.5 mg twice daily) in a study population exclusively comprised of provoked VTE patients with persistently provoking risk factors for VTE.

Rationale for the Proposed Study and Trial Design

The rationale for the study design is focused on the lack of data on the safety and efficacy of extended-duration low-dose apixaban for secondary prevention in patients with provoked VTE. A single-center, randomized placebo-controlled trial of extended low-intensity apixaban with a study population enriched for recurrent VTE event rates will be able to provide such data.

The rationale for a single-center study is that Watkins Cardiovascular Clinic at BWH is a Center of Excellence for thrombosis care not only in the New England region but also along the East coast. The BWH Thrombosis Center evaluates an average of 1200 new and follow-up outpatients with VTE per year. In addition, the Vascular Medicine Section at BWH includes 4 additional full-time faculty and 4 full-time Vascular Medicine fellows who also see a high volume of VTE patients. Accordingly, enrollment of 600 patients meeting the entry criteria and none of the exclusion criteria will be accomplished efficiently at our single center.

The rationale behind using a low-dose of apixaban is three-fold. First, low-dose rivaroxaban 10 mg orally daily was effective and safe in the EINSTEIN CHOICE trial (2) for extended-duration anticoagulation in secondary prevention after unprovoked VTE. Second, AMPLIFY-EXT demonstrated efficacy and enhanced safety to a low-dose apixaban regimen (2.5 mg orally twice daily) for extended-duration anticoagulation in secondary prevention after predominantly unprovoked VTE (7). Finally, because the relative risk of recurrence is less (although still unacceptably high) for provoked VTE than unprovoked VTE, a lower dose of apixaban may maintain efficacy while offering a reduction in the risk of major and clinically-relevant non-major bleeding.

The rationale for using low-dose apixaban in a study population that will include obese patients is that an analysis of the AMPLIFY-EXT data by weight demonstrated results for the primary efficacy outcome and the composite outcome of major and clinically relevant nonmajor bleeding were consistent with overall study results (7).

The rationale for using a placebo-control is that current evidence-based guidelines do not recommend any extended thromboprophylactic measures after provoked VTE. Trials of low-dose aspirin for secondary prevention of VTE have largely focused on unprovoked VTE or a mixed population of unprovoked and provoked VTE. In the EINSTEIN CHOICE trial, low-dose aspirin was associated with a bleeding risk similar to anticoagulation with rivaroxaban and a recurrent VTE rate 70% higher than anticoagulation with rivaroxaban (2).

The rationale for inclusion of eligible patients who are already taking ≤ 81 mg of aspirin is based on several factors. First, the HI-PRO trial will include atherosclerotic cardiovascular disease, which will enrich the study population in VTE events because of the strong pathophysiological link between the two (18–21). Many of these patients will be receiving low-dose aspirin (≤ 81 mg). Second, many potentially eligible patients will be receiving low-dose aspirin (≤ 81 mg) for primary prevention of cardiovascular events. Excluding these patients would significantly hinder enrollment. Finally, none of the major landmark trials of low-intensity apixaban (2.5 mg twice daily) excluded patients taking low-dose aspirin (≤ 81 mg). AMPLIFY-EXT and ADOPT allowed up to 165 mg of aspirin daily (7,22).

Atherosclerosis is associated with an increased risk of VTE. A link between atherosclerotic cardiovascular disease and VTE was first suggested by Prandoni and colleagues, who observed that the presence of carotid plaque was associated with a doubling in VTE risk (23). Many risk factors for VTE, such as obesity, hypertension, dyslipidemia, diabetes, and smoking, overlap with those for atherosclerosis (21,24). The link between VTE and atherosclerotic cardiovascular disease also appears to be reciprocal. A recent analysis of TRA2P-TIMI 50 (Thrombin Receptor Antagonist in Secondary Prevention of Atherothrombotic Ischemic Events-Thrombolysis in Myocardial Infarction) and PEGASUS-TIMI 54 (Prevention of Cardiovascular Events in Patients With Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin-Thrombolysis in Myocardial Infarction 54) demonstrated the

risk of VTE increased with the number of symptomatic vascular territories affected by atherosclerosis (18). A recent editorial in Circulation called for medicine to abandon the dichotomized view of VTE as provoked or unprovoked and called for the basis of the optimal duration of anticoagulation to be determined by persisting risk factors, including cardiovascular disease (5). Because of the potential for a majority of patients in the study to have atherosclerotic cardiovascular disease limiting the generalizability of the results, up to 35% in each study group may have atherosclerotic cardiovascular disease as a qualifying persistent risk factor.

The rationale for enrollment at 3-months is derived from the 2016 American College of Chest Physicians (ACCP) evidence-based clinical practice document entitled "Antithrombotic Therapy for VTE Disease: CHEST Guideline and Expert Panel Report, "In patients with proximal DVT or pulmonary embolism (PE), we recommend long-term (3 months) anticoagulant therapy over no such therapy (Grade 1B)" (Kearon C, Akl EA, Ornelas J, et al. Antithrombotic Therapy for VTE Disease: CHEST Guideline and Expert Panel Report. Chest 2016;149:315-52). This statement supports the 3-month timepoint as an appropriate juncture to determine whether extended duration anticoagulation or discontinuation of antithrombotic therapy is appropriate.

The 2016 ACCP evidence-based clinical practice guidelines rely upon a more traditional classification for determining the risk of VTE recurrence after 3 months, a dichotomous approach distinguishing "provoked" from "unprovoked" (idiopathic) VTE, that has subsequently fallen out of favor. The 2016 ACCP guidance document states the following regarding extended-duration antithrombotic therapy for prevention of recurrent VTE:

"In patients with a proximal DVT of the leg or PE provoked by surgery, we recommend treatment with anticoagulation for 3 months over (i) treatment of a shorter period (Grade 1B), (ii) treatment of a longer time-limited period (eg, 6, 12, or 24 months) (Grade 1B), or (iii) extended therapy (no scheduled stop date) (Grade 1B).

In patients with a proximal DVT of the leg or PE provoked by a nonsurgical transient risk factor, we recommend treatment with anticoagulation for 3 months over (i) treatment of a shorter period (Grade 1B) and (ii) treatment of a longer time-limited period (eg, 6, 12, or 24 months) (Grade 1B). We suggest treatment with anticoagulation for 3 months over extended therapy if there is a low or moderate bleeding risk (Grade 2B), and recommend treatment for 3 months over extended therapy if there is a high risk of bleeding (Grade 1B)."

These guidelines fail to address the large population of patients with VTE who may have had a provoking factor but also have enduring risk factors for recurrence, such as those with persistent immobility, obesity, heart failure, chronic lung disease, chronic kidney disease, chronic inflammatory/autoimmune disorder, and atherosclerotic cardiovascular disease (Albertsen IE, Piazza G, Goldhaber SZ. Let's

Stop Dichotomizing Venous Thromboembolism as Provoked or Unprovoked. Circulation. 2018 Dec 4;138(23):2591-2593 and Albertsen IE, Piazza G, Søgaard M, Nielsen PB, Larsen TB. Extended oral anticoagulation after incident venous thromboembolism - a paradigm shift? Expert Rev Cardiovasc Ther. 2020 Apr;18(4):201-208).

More recently, the 2019 European Society of Cardiology Guidelines for the Diagnosis and Management of Acute Pulmonary Embolism, developed in collaboration with the European Respiratory Society (ERS), have recognized the importance of identifying persistent, or enduring, risk factors for VTE recurrence (Konstantinides SV, Meyer G, Becattini C, et al. 2019 ESC Guidelines for the diagnosis and management of acute pulmonary embolism developed in collaboration with the European Respiratory Society (ERS). Eur Heart J 2019). This paradigm shift away from the previous practice of dichotomizing VTE into “provoked” and “unprovoked” has also been endorsed by the International Society on Thrombosis and Haemostasis (ISTH), which recommends that clinicians consider persistent predisposing factors when determining whether to extend anticoagulation beyond 3 months (Kearon, C, Ageno, W, Cannegieter, SC, Cosmi, B, Geersing, G-J and Kyrle, PA, for the Subcommittees on Control of Anticoagulation, and Predictive and Diagnostic Variables in Thrombotic Disease. Categorization of patients as having provoked or unprovoked venous thromboembolism: guidance from the SSC of ISTH. J Thromb Haemost 2016; 14: 1480-3).

Accordingly, the 2019 European Society of Cardiology Guidelines state that the decision to pursue extended-duration anticoagulation should rest upon recognition of both transient risk factors for VTE but also the presence of persistent, or enduring, conditions that result in a prolonged risk of VTE recurrence after an initial event. These include chronic medical disorders like inflammatory bowel disease, connective tissue disease, and other hypercoagulable states. Rather than dichotomizing VTE patients into “unprovoked” or “provoked”, the 2019 European Society of Cardiology Guidelines recommend assessment of persistent predisposing factors and an estimated long-term recurrence risk (if anticoagulation is discontinued after 3 months). The Guidelines suggest that only patients with an estimated recurrence risk of less than 3% per year should receive time-limited treatment (see figure below). Patients with greater than 8% risk of recurrence per year (for example, those with cancer-related VTE) are mandated to receive indefinite duration anticoagulation. There is clinical and research equipoise for the patient population that has an intermediate risk for recurrence (3-8% risk of recurrence per year).

The inclusion and exclusion criteria for the current study follows the evidence-based clinical practice guideline recommendations from the ESC and ISTH and identify a population of patients with VTE who have a 3-8% of VTE recurrence per year. We have estimated a 12-month VTE recurrence rate of 6% in our proposed study population, exactly within this range of clinical and research equipoise.

Study Objectives

Primary Safety Objective: To quantitatively assess the International Society on Thrombosis and Haemostasis (ISTH) major bleeding at 12 months.

Primary Efficacy Objective: To quantitatively assess the 12-month rate of symptomatic, recurrent VTE, defined as the composite of deep vein thrombosis and/or pulmonary embolism.

Secondary Safety Objective: To quantitatively assess the 12-month rate of ISTH clinically relevant non-major bleeding.

Secondary Efficacy Objective: To quantitatively assess the composite of death due to cardiovascular cause, nonfatal myocardial infarction, stroke or systemic embolism, critical limb ischemia, or coronary or peripheral ischemia requiring revascularization (major adverse cardiovascular events, including major adverse limb events) at 12 months.

Study Design

600-patient U.S.-based, single-center, randomized, double-blinded, placebo-controlled study of apixaban 2.5 mg orally twice daily for extended prevention of recurrence after provoked VTE in patients with at least one persistent provoking factor who have completed at least 3 months of standard therapeutic anticoagulation and who have a low risk of bleeding.

Study Duration

The study will be completed in 36 months: 2 months for start-up (including Human Research Committee/Institutional Review Board [IRB] approval and finalizing the Case Report Form), 32 months for patient enrollment, follow-up, and data collection, and 2 months for data analysis and writing up the results (**Table 1**).

Table 1. Study timeline.

Milestone	**Duration (months)**
Start-up	2
Patient enrollment	20
Completion of data collection	12
Data analysis and completion of study report	2
TOTAL	**36**

Study Population

Patients who are 18 years of age or older with provoked deep vein thrombosis and/or pulmonary embolism, have completed at least 3 months of therapeutic anticoagulation, have a low risk of bleeding, and have at least one persistent provoking risk factor.

Low risk of bleeding is defined by several of the exclusion criteria:

- have contraindications to antithrombotic or antiplatelet therapy
- have a requirement for ongoing anticoagulant therapy, dual antiplatelet therapy, or aspirin at a dose of > 81 mg daily
- have a hemoglobin level < 9 mg/dL, a platelet count < 100,000/mm^3, a serum creatinine level > 2.5 mg/dL, an ALT or AST level > 2 times the upper limit of the normal range, or a total bilirubin level > 1.5 times the upper limit of the normal range
- have history of bleeding diathesis or have had recent active bleeding
- have active hepatobiliary disease

In a recent propensity score-matched analysis of data from 15,254 “all-comers” newly diagnosed VTE patients in the Truven Health MarketScan commercial and Medicare Supplement claims databases in the U.S., apixaban compared with rivaroxaban was associated with an optimal balance of decreased risk of recurrent VTE (HR 0.37 [95% CI 0.24–0.55]; p<0·0001) and major bleeding events (0·54 [0·37–0·82]; p=0.0031) (25). Based on these data, we believe that apixaban will provide superb efficacy and safety compared with placebo in the prespecified high-risk for VTE recurrence and low-risk for bleeding patient population of HI-PRO.

Study Inclusion Criteria

- Man or woman
- Age ≥ 18 years
- Objectively-confirmed DVT and/or PE
- Treated for at least 3 months with standard therapeutic anticoagulant therapy
- Has not suffered symptomatic recurrence during prior anticoagulant therapy
- Outpatient follow-up at BWH
- AND have at least one of the following persistent provoking VTE risk factors:
    - Persistent immobility (defined as paralysis, other inability to ambulate freely, bed-bound, wheelchair-bound)
    - Obesity (defined as BMI ≥ 30 kg/m2)
    - Heart failure (systolic, diastolic, or combined)
    - Chronic lung disease (COPD, asthma, interstitial lung disease)
    - Chronic kidney disease (eGFR <60 mL/min/1.73m2)
    - Chronic inflammatory/autoimmune disorder (inflammatory arthritis, vasculitis, inflammatory bowel disease, chronic infection)
    - Atherosclerotic cardiovascular disease (coronary, cerebrovascular, or peripheral artery disease) (up to 35% in each study group may have

atherosclerotic cardiovascular disease as a qualifying persistent risk factor)
    - **NOTE:** Eligible patients will be allowed to have multiple risk factors, and there will not be a limit as to how many of the above risk factors a subject may have. In addition, we will place no limit on the number of patients included with multiple risk factors. A study population with multiple risk factors is highly representative of the provoked VTE population and will provide the greatest generalizability of the study results to real-world clinical practice. Including patients with single and multiple persistent provoking risk factors will also facilitate enrollment. As noted, there is clinical and research equipoise regarding whether patients with a single or multiple persistent provoking VTE risk factors should receive extended duration thromboprophylaxis for secondary prevention.
- Willing to provide written informed consent

Study Exclusion Criteria

- Women who are pregnant or breastfeeding
- Women of child-bearing potential who are unwilling or unable to use an acceptable method of birth control (such as oral contraceptives, other hormonal contraceptives [vaginal products, skin patches, or implanted or injectable products], or mechanical products such as an intrauterine device or barrier methods [diaphragm, condoms, spermicides]) to avoid pregnancy for the entire study
- Active cancer within the past 5 years
- Contraindication to antithrombotic or antiplatelet therapy
- Requirement for ongoing anticoagulant therapy, dual antiplatelet therapy, P2Y12 inhibition, or aspirin at a dose of > 81 mg daily
- Hemoglobin level < 9 mg/dL, a platelet count < 100,000/mm3, a serum creatinine level > 2.5 mg/dL or CrCl <25 mL/minute (as determined by Cockcroft-Gault equation), an ALT or AST level > 2 times the upper limit of the normal range, or a total bilirubin level > 1.5 times the upper limit of the normal range
- History of a platelet disorder such as Von Willebrand Disease
- History of bleeding diathesis or have had recent active bleeding
- Active severe hepatobiliary disease
- More than 6 months that have elapsed without taking an anticoagulant or low-dose aspirin
    - **NOTE:** The risk of recurrent VTE following cessation of anticoagulation rises slowly over the first 3-6 months (26). After this initial period, the cumulative risk of recurrent VTE steepens. Using a limit of no greater than 6 months of interruption in anticoagulation before potential re-initiation of anticoagulation as part of this trial will safely facilitate

enrollment as opposed to restricting the population to no greater than 3 months of interruption.

- Known severe thrombophilia (any increased titer antiphospholipid antibody or positive lupus anticoagulant/DRVVT or deficiency of antithrombin, protein C, or protein S) which would indicate long-term full therapeutic anticoagulation with a vitamin K antagonist
- Life expectancy < 12 months or hospice care
- Prisoners or subjects who are involuntarily incarcerated
- Subjects who are compulsorily detained for treatment of either a psychiatric or physical (e.g., infectious disease) illness
- Receiving concurrent non-FDA-approved or investigational agents or has received an investigational agent within the past 30 days prior to the first dose of study treatment (with the exception of approved medications being used for an approved indication, e.g., investigating a new dosing regimen for an approved indication)
- Any condition, which in the opinion of the investigator, would put the subject at an unacceptable risk from participating in the study
- Any other medical, social, logistical, or psychological reason, which in the opinion of the investigator, would preclude compliance with, or successful completion of, the study protocol
- History of a severe hypersensitivity reaction to apixaban
- Required prescription of a medication that is contraindicated to be co-administered with apixaban

Enrollment of Women of Childbearing Potential and Partners

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

Investigators will counsel women of childbearing potential and male subjects who are sexually active with women of childbearing potential on the importance of pregnancy

prevention and the implications of an unexpected pregnancy Investigators will advise women of childbearing potential and male subjects who are sexually active with women of childbearing potential on the use of highly effective methods of contraception. Highly effective methods of contraception have a failure rate of < 1% when used consistently and correctly.

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

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

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

A woman of childbearing potential is defined as any female who has experienced menarche and who has not undergone surgical sterilization (hysterectomy or bilateral oophorectomy) and is not postmenopausal. Menopause is defined as 12 months of amenorrhea in a woman over age 45 years, in the absence of other biological or physiological causes. In addition, females under the age of 55 years must have a serum follicle stimulating hormone (FSH) level > 40mIU/mL to confirm menopause.

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

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

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

Screening Procedures

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

1. The Principal Investigator or designee will be contacted by the responsible provider to initiate screening.

2. The Principal Investigator or designee will confirm that patient is ≥ 18 years of age or older.

3. The Principal Investigator or designee will confirm fulfillment of the study inclusion criteria and the absence of **all** exclusion criteria.

4. The Principal Investigator or designee will provide the potential study subject with the study Informed Consent Form to review, sign, and date. Informed consent must be obtained from a subject with the capacity for medical decision-making. The process for obtaining informed consent must be in compliance with the Partners IRB guidelines and policies. Informed consent may be obtained by the Principal Investigator or Co-Investigators. Potential study subjects will not be enrolled if Informed Consent cannot be obtained. A copy of the signed Informed Consent Form must be provided to the subject. Signed Informed Consent Forms must remain in each subject's study file and must always be available for verification.

5. A research staff member will enter the patient demographic data into the screening portion of the electronic case report form (eCRF).

6. Subjects who agree to participate in the study and sign the Informed Consent Form will be considered for enrollment in the study and should have baseline data which includes:
    a. History and physical examination within the past 6 months
    b. Review of relevant laboratory data from within the past three months. If laboratory data for a complete blood count, basic chemistry panel, and coagulation (prothrombin time and activated partial thromboplastin time) are not available from the past three months, these will be drawn at the initial study visit and paid for by the study.
    c. Serum (β-HCG) or urine pregnancy test (u-HCG) for women of child-bearing potential

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

Assessment of Enrollment

After 10 months of study recruitment, an assessment of enrollment will be conducted. If 300 study subjects have not been recruited by 10 months, activation of second study site, Brigham and Women's Faulkner Hospital, will be considered by the Study Investigators. Activation of the Brigham and Women's Faulkner Hospital as a study site will require submission to and approval by the Partners Human Research Committee/IRB.

Treatment Description

Subjects will begin anticoagulation within 3 weeks of passing the screening procedure. Subjects who are 18 years of age or older with provoked DVT and/or PE, have completed at least 3 months of therapeutic anticoagulation, have a low risk of bleeding, and have at least one persistent provoking risk factor will be randomly assigned to receive apixaban 2.5 mg orally twice daily or oral placebo for extended secondary prevention of VTE for a duration of 12 months.

If during the study period the patient requires an invasive procedure or surgery that necessitates the discontinuation of anticoagulation (study drug), apixaban should be held as per the prescribing guidelines (**Appendix**, http://packageinserts.bms.com/pi/pi_eliquis.pdf). If appropriate based on the judgment of the responsible clinician, apixaban should be restarted when safe to do so postoperatively.

Patients and providers will be blinded as to the study group assignment.

Both study drug and placebo will be dispensed by the BWH Investigation Drug Service in 3-month allotments either in person at the screening visit, other non-study related office visit at BWH, or directly to the patient within 2 business days of the enrollment visit via mail or courier in accordance with BWH Investigation Drug Service policy. Subsequent allotments will be dispensed via mail or courier in accordance with BWH Investigation Drug Service policy. Our Research Nurse will communicate with study subjects by telephone at 3 months intervals in advance of releasing a 3-month allotment of study drug or placebo to ensure that treatment is not interrupted due to the subjects' supplies running out.

Randomization

Subjects who are 18 years of age or older with provoked DVT and/or PE, have completed at least 3 months of therapeutic anticoagulation, have a low risk of bleeding, and have at least one persistent provoking risk factor will be randomly assigned by computer in a 1:1 ratio to receive apixaban 2.5 mg orally twice daily or oral placebo for extended secondary prevention of VTE for a duration of 12 months.

Safety Outcomes

Primary Safety Outcome

The primary safety outcome will be major bleeding at 12 months. Major bleeding is defined as overt bleeding that is associated with a decrease in the hemoglobin level ≥ 2 g/dL, leads to transfusion ≥ 2 units of packed red blood cells, occurs in a critical site, or contributes to death (27). The primary safety outcome will be independently adjudicated by a blinded Clinical Endpoints Committee (CEC) review.

Secondary Safety Outcome

Clinically relevant non-major bleeding at 12 months will be evaluated (please see below) and is defined as overt bleeding that does not meet the criteria for major bleeding but that is associated with the need for medical intervention, unscheduled contact with a physician, interruption or discontinuation of the study drug, or discomfort or impairment of activities of daily living (28).

Efficacy Outcomes

Primary Efficacy Outcome

The primary efficacy outcome will be symptomatic, recurrent VTE, defined as the composite of deep vein thrombosis and/or pulmonary embolism at 12 months. The primary efficacy outcome will be independently adjudicated by a blinded CEC review.

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

PE is diagnosed based on new mismatched perfusion defect(s) on ventilation perfusion scan, the presence of a new pulmonary artery filling defect on contrast-enhanced chest CT, a new finding of intraluminal filling defect on invasive pulmonary angiography, or evidence of PE at autopsy.

Secondary Efficacy Outcome

A secondary efficacy outcome will be the composite of death due to cardiovascular cause, nonfatal myocardial infarction (MI), stroke or systemic embolism, critical limb ischemia (CLI), or coronary or peripheral ischemia requiring revascularization (major adverse cardiovascular events, including major adverse limb events) at 12 months. The secondary efficacy outcome will be independently adjudicated by a blinded CEC review.

An acute MI is defined as the presence of at least 2 of the 3 following conditions (29):

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

An acute stroke is defined as a new, focal neurologic deficit of sudden onset, lasting at least 24 hours, not due to a readily identifiable nonvascular cause (i.e. brain tumor, trauma), as confirmed by a neurologist and neuroimaging (7). All strokes during the study will be assessed by imaging or autopsy, and classified as primary hemorrhagic, non-hemorrhagic, infarction with hemorrhagic conversion, or unknown, as defined by the American College of Cardiology.

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

Cardiovascular death is defined as a death for which a definite non-cardiovascular cause (e.g. cancer) has not been identified. Uncertain causes of deaths are presumed to be cardiovascular unless proven otherwise.

Major adverse limb events include acute limb ischemia (ALI) and critical limb ischemia (CLI) (30). Acute limb ischemia is defined as limb-threatening ischemia which is confirmed by limb hemodynamics or imaging and leads to an acute vascular intervention (i.e. pharmacologic [heparin, thrombolysis], peripheral arterial surgery/reconstruction, peripheral angioplasty/stent, or amputation) within 30 days of onset of symptoms. In the absence of confirmation by limb hemodynamics or imaging, absent pedal pulses is acceptable as hemodynamic criterion for acute limb ischemia. If the event does not meet the definition for ALI it may be classified as

chronic limb ischemia, peripheral vascular intervention or other peripheral vascular hospitalization.

CLI is defined as continuing ischemic limb, foot or digit pain leading to hospitalization and intervention and not meeting the definition of ALI, or Fontaine 3 or 4 at baseline with peripheral intervention during the trial.

Peripheral vascular intervention is defined as peripheral vascular intervention not meeting the definition for ALI or CLI.

Additional Study Outcomes: Admission for heart failure will also be assessed at 12 months. Adherence to the twice-daily regimen of apixaban (and placebo) will be recorded as the total number of doses taken divided by the total number of doses prescribed. Adherence data will be recorded on patient-maintained drug diaries.

Clinical Endpoints Committee Adjudication of Study Outcomes

Primary and secondary safety and efficacy outcome will be independently adjudicated by a Clinical Endpoints Committee (CEC) that is blinded with regards to the subject's treatment allocation (randomization). The CEC will include a chairperson and independent reviewers who are physicians with experience in vascular medicine and thrombosis. The CEC will adjudicate all index events (proximal DVT and/or PE). During the study period and the post-treatment observation period, the CEC will adjudicate all suspected occurrences/recurrences of venous or arterial thromboembolic events, deaths, and the following events of special interest: acute myocardial infarction, acute stroke, and thrombocytopenia. The CEC will also review all suspected episodes of bleeding, and categorize adjudicated bleeding as major, clinically relevant non-major, or minor bleeding. The Committee will be provided with all relevant documentation related to the events but will be blinded as to the subject's treatment allocation. The criteria and definitions of the study outcomes as well as the procedures followed by the Committee are described in this protocol.

Drug Accountability

Study drug and placebo will be physically stored at BWH in our Investigational Drug Pharmacy. Drug handling and dispensing will be accomplished through our BWH Investigational Drug Service. The Director of Pharmacy at BWH will oversee the Investigational Drug Service in this regard for the purposes of the clinical trial. Documentation of administration will by accomplished by our Electronic Health Record (EHR; EPIC) in addition to a patient drug diary, which is being kept to assess medication adherence. The Investigational Drug Service will collect empty study drug containers and unused drug via mail using prepaid labels that will be provided to the patient or courier as per Investigational Drug Service policy. We will perform drug accountability assessment when the drug containers are collected at each 3-month interval.

Follow-Up

Follow-Up Evaluation

Routine laboratory testing is neither recommended nor required in patients receiving extended duration apixaban, including the 2.5 mg twice daily dosing regimen. Patients enrolled in the study will either have been identified from one of the practices of our Vascular Medicine faculty or will be assigned to one of our faculty for long-term management of VTE. Accordingly, every patient enrolled in the study will have ongoing medical care with a dedicated Vascular Medicine provider. Study patients will be encouraged to follow-up with their primary care, , and other appropriate clinicians. Specifically, at the end of the treatment visit, every patient will be reminded to follow-up with a PCP as dictated by routine care and best clinical practice. Demographic, clinical characteristics, medication records, and outcomes will be abstracted from the BWH Electronic Health Record (EPIC).

When our Research Nurse conducts the every 3-month telephone call in advance of releasing a 3-month allotment of study drug or placebo the subject will be queried for any issues with the study or adverse events.

We will conduct an end-of-treatment visit to obtain data relevant to the study end points.

We will assess medication adherence via pill count. Medication adherence will be calculated in three month intervals as the total number of doses taken divided by the total number of doses prescribed for that time period ([x / 180] x 100 = medication adherence [%]) and also for the total 360-day study period ([x / 720] x 100 = medication adherence [%]). Subjects will be given a study drug diary to fill out at home each day. Subjects will write down the time they take their study drug and any side effects. The study drug diary will be collected at a regularly scheduled office visit or the end-of-treatment visit at conclusion of the study period.

Subject Retention, Withdrawal, and Termination

Continued participation of study subjects will be encouraged at the time of outpatient evaluation through the 12-month follow-up interval. However, study subjects will be informed that they retain the right to withdraw from the study at any time without compromise to their current or subsequent medical care. Subjects will be terminated from the study if they expire or elect to withdraw.

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

1. Be contacted by telephone **AND**
2. Have their physicians contacted

Withdrawal criteria will include:

1. Patient requests to withdraw
2. Reasons related to SAE:
    a. Initiating or continuing study drug places the subject at undue hazard as determined by the Investigator;
    b. SAE or other safety concern that is related to study drug treatment;
    c. Major or life-threatening bleeding (as defined in the protocol)
    d. ALT or AST ≥ 3 ULN, if suspected to be due to the study drug
    e. Calculated CrCL decreased to < 30 mL/min confirmed by repeat testing at least one week later, or need for dialysis
3. Pregnancy
4. Patient develops severe hepatic impairment (Child-Pugh class C) during the trial
5. Death
6. Lost to follow-up (every attempt will be made by the Investigator not to have subjects "lost to follow-up")
7. Study terminated by sponsor (termination of all or part of the study by the sponsor, in concert with the study leadership)

Safety Monitor

An independent Safety Monitor has been selected for this study. The Safety Monitor is an expert in VTE and is distinct from the DMSB and Study Staff and will be available throughout the study to assess patient safety issues that may arise, objectively. The Safety Monitor will have the ability to break the blind of a study patient as the need arises (immediately, in real-time). If the Safety Monitor is unavailable because of travel, one of the Physician Study Investigators will serve as back-up. The Safety Monitor will attend DSMB meetings, although will be non-voting. The Safety Monitor will have the ability to request an ad hoc DSMB meeting should a safety issue arise that warrants further review.

Assessment and Reporting of Adverse Events

Definitions

Adverse events

An adverse event (AE) is defined as any new untoward medical occurrence or worsening of a pre-existing medical condition in a patient or clinical investigation subject administered an investigational (medicinal) product and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of investigational product, whether or not considered related to the investigational product. The causal relationship to study drug is determined by a physician and should be used to assess all AEs.

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

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

Serious Adverse Events

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

- results in death
- is life-threatening (defined as an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- requires inpatient hospitalization or causes prolongation of existing hospitalization
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect
- is an important medical event, defined as a medical event that may not be immediately life-threatening or result in death or hospitalization but, based on appropriate medical and scientific judgment, may jeopardize the subject or may require intervention (e.g., medical, surgical) to prevent one of the other serious outcomes listed above. Examples of such events include but are not limited to intensive treatment in an emergency department or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization.

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

The following hospitalizations are not considered SAEs:

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

lack of housing, economic inadequacy, caregiver respite, family circumstances, administrative reason)

Adverse Events of Special Interest

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

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

Pre-Existing Medical Conditions

A pre-existing medical condition is one that is present at the start of the study. Pre-existing medical conditions should be recorded in the baseline and demographic data section of the electronic case report form (eCRF). Pre-existing medical conditions should be reassessed during the trial and reported as an adverse event or severe adverse event only if the frequency, severity, or character of the conditions worsens significantly or unexpectedly during the study. When reporting such adverse events, the description should convey that the pre-existing condition has changed by including applicable descriptors (e.g., "more frequent" headaches). Previously scheduled hospitalizations and hospitalizations required for diagnostic or elective surgical procedures for the management of unchanged pre-existing medical condition should not be considered adverse events.

Serious Adverse Event Collecting and Reporting

Following the subject's written consent to participate in the study, all SAEs, whether related or not related to study drug, must be collected, including those thought to be associated with protocol-specified procedures. All SAEs must be collected that occur during the screening period and within 30 days of discontinuing dosing. If applicable, SAEs must be collected that relate to any later protocol-specific procedure.

When our Research Nurse conducts the every 3 month telephone call in advance of releasing a 3-month allotment of study drug or placebo the subject will be queried for any issues with the study or adverse events. The Electronic Health Record, Epic, will notify study staff when a study subject is admitted to the hospital or presents to the Emergency Department. This notification will be an additional avenue for detection of SAEs. Providers will also be able to see that the patient is enrolled in the study and how to contact study staff through the EHR.

SAEs will be detected via report from the study subject, the subject's care providers, a study physician or staff member, or identification from the EHR during data collection. Patients that report AEs to the study staff will be contacted by a study physician and triaged to the appropriate setting for care depending on the nature and severity of the AE and in accordance with best clinical practices.

The investigator should report any SAE occurring after these time periods that is believed to be related to study drug or protocol-specified procedure. An SAE report should be completed for any event where doubt exists regarding its status of seriousness. If the investigator believes that an SAE is not related to study drug, but is potentially related to the conditions of the study (such as withdrawal of previous therapy, or a complication of a study procedure), the relationship should be specified in the narrative section of the SAE Report Form.

SAEs, whether related or unrelated to the study drug, and pregnancies must be reported to BMS within 1 business day of becoming aware of the event:

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

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

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

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

SAE Reconciliation

The Sponsor will reconcile the clinical database AE cases (**case level only**) transmitted to BMS Global Pharmacovigilance (GPV&E) (Worldwide.Safety@bms.com).

- The Investigator will request from BMS GPV&E, aepbusinessprocess@bms.com the SAE reconciliation report and include the BMS protocol number every 3 months and prior to data base lock or final data summary
- GPV&E will send the investigator the report to verify and confirm all SAEs have been transmitted to BMS GPV&E.
- 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 should be sent immediately to BMS (Worldwide.Safety@bms.com).

Health Authority Reporting (U.S. FDA IND)

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

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

MedWatch SAE forms should be sent to the FDA at:

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

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

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

In addition to the Sponsor Investigator's responsibility to report events to their local Health Authority (HA), suspected serious adverse reactions (whether expected or unexpected) shall be reported by BMS to the relevant competent health authorities in all concerned countries according to local regulations (either as expedited and/or in aggregate reports).

- In accordance with local regulations, BMS will notify sponsor investigators of all reported SAEs that are suspected (related to the investigational product) and unexpected (ie, not previously described in the Investigator's Brochure (IB)). An event meeting these criteria is termed a Suspected, Unexpected Serious Adverse Reaction (SUSAR). Sponsor investigator notification of these events will be in the form of either a SUSAR Report or a Semi-Annual SUSAR Report.
  - ✓ Other important findings which may be reported by BMS as an Expedited Safety Report (ESR) include: increased frequency of a clinically significant expected SAE, an SAE considered associated with study procedures that could modify the conduct of the study, lack of efficacy that poses significant hazard to study subjects, clinically significant safety finding from a nonclinical (eg, animal) study, important safety recommendations from a

study data monitoring committee, or sponsor or BMS decision to end or temporarily halt a clinical study for safety reasons.

- ✓ Upon receiving an ESR from BMS, the investigator must review and retain the ESR with the IB. Where required by local regulations or when there is a central IRB/Independent Ethics Committee (IEC) for the study, the sponsor will submit the ESR to the appropriate IRB/IEC. The investigator and IRB/IEC will determine if the informed consent requires revision. The investigator should also comply with the IRB/IEC procedures for reporting any other safety information.

Non-Serious Adverse Events

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

Non-Serious Event Collecting and Reporting

The collection of non-serious AE information should begin following the subject's written consent to participate in the study. 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.

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.

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 captured and reported as appropriate:

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

- Any laboratory test result abnormality that required the subject to receive specific corrective therapy.

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

Pregnancy

If, following initiation of apixaban, it is subsequently discovered that a study subject is pregnant or may have been pregnant at the time of apixaban exposure, including during at least 5 half-lives after product administration, the investigational product will be permanently discontinued in an appropriate manner. The investigator must immediately notify WorldwideSafety@BMS.com of this event via the Pregnancy Surveillance Form within 24 hours and in accordance with SAE reporting procedures.

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

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

Protocol-required procedures for study discontinuation and follow-up must be performed on the subject unless contraindicated by pregnancy. Other appropriate pregnancy follow-up procedures should be considered if indicated.

Other Safety Considerations

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

Documentation of Adverse Events

Information about potential adverse events should be reviewed during the 6-month follow-up period. Subjects should be encouraged to report adverse events spontaneously or in response to non-directed questioning by their usual healthcare providers. If it is determined that an adverse event has occurred, the study staff

member entering data into the eCRF should obtain all of the information necessary to complete the Adverse Event section. All observed or reported adverse events, regardless of the suspected causal relationship to study treatment must be recorded in the Adverse Event section of the eCRF. The Sponsor will be notified when an event has been entered into the database.

Duration of Adverse Event Reporting Period

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

Specific Adverse Event Reporting Guidelines

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

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

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

Categorization of Adverse Events

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

Intensity or Severity

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

Mild	Awareness of a symptom or sign that does not interfere with the patient's usual activity or is transient and resolves without treatment and without sequelae
Moderate	Interferes with the patient's usual daily activities, but he or she is still able to function
Severe	Interrupts a patient's usual daily activities and generally requires medication, surgery, or other intervention for treatment

Expectedness

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

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

Relatedness

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

Definite	An adverse event is clearly related to apixaban

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

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

Outcome

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

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

Treatment or Action Taken

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

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

Expedited Reporting of Serious Adverse Events (SAE)

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

1. Report any serious adverse event that occurs to the Sponsor within 24 hours of knowledge of the event (Monday through Friday). If the investigator does

not have all information regarding the SAE, ***he/she will not wait to receive additional information before notifying the Sponsor*** of the event and completing the eCRF. The investigator shall provide an event update when additional information is received.

NOTE: The Sponsor will automatically be notified when an adverse event or serious adverse event has been entered into the database when the investigator fills in an eCRF.

2. In the reporting of serious adverse events, the study investigator shall provide any potentially relevant information including:
    a. Subject demographics
    b. Pre-existing conditions
    c. The complete description of the adverse event.
    d. Date and time of adverse event onset
    e. Severity
    f. Treatment
    g. Results of diagnostic testing
    h. Duration of sequelae
    i. Outcome (if known)
    j. Date and time of adverse event resolution.
    k. Information on suspected medications including dose, route of administration, frequency, dates, lot number, expiration date, and concomitant medications

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

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

Sponsor Unanticipated Adverse Drug Effects (UADEs) Reporting Responsibilities

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

<u>Data Reporting, Processing, and Quality Control</u>

Data Acquisition, Monitoring, and Quality Control

Subject data will be collected using a web-based electronic case report form (eCRF) called REDCap. Database monitoring and quality control will be performed by the Data Safety Monitoring Board (DSMB).

Monitoring Plan

Monitoring procedures will consist of the following:

During the study, the study staff shall perform monthly random reviews of data with checks for accuracy and completeness, and document that corrective actions have been taken in response to protocol deviations or other forms of non-compliance. These reports will be provided to the Data Safety Monitoring Board.

Data Safety Monitoring Board

Three independent individuals with relevant expertise in VTE and anticoagulation will be appointed to a data safety monitoring board (DSMB) whose primary responsibility is to protect the safety of study subjects and to provide ongoing, critical, and unbiased evaluation of the progress of the study. The DSMB will be comprised of two independent physicians and an independent statistician. To further ensure idependence of the DSMB, the DSMB Chair has been selected and is an expert in VTE AND comes from outside the Mass General Brigham Network.

The DSMB will:

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

The DSMB will meet virtually via Zoom under the restrictions imposed by the COVID-19 pandemic. The DSMB will meet once before the initiation of the trial and then at least once every three months for the duration of the trial in addition to prespecified meetings at 10 months and 50% of enrollment (Table). In addition, the DSMB may be convened on an *ad hoc* basis at the request of the study investigators if the need (for example, due to a study-related concern) arises in between regularly scheduled meetings. The DSMB chair may call an emergency meeting at any time should questions of patient safety arise or at the request of the Study Safety Monitor. The exact dates and times of the DSMB meetings will be determined based on the availability of all three members to meet and will take place within the first two weeks of the given month.

1. Prior to the first meeting, the DSMB will be provided with FDA- and IRB-approved protocol, DSMB Charter, and DSMB Adjudication Report Form to allow for review and charter revisions prior to the first meeting called the DSMB Kick-off meeting.
2. The DSMB Kick-Off meeting will provide formal training on the protocol provided by the Thrombosis Research Group staff. During the first meeting, the DSMB will review and approve the final Charter. The DSMB will determine reports needed for safety review and establish stopping rules.
3. Planned DSMB meetings will take place every three months. The DSMB will review all safety data collected to date on the initial subjects enrolled. The DSMB will also assess whether the study is on-track to meet its enrollment goal. Once the review is complete and no safety or enrollment concerns are raised, the trial will continue.
4. A DSMB meeting will be held at the halfway point through the enrollment period (10 months). At this point the DSMB will assess whether the study is on-track to meet its enrollment goal. The DSMB will also assess any safety concerns at that time. Once the review is complete and no safety or enrollment concerns are raised, the trial will continue.
5. A DSMB meeting will also occur when 50% of the planned enrollment population has completed 12-month follow-up as part of the prespecified interim analysis. This planned interim analysis will inform the DSMB on whether the study should be stopped early due to efficacy, safety concerns, or futility or continue to enroll the full 600-patient cohort.
6. A final DSMB meeting will take place after follow-up completion of the last subject. The DSMB will review all remaining safety data collected on the subjects enrolled.
7. The DSMB chair may call an emergency meeting at any time should questions of patient safety arise or at the request of the independent Study Safety Monitor. All materials, discussions, and proceedings of the DSMB are completely confidential. The Chair and other participants present at DSMB meetings are expected to maintain confidentiality.

Table. Schedule of Planned DSMB Assessments.

Milestone-Based Meetings	Timing
Kick-Off	1 month before enrollment of first patient
Halfway Point of Enrollment Period	10 months after first patient enrolled
300th Patient Interim Analysis	After follow-up completion in the 300th patient
Final Meeting	After follow-up completion in last patient

Recurring Meetings	
#2	3 months after first patient enrolled
#3	6 months after first patient enrolled
#4	9 months after first patient enrolled
#5	12 months after first patient enrolled
#6	15 months from first patient enrolled
#7	18 months from first patient enrolled
#8	21 months from first patient enrolled

Interim Safety and Efficacy Analysis

The DSMB will meet to review the safety and efficacy outcomes for the first 300 patients enrolled in the study when they have completed 12-month follow up. Whether to continue, amend, suspend, or terminate the study will be made based in this interim analysis. The DSMB will review the safety and efficacy outcomes again at the completion of follow up completion of the last patient enrolled in the study.

The DSMB will be responsible for:

1. Assessing study enrollment and likelihood of completion of 600 patients randomized
2. Assessing the study event rate in the placebo group and likelihood of obtaining enough events to satisfy the requirements for the primary efficacy analysis
3. Assessing the event rates in the treatment and placebo groups
4. Assessing the accumulated SAEs to determine whether the safety stopping criteria have been meet

Actions taken by the DSMB will include the following recommendations:

1. Study termination if stopping criteria for safety or futility have been met
2. Study modification if the DSMB deems that remediation measures have a reasonable probability of successful completion of the study
3. Continuation of the study as is

Blinding/Unblinding

This study will be conducted in a blinded fashion. To maintain blinding of study treatment, study medications will be prepared using placebo matching the active treatments. Subjects, Investigators, members of any of the administrative and adjudicating committees, and the Sponsor's staff conducting the study, will not have access to individual subject treatment assignments.

Blinding is critical to the integrity of this clinical study. However, in the event of a medical emergency or pregnancy in an individual subject, in which knowledge of the investigational product is critical to the subject's management, the blind for that

subject may be broken by the Safety Monitor (or if unavailable, the treating investigator). Before breaking the blind of an individual subject's treatment, the Safety Monitor should have determined that the information is necessary, i.e., that it will alter the subject's immediate management. In many cases, particularly when the emergency is clearly not investigational product-related, the problem may be properly managed by assuming that the subject is receiving active product without the need for unblinding.

The Safety Monitor should ensure that health care professionals who may provide any elective, urgent or emergent medical or surgical care for a subject after randomization are informed that:

1. The subject is enrolled in a clinical study and is receiving blinded oral study treatment, consisting of:
    a. Factor Xa inhibitor, OR
    b. Placebo
2. The factor Xa inhibitor is an anticoagulant, with a half-life of approximately 12 hours, which cannot be monitored using standard laboratory tests, such as PT, PTT, ACT, and INR
3. In the event of an emergency, this person should be treated symptomatically as would any other person being treated with anticoagulants. Treatment in an emergency may include discontinuation of all study treatment, and the use of standard resuscitative management and hemostatic agents such as prothrombin complex concentrate or andexanet alfa, if appropriate.

When knowledge of the subject's randomized treatment assignment would have a meaningful impact on individual management, for example in many cases of clinically significant bleeding or the need for urgent invasive procedures, the subject's treatment assignment should be unblinded. This information should be provided to those who are caring for the subject and as few other people as possible. In these cases, we will minimize bias by assuring that the clinical events committee remains blinded to treatment assignment, even if the investigator has been unblinded. Every subject will be provided with an alert card.

The alert card:

- Will indicate that the subject is participating in a double-blind clinical trial.
- Provides the sponsor's name and trial number.
- Will note that the subject may be receiving either placebo or an investigational anticoagulant drug (a factor Xa inhibitor).
- Provides the Study Safety Monitor's name and emergency contact information to provide information to emergency medical personnel

The need to break the blind must first be discussed with the responsible Safety Monitor who will be available to page at all times by the responsible care provider. The Safety Monitor will have electronic access to the subject's study allocation and can thereby break the blind.

Invasive Procedures and Surgery

Several factors govern the management of anticoagulation in this study with respect to surgery and invasive procedures, as well as the management of bleeding that may occur in subjects on study drugs. These are:

- The risk of thromboembolism in an individual subject (low, intermediate or high).
- The risk of bleeding associated with the procedure or surgery.
- Whether the surgery or invasive procedure is elective or emergent in nature.
- The desirability of maintaining blinding, if at all possible, without creating risk for the subject.
- The times of onset and offset of anticoagulant effect for apixaban

Elective Procedures

In general, local standards of care for discontinuation of anticoagulation prior to elective procedures/surgery should be employed; these may be informed by current guidelines.

These are summarized below:

- Stop apixaban/apixaban-placebo 2-4 days before the planned procedure.
- If the procedure is associated with an increased risk of thrombosis, brief postoperative protection with UFH or LMWH may be considered.
- Restart apixaban/apixaban-placebo postoperatively (usually the day after surgery) when it is deemed safe to do so. If UFH/LMWH is used in the postoperative period, it is recommended that apixaban/apixaban-placebo begin:
    - ≥ 2 hours after the last dose of UFH;
    - ≥ 6 hours after the last dose of LMWH indicated for twice daily administration; or
    - ≥ 12 hours after the last dose of LMWH indicated for once daily administration (or fondaparinux).

Emergency Procedures

For urgent or emergent invasive procedures, when waiting 4 - 5 days is not an option, management will in part depend on the randomized treatment assignment (placebo or apixaban) and unblinding may be necessary (see Section on Blinding/Unblinding). Regardless of treatment, study drugs should be discontinued and standard laboratory coagulation tests (PT/INR, aPTT, platelet count, etc.) performed. The procedure should be carried out and in such a way to minimize the risk of bleeding. For subjects receiving apixaban, the risk of bleeding with invasive procedures is unknown. At therapeutic doses, the anticoagulant effects of apixaban will not be reflected in standard coagulation tests. Given its half-life (12 hours), however, the anticoagulant effect of apixaban abates in 24 - 48 hours. Depending on the subject's risk of

bleeding with the procedure, subjects receiving apixaban who require an invasive or surgical procedure within 24 hours of their last dose may be treated with prothrombin complex concentrate or andexanet alfa. If treatment with an alternative open label anticoagulant/antithrombotic is indicated for the procedure, it should be used at the lowest therapeutic dose (if at all) in the 12 hours following last dose of apixaban.

Treatment Guidelines for Bleeding/Suspected Bleeding

Subjects with bleeding or suspected bleeding will undergo confirmatory laboratory or other testing (e.g., US, CT, MRI) and a (S)AE CRF must be completed. The date and time of the onset of the bleeding event will be recorded on the CRF.

For subjects with minor bleeding, study drug may or may not be held at the discretion of the local physician and investigator. A risk/benefit determination should be made weighing the subject's risk of further bleeding against the subject's risk of thromboembolism and benefit from continued anticoagulation. Minor bleeding should otherwise be managed according to local standard of care.

For subjects with clinically significant bleeding, the study drugs should generally be held. Bleeding should be managed according to local standard of care and may include measures such as:

- Local measures to stop the bleeding
- Volume resuscitation, and transfusion of blood products as appropriate
- Standard laboratory tests (e.g., hemoglobin, hematocrit, platelet count, etc.)

Note: Neither apixaban nor the comparator affects standard coagulation tests.

The management of clinically significant bleeding will in part depend on the randomized treatment assignment (placebo or apixaban) so unblinding may be necessary (see Section on Blinding/Unblinding). Should unblinding occur, subjects receiving placebo should be managed according to the local standard of care. Given its half-life (12 - 15 hours), however, the anticoagulant effect of apixaban abates in 24 - 48 hours. Subjects receiving apixaban with clinically significant bleeding that does not respond to local measures may be treated with prothrombin complex concentrate (PCC) or andexanet alfa as per Good Clinical Practice and local anticoagulant reversal protocols.

Management of Recurrent Venous Thromboembolic Events

If a subject has a confirmed recurrent symptomatic VTE (DVT or PE), as deemed by the primary investigator, then the patient must discontinue study treatment and transition to the appropriate standard of care. The subject should remain in the study and should be followed in the same manner as a subject who has discontinued study treatment as described in the protocol.

Prohibited and/or Restricted Treatments

Prohibited Treatments:

The following medications or therapies are prohibited during the study treatment period:

- Potent inhibitors of CYP3A4 (e.g., azole antifungals [itraconazole and ketoconazole], macrolide antibiotics [clarithromycin and telithromycin], protease inhibitors [ritonavir, indinavir, nelfinavir, atazanavir, and saquinavir], and nefazadone)
- Aspirin > 81 mg/day
- Dual antiplatelet therapy such as concomitant (simultaneous) use of both aspirin and a thienopyridine (e.g., clopidogrel, ticlopidine)
- Other antithrombotic agents (e.g., UFH, LMWH, direct thrombin inhibitors, fondaparinux)
- GP IIb/IIIa inhibitors (e.g., abciximab, eptifibatide, tirofiban)

If treatment with a prohibited agent becomes necessary, study drug should be temporarily interrupted, and restarted as soon as possible following discontinuation of the prohibited medication or therapy.

Restricted Treatments:

The administration of the following agents in subjects on study drug should be done cautiously given the increased risk of bleeding. In such cases, consideration of interruption of the study drug may be warranted; this decision should be made after a careful assessment of the risks and potential benefits.

Examples:

- Chronic (> 3 months) daily NSAIDs. NSAIDs should not be administered in doses that exceed those in the approved label
- Cytotoxic/myelosuppressive therapy

In addition, if a subject is currently receiving an agent that is a potent inducer of CYP3A4 (e.g., rifampin), the investigator should carefully evaluate that subject's risk of thromboembolism, as the plasma concentration of apixaban may be lower than that in subjects not receiving a potent inducer of CYP3A4

Stopping Criteria

The DSMB will consider efficacy events, in addition to safety events, before making any study stopping recommendations to the principal investigator.

1. General Stopping Rules

A. The DSMB, IRBs, regulatory authorities, or the Investigator may make recommendations to terminate the study if the safety and well-being of the subjects is in jeopardy.
B. If the study is terminated or suspended, prompt notification will be provided to all parties of the study.
C. Patient enrollment may be paused or terminated early if the DSMB determines that the potential benefits of continuing the trial are unlikely to outweigh the risks. For example, if the probability of achieving the target primary endpoints falls below a certain threshold, the trial will be stopped or paused for re-evaluation.

2. Safety Stopping Rules

   The study will be terminated by the DSMB and principal investigator at any point if the following stopping criterion is met:

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

3. Stopping Rules for Futility

   The study will be terminated by the DSMB and principal investigator if any of the following stopping criteria is met:

   a. Fewer than 36 events are observed in the placebo group at the time of the 300th patient interim statistical analysis
   b. Enrollment progress has been limited such that the study does not have a reasonable chance of randomizing 600 patients even after efforts to remediate recruitment

Protocol Violations

The study staff will rapidly and firmly address any protocol violations with the DSMB. If a protocol violation is detected or suspected, the investigator(s) will first be asked to provide a written explanation. After reviewing the available information, the study staff will categorize protocol violations as either major (eligibility or

primary/secondary endpoint determination compromised or indefinite) or minor (data still able to be used for endpoint determination), and will record and track them. Protocol violations with be reviewed by the DSMB. Major protocol deviations will be reported to the Partners Human Research Committee within five working days of the date the investigator becomes aware of the unapproved deviation. Minor deviations will be recorded in a Minor Deviation Log and this will be submitted to the Partners IRB with the continuing review.

Data Confidentiality

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

Compliance with Laws and Regulations

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

Statistical Methods

Sample Size Calculation

This study is a 600-patient single-center, randomized controlled trial utilizing an enriched population. Based on the contemporary (within the last 10 years) large pivotal trials of extended duration anticoagulation (2,3,7) and a large meta-analysis of low-dose aspirin (31) for prevention of recurrent events in patients with initial unprovoked VTE or clinically suspected to have a high risk of recurrence, we conservatively estimate an average 12-month VTE recurrence rate in patients not treated with extended-duration anticoagulation (placebo group) of 6% (Table 2).

VTE Recurrence Rates in the Control Arm in Major Extended Duration Secondary Prevention Trials including Provoked Events

Trial	% Provoked	Control	Rate	Follow-Up Period
EINSTEIN CHOICE	60%	Aspirin 81 mg QD	**3.6%**	<12 months (follow-up shorter than planned in

				subset of patients)
EINSTEIN VTE Continued Treatment	25%	Placebo	**7.1%**	12 months
AMPLIFY EXT	9%	Placebo	**8.8%**	12 months

In EINSTEIN CHOICE which randomized 60% of patients with provoked VTE, the control group received low-dose aspirin (which based on a meta-analysis in unprovoked VTE patients confers about a 33% relative risk reduction) had a recurrence rate of 3.6% (2,31). Accordingly, we would expect the 12-month VTE recurrence rate to be at least 33% higher in patients assigned to placebo in the proposed study and therefore approximately 5-6%. The recurrent VTE rate among placebo patients in the AMPLIFY-EXT trial of apixaban was quite a bit higher at 8.8% (7). By requiring that at least one additional persistent provoking VTE risk factor be present (persistent immobility, obesity, heart failure, chronic lung disease, chronic kidney disease, inflammatory disorder, or atherosclerotic cardiovascular disease), we will expect an "enriched" event rate in the population of the proposed study by at least 2-fold (all of these persistent provoking risk factors increase the risk of VTE by 2-4-fold; Table 3) (32). Many patients enrolled in the study will have multiple persistent provoking VTE risk factors (for example, heart failure, obesity, and atherosclerotic cardiovascular disease) and thereby have an even higher risk for recurrence. In an effort to be ultra-conservative, we kept the multiplier for this enriched study population to 2-fold (while in reality for many study patients it could be 4-fold or even higher). Accordingly, our estimate of a 12-month VTE recurrence rate of 6% is very conservative and still below the VTE recurrence rates reported in EINSTEIN VTE Continued Treatment and AMPLIFY EXT (neither of which included an enriched population).

Table 3. Relative risk of VTE by persistent provoking risk factor.

Persistent Provoking Risk Factor	**Relative Risk**
Persistent immobility	4-fold
Obesity (BMI ≥ 30)	2-3-fold
Heart failure	2-fold
Chronic lung disease	2-fold
Chronic kidney disease	2-fold
Inflammatory/autoimmune disorder	3-fold
Atherosclerotic cardiovascular disease	4-fold

Based on the data from EINSTEIN CHOICE, we conservatively estimate that low-intensity apixaban (2.5 mg twice daily) compared with placebo will provide a similar

reduction (75%) in recurrent VTE as low-intensity rivaroxaban (10 mg daily) compared with low-dose aspirin (2). The 75% relative risk reduction was reported specifically for recurrent VTE and in the provoked VTE patient population, comparing rivaroxaban 10 mg daily versus low-dose aspirin. This relative risk reduction specifically pertains to our primary study outcome and our exact patient population and comes from a robust randomized controlled trial analysis. If anything, the reduction in the proposed study should be even greater since we propose a placebo-control instead of active (aspirin) control and we will be following our patients for 12 months, instead of allowing shorter follow-up as was reported in EINSTEIN CHOICE. Accordingly, assuming an estimated incidence in the placebo group of 6% at 12 months and a decrease in the primary outcome of 75% with apixaban 2.5 mg twice daily as compared with placebo, we calculated that we would need to enroll 279 patients in each group for the study to have 80% power to show the superiority of low-intensity apixaban over placebo, at a two-sided alpha level of 0.05. To account for patients who may be lost to follow-up or withdraw from the study, we will recruit 300 in each arm and 600 total.

EINSTEIN-CHOICE enrolled patients after a required 6 to 12 months of anticoagulant therapy. Our study requires that patients complete at least 3 months of anticoagulant therapy in accordance with current and widely-accepted evidence-based clinical practice guidelines (Eur Heart J. 2020; 41: 543–603, Chest. 2016;149:315-352, and Circulation. 2011;123:1788–1830). Data from the PADIS-PE study showed that the rate of VTE recurrence is higher closer in temporal proximity to the initial event, such that the recurrence rate is higher at 3-6 months after diagnosis than it is at 6-12 months (Couturaud F, et al. Six Months vs Extended Oral Anticoagulation After a First Episode of Pulmonary Embolism. JAMA. 2015;314(1):31-40). Accordingly, the anticipated event rate should be higher in our study than EINSTEIN-CHOICE and the resultant observed relative risk reduction is likely to be higher.

Sensitivity analyses performed for the comparison between apixaban 2.5 mg twice daily and placebo (Tables 4 - 6) show that our sample size is most sensitive to change in the impact of the extended duration anticoagulation. However, we have been very conservative in our effect size calculation and baseline recurrent VTE rate (for example, we have not taken into account the increase in event rates of an enriched population with persistent immobility, obesity, heart failure, chronic lung disease, chronic kidney disease, inflammatory disorder, or atherosclerotic cardiovascular disease), as above.

Table 4. Sensitivity of sample size to changes in power.

Power	Total Sample Size
60%	350
70%	440
80%	**558**
90%	746
99%	1300

(assuming event rate of 6%; 75% risk reduction attributed to low-dose apixaban)

Table 5. Sensitivity of sample size to changes in VTE event rate.

VTE Event Rate	Total Sample Size
3%	1140
4%	848
6%	**558**
8%	412
10%	326

(assuming 80% power; 75% risk reduction attributed to low-dose apixaban)

Table 6. Sensitivity of sample size to changes in impact of extended duration anticoagulation with low-intensity apixaban (effect size).

Relative Risk Reduction	Total Sample Size
45%	1908
55%	1198
65%	800
75%	**558**
80%	472

(assuming 80% power; event rate of 6%)

The sample size calculation for the trial was calculated based upon 12-month rates of recurrent VTE from pivotal randomized controlled trials (2,3,7,33) and a large meta-analysis of low-dose aspirin vs. placebo (31). Accordingly, assuming an estimated incidence in the placebo group of 6% at 12 months and a decrease in the primary outcome of 75% with apixaban 2.5 mg twice daily as compared with placebo, we calculate that we will need to enroll 279 patients in each group for the study to have 80% power to show the superiority of low-intensity apixaban over placebo, at a two-sided alpha level of 0.05. If the trial utilized 6-month follow-up instead of 12-month, we would observe fewer recurrent VTE events and would require an increase in the sample size, which would require a longer enrollment period and would incur greater cost. As such, we have determined 12-month follow-up to facilitate the most efficient and cost-effective trial.

We have conducted a retrospective analysis using an ongoing BWH registry of 405 patients with pulmonary embolism/deep vein thrombosis. We identified 83 patients without active cancer and with at least one provoking risk factor. Among those who received 3-6 months of anticoagulation, 11.1% developed symptomatic recurrent venous thromboembolism in the ensuing year after stopping anticoagulation. If we utilize this baseline rate of recurrent VTE in our sample size calculation, we will require 212 patients in each study group, assuming a 75% relative risk reduction with apixaban 2.5 mg twice daily compared with placebo and 90% power to show the superiority of low-intensity apixaban over placebo, at a two-sided alpha level of 0.05.

We have also consulted with an independent biostatistician from the Harvard Catalyst Biostatistics Program (Shelley Hurwitz, PhD) to review our sample size requirement. She confirmed our sample size calculation using a recurrent VTE rate in the placebo

group of 6% from the best available literature and also using the rate of 11.1% from our observational cohort of patients that would be eligible for this study (see Table 7. below).

Table 7. Harvard Catalyst Biostatistics Program Consultant Sample Size Calculations (performed by Dr. Hurwitz using STATA).

Anticipated Event Rate = 6%	Anticipated Event Rate = 11.1%
. power twoproportions .06 .015, test(chi2) n(558) Estimated power for a two-sample proportions test Pearson's chi-squared test Ho: p2 = p1 versus Ha: p2 != p1 Study parameters: alpha = 0.0500 N per group = 279 p1 = 0.0600 p2 = 0.0150 Estimated power: power = 0.8005	. power twoproportions .111 .0278, test(chi2) n(424) Estimated power for a two-sample proportions test Pearson's chi-squared test Ho: p2 = p1 versus Ha: p2 != p1 Study parameters: alpha = 0.050 N per group = 212 p1 = 0.1110 p2 = 0.0278 Estimated power: power = 0.9236
Required N = 279 per group	Required N = 212 per group

It was also suggested that we consider using the lower limit of the 95% confidence interval around our estimate of 11.1%, which would be 8.2%. The statistician suggested that this would also provide a conservative estimate of the frequency of recurrent VTE for the sample size calculation (see Table 8 below).

Table. 8 Harvard Catalyst Biostatistics Program Consultant Sample Size Calculation Using Lower Limit of 95% Confidence Interval of Our Observational Cohort Estimate (performed by Dr. Hurwitz using STATA).

Anticipated Event Rate = 8.2%
. power twoproportions .082 .0205, test(chi2) n(558) Estimated power for a two-sample proportions test Pearson's chi-squared test Ho: p2 = p1 versus Ha: p2 != p1 Study parameters: alpha = 0.0500 N = 558 N per group = 279 p1 = 0.0820 p2 = 0.0205 Estimated power: power = 0.9111
Required N = 279 per group

Using this more conservative sample size calculation, we would aim to enroll 300 patients in each arm for a total trial population of 600.

Statistical Analysis Plan

For this study, we will calculate:

1) the 12-month frequency of major and clinically relevant non-major bleeding
2) the 12-month frequency of symptomatic recurrent VTE

The primary efficacy objective of this trial is to determine whether apixaban 2.5 mg twice daily is superior to placebo for the primary endpoint of symptomatic, recurrent VTE after 12 months of extended therapy. The analysis will include descriptive statistics of event rates and 95% CI, and risk difference and 95% CI. The Mantel-Haenszel statistic will be used to test this hypothesis formally. Superiority over placebo will be claimed for a dose if the Hochberg adjusted p-value is ≤ 0.05 and the RR is < 1. The analysis will be supported by Kaplan-Meier curves. The primary efficacy outcome analysis will be intention-to-treat. We will also perform an on-treatment analysis.

The primary safety objective will be to determine whether apixaban 2.5 mg twice daily results in a statistically significant difference in major bleeding at 12 months (during the treatment period) compared with placebo. Analysis of incidence of these endpoints will be based on the safety analysis set. The analysis will include descriptive statistics of event rates and 95% CI, and risk difference and 95% CI. Hypotheses will be tested using Mantel-Haenszel statistic. The analysis will be supported by Kaplan-Meier curves of the time to first adjudicated major bleeding event. All bleeding analyses will be conducted on the safety dataset.

Baseline characteristics will be summarized by group. Any imbalances between the treatment groups for any demographic or baseline characteristic will be assessed based on clinical relevance in reviewing the summaries. For any differences deemed clinically relevant to the efficacy comparisons, exploratory analyses that include the imbalanced factor as a categorized covariate will be performed.

To account for the effect of baseline low-dose aspirin use in the study population on the rate of recurrent VTE after an initial provoked event, we will perform a pre-specified stratified efficacy analysis of patients receiving low-dose apixaban or placebo with low-dose aspirin compared with patients just receiving low-dose apixaban or placebo. We will calculate stratum-specific risk ratios (RR). Comparing the “crude” (overall or unadjusted) and stratum-specific risk ratios will enable us to determine whether aspirin modifies the effect of low-dose apixaban and to what extent. If the stratum-specific risk ratio is similar to the crude risk ratio, then there is minimal impact of low-dose aspirin. However, if the stratum-specific risk ratio differs from the unadjusted estimate by 10% or more, then low-dose aspirin modifies the effect of low-dose apixaban. We will conduct a similar analysis for the safety outcome of major bleeding.

We will also pre-specify subgroup analyses focused on the safety and efficacy of major populations of interest, in particular, elderly patients (age ≥ 65 years), women, and those with persistent provoking factors of immobility, obesity, heart failure, chronic lung disease, chronic kidney disease, hemodialysis, chronic inflammatory/autoimmune disorder, and atherosclerotic cardiovascular disease.

Means, medians, and frequency distributions will be calculated for continuous variables. Number and percentages will be reported for binary and categorical variables. Differences between subgroups of interest will be examined using the chi-square or Fisher's exact test for binary and categorical variables and t-test or Wilcoxon Rank Sum for continuous variables (if the subgroups are of sufficient size for statistical comparison).

Safety outcome analyses will be performed among patients who received one or more doses of a study drug (Safety Population). All p-values reported will be two-sided. A p-value < 0.05 will be considered significant. All analyses will be performed using SAS software.

Interim Analysis

We will conduct a pre-specified interim analysis to assess the primary safety and efficacy outcomes after 50% of the planned enrollment population has completed 12-month follow-up. This planned interim analysis will inform the Data Safety Monitoring Board on whether the study should be stopped early due to efficacy, safety concerns, or futility or continue to enroll the full 600-patient cohort.

The DSMB will be responsible for:

5. Assessing study enrollment and likelihood of completion of 600 patients randomized
6. Assessing the study event rate in the placebo group and likelihood of obtaining enough events to satisfy the requirements for the primary efficacy analysis
7. Assessing the event rates in the treatment and placebo groups
8. Assessing the accumulated SAEs to determine whether the safety stopping criteria have been meet

Actions taken by the DSMB will include the following recommendations:

4. Study termination if stopping criteria for safety or futility have been met
5. Study modification if the DSMB deems that remediation measures have a reasonable probability of successful completion of the study
6. Continuation of the study as is

Investigator Responsibilities

Study Initiation

Before enrollment of the first subject at the study site, the following documents must be on file with the funding provider (BMS/Pfizer):

1. Current *curriculum vitae* of the principal investigator and all co-investigators
2. Current, dated Institutional Review Board (IRB) membership list
3. Written documentation of IRB protocol approval (protocol number/title and approval date) and Informed Consent Form (protocol number/title and approval date)
4. A copy of the IRB-approved Informed Consent Form (The Informed Consent Form must be reviewed by the study Principal Investigator prior to IRB submission.)

Study Completion

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

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

Informed Consent

The Informed Consent Form must be signed by the subject before enrollment into the study. A hardcopy of the Informed Consent Form must be provided to the subject. If applicable, informed consent should be obtained using Interpreter Services. If an interpreter is required to explain the study, the informed consent form will be reviewed with translation in the patient's native tongue, and a short consent document will presented to the patient for signature in the language in which the patient is literate.

Signed Informed Consent Forms must remain in each subject's study file and be available for verification by the Study Sponsor at all times. Documentation of the date informed consent was obtained and a notation that a signed copy of the Informed Consent Form was provided to the study subject should be recorded. The informed consent process must always be conducted in a non-coercive manner.

Disclosure of Data

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

Retention of Records

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

Feasibility

Brigham and Women's Hospital

Brigham and Women's Hospital (BWH) is a 793-bed acute tertiary care facility providing medical and surgical care for patients with general medical, cardiothoracic, orthopedic, oncologic, neurologic, obstetric, gynecologic, and gastrointestinal conditions. With the opening of the Heart and Vascular Center in 2014, BWH has solidified its position as a world leader in cardiovascular care and research, supporting an integrated care model in a single location. The Watkins Cardiovascular Clinic provides care to a large a growing outpatient population from the metropolitan Boston area, surrounding suburbs, and New England region. Dr. Piazza's cardiovascular medicine outpatient practice in the Watkin Cardiovascular Clinic, which is based in the Heart and Vascular Center, includes a large number of referrals for VTE and determination of the optimal duration of anticoagulation. The Watkin Cardiovascular Clinic also houses the outpatient practices of an additional seven Vascular Medicine faculty members and four Vascular Medicine fellows. These providers will serve as an important additional source of eligible study patients. The Vascular Medicine Section at BWH also staffs the Cardiovascular Medicine Consultation Service which evaluates and treats several hundred patients with VTE each year. The vast majority of these patients follow up in our outpatient clinics.

The BWH Thrombosis Research Group

The Thrombosis Research Group (TRG), directed by Dr. Goldhaber, Professor of Medicine, Harvard Medical School and Interim Chief of the Division of Cardiovascular Medicine and Section Head of Vascular Medicine, is based at BWH and Harvard Medical School. The Thrombosis Research Group has a decades-long commitment to VTE prevention and a dedication to improving the outcomes of all patients at risk for VTE. Dr. Piazza, Associate Professor of Medicine, Harvard Medical School, is the Associate Director of the Thrombosis Research Group and Assistant Section Head of Vascular Medicine at BWH as well as the Director of the Vascular Medicine Training Program. Dr. Piazza is the Chair of the ACC PVD Section Leadership Council and serves on the Scientific Session Planning Committees for the AHA and SVM. Dr. Piazza appreciates the national and global burden of recurrent VTE from his roles leading the Vascular Medicine educational initiatives for the ACC and AHA and from his perspective as a Co-Investigator on a number of VTE-related clinical trials (34–36) and observational studies (37). Dr. Piazza is currently leading a clinical trial evaluating the safety and efficacy of apixaban for primary prevention of VTE in multiple myeloma patients on immunomodulatory regimens known to increase the risk of thrombosis (38). Drs. Piazza and Goldhaber's dedication to and expertise in subject recruitment is clearly highlighted in their participation in the 7000-patient, multi-center, National Heart Lung and Blood Institute-sponsored Cardiovascular Inflammation Reduction Trial (CIRT) (39). Drs. Piazza and Goldhaber's efforts have made BWH the top enrolling site for CIRT. Dr. Goldhaber was the Principal Investigator of the ADOPT Trial of apixaban 2.5 mg twice daily for prevention of VTE in acutely ill medical patients during hospitalization and in the extended period after their discharge from the hospital (22).

The Thrombosis Research Group has an infrastructure of experienced leadership, with trained personnel in a multidisciplinary academic team (research pharmacists, cardiology fellows, research nurses, research coordinators, biostatisticians, administrators, and medical informatics specialists). Data storage and computing resources, as well as a network of regional, national, and international collaborating investigators, facilitate our execution of ongoing research projects and our planning of future research projects. The Thrombosis Research Group has studied all aspects of VTE, including epidemiology, diagnosis, treatment, and prevention. According to www.pubmed.gov, the group has authored more than 100 Original Reports since 2010.

Drs. Piazza and Goldhaber have extensive experience leading randomized controlled trials focused on prevention and treatment of thromboembolic disease. Examples of major Thrombosis Research Group-lead trials in this area include the 2500-patient multicenter Electronic Alert Trial (40), the 2500-patient multicenter Physician Alert Trial (41), the 2500-patient Discharge Alert Trial (42), and the 85-patient multicenter eTRIS trial (35).

Vascular Medicine at BWH is a regional Center of Excellence for VTE care. An EPIC Electronic Health Record query of the outpatient clinic volume of the five Vascular Medicine faculty providers and the 4 full-time Vascular Medicine fellows

demonstrated a provoked VTE volume of approximately 1500 new and follow-up patients.

Table 7. EPIC query estimate of new and follow-up provoked VTE patient volume in 2018.

Provider	Provoked VTE Volume (patients/year)
Piazza	300
Goldhaber	400
Campia	400
Gerhard-Herman	100
Sobieszczyk	100
4 Full-Time Vascular Medicine Fellows	200
TOTAL	**1500**

Since running this EPIC analysis, we have also added two additional full-time Vascular Medicine faculty, Dr. Arvind Pandey and Dr. Laurel Lee. Both specialize in the care of patients with VTE and see frequent referrals for determination of optimal duration of anticoagulation and long-term secondary prevention of recurrent events. Furthermore, we will recruit from our inpatient cardiovascular medicine consult service and cardiovascular medicine ward service which receive a high volume of provoked VTE referrals. Accordingly, we anticipate having the ability to draw on these additional sources of provoked VTE patients for at least another 100 provoked VTE patients per year.

Even without the added VTE patient volumes of Dr. Pandey and Dr. Lee, we calculate 1600 new and follow-up provoked VTE patients who present for outpatient visits at BWH per year and we conservatively estimate that 25% will fail to meet all the inclusion criteria or will meet at least one exclusion criterion. Therefore, an estimated 1200 patients will be eligible for enrollment in the trial in the first year.

We will also have our research nurse run reports from EPIC to identify other patients in our non-Vascular Medicine cardiology practices that will be eligible but may not be scheduled to see us. We will also aggressively communicate the launch of the study to our non-Vascular Medicine cardiology colleagues. Furthermore, we will recruit from our inpatient cardiovascular medicine consult service and cardiovascular medicine ward service which receive a high volume of provoked VTE. Accordingly, we anticipate having the ability to draw on these additional sources of provoked VTE patients for at least another 100 provoked VTE patients per year.

As the trial will enroll over 20 months, we estimate that we will be able to draw from 1200 patients in the first year and 800 patients in the 8 months that comprise the second year of enrollment. This will yield 2000 patients from which to enroll 600 subjects for the trial.

Based on our prior clinical trial experience at the BWH Thrombosis Research Group, we conservatively estimate that 50% of the patients who are screened and found to be eligible for the trial will consent to participate. Therefore, an estimated 1000 eligible patients would be willing to provide informed consent to participate in the HI-PRO trial. Accordingly, enrollment of the planned 600-patient study population should be feasible and efficiently accomplished at BWH.

Additionally, the BWH Thrombosis Research Group has the infrastructure to operationalize this enrollment plan. The Thrombosis Research Group has two full-time dedicated research assistants, a research intern, a research nurse, three faculty physicians, a full-time advanced Vascular Medicine fellow, and a number of general Cardiovascular Medicine fellows who participate in our research studies. We have coordinated our ongoing research projects to accommodate the percent efforts required by our research staff and physician team members to maximize our success at enrollment for this trial. Accordingly, we have adequate staffing and physician support to add to the research personnel for this trial, identify eligible patients, and maintain our enrollment on track. We also have an adequate reserve in staffing and flexibility to augment our effort should enrollment require it.

TRG led the patient recruitment effort for the Cardiovascular Inflammation Reduction Trial (CIRT), a randomized, double-blind trial of low-dose methotrexate in 4786 patients with previous myocardial infarction or multivessel coronary disease who additionally had either type 2 diabetes or the metabolic syndrome (39). CIRT was a landmark study which involved a novel application of a challenging anti-inflammatory drug, serial laboratory evaluations, and a high number of follow-up phone calls and in-person office visits, which required patients to travel from as far as California to Boston. Despite these challenges, TRG made BWH the overall top enrolling site in the CIRT trial.

We anticipate rapid enrollment in the HI-PRO trial. First, all the patients in the study will be familiar with anticoagulation and many will have received apixaban. Second, there are no study-mandated laboratory tests or office visits. Third, many patients with provoked VTE are reluctant to discontinue anticoagulation after the acute treatment phase because of the fear of recurrent events. We anticipate that many patients with provoked VTE will be highly interested in participating in a clinical trial of extended secondary prevention thromboprophylaxis, especially with the favorable safety and efficacy profile of low-intensity apixaban. It is quite possible that greater than 50% of eligible patients will want to participate and provide informed consent. In such a scenario, we would expect to enroll more quickly.

Potential Risks and Benefits

Potential benefits to the subject

The potential benefit of treatment with low-dose apixaban in patients with provoked VTE is secondary prevention of VTE, including fatal PE.

Potential Benefits to Society

The major potential benefit to society of the proposed trial of apixaban for secondary prevention of VTE in patients with provoked VTE is that if successful, the study will provide the foundation for a new indication for extended-duration anticoagulation for VTE prevention. The data acquired from this randomized, placebo-controlled trial will establish the safety and efficacy of low-dose apixaban versus placebo for extended prevention of recurrence after provoked VTE in patients with at least one persistent provoking factor. The study will draw widespread interest for apixaban in the extended prevention of recurrence after provoked VTE and will most certainly be of interest to high-impact peer-reviewed journals and to a broad spectrum of clinicians who will be better able to care for their VTE patients using these data.

Potential Risks to the Subject

The foreseeable risk of apixaban for secondary prevention of VTE in patients with provoked VTE is major bleeding.

Risks of Research Procedures Performed on Subjects

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

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

Anticipated Risks of Drug

Adverse reactions occurring in ≥1% of patients treated for DVT and PE in the AMPLIFY study (source table 6 USPI)

- Epistaxis
- Contusion
- Hematuria
- Menorrhagia
- Hematoma
- Hemoptysis
- Rectal hemorrhage
- Gingival bleeding

Less common adverse reactions occurring in Eliquis-treated patients in AMPLIFY or AMPLIFY-EXT studies occurring with a frequency of ≥0.1% to <1%:

- Blood and lymphatic system disorders: hemorrhagic anemia
- Gastrointestinal disorders: hematochezia, hemorrhoidal hemorrhage, gastrointestinal hemorrhage, hematemesis, melena, anal hemorrhage
- Injury, poisoning, and procedural complications: wound hemorrhage, postprocedural hemorrhage, traumatic hematoma, periorbital hematoma
- Musculoskeletal and connective tissue disorders: muscle hemorrhage
- Reproductive system and breast disorders: vaginal hemorrhage, metrorrhagia, menometrorrhagia, genital hemorrhage
- Vascular disorders: hemorrhage
- Skin and subcutaneous tissue disorders: ecchymosis, skin hemorrhage, petechiae
- Eye disorders: conjunctival hemorrhage, retinal hemorrhage, eye hemorrhage
- Investigations: blood urine present, occult blood positive, occult blood, red blood cells urine positive
- General disorders and administration-site conditions: injection-site hematoma, vessel puncture-site hematoma

Additional information about the risks of apixaban can be found in the Apixaban Med Guide (see Appendix).

Protection of Subjects against the Risks of Research Procedures

Before Study Enrollment

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

During Follow-Up

Changes in health status during the 12-month follow-up period will be evaluated by the patient's primary physician, and other routine providers. All subjects enrolled will also have ongoing medical care with a dedicated Vascular Medicine provider. As apixaban is an FDA-approved drug commonly used for thromboprophylaxis and does not require routine follow-up clinical or laboratory monitoring for toxicity, the study will not mandate any follow-up visits or procedures other than those required for the patient's routine care.

Protection against Loss of Confidentiality

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

Use of Information and Publication

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

Ethical Considerations

In this prospective, single-center randomized placebo-controlled study, we will be evaluating the impact of apixaban for secondary prevention of VTE in patients with provoked VTE with at least one persistent provoking factor. The benefits of apixaban for secondary prevention of VTE in patients with provoked VTE have not been assessed. The risk of bleeding in provoked VTE patients receiving apixaban has not been determined.

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

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Table 8. Study Calendar

Procedure	Screening	12-Month Follow-Up
Informed Consent	X	
Inclusion/Exclusion	X	
Demographics	X	
Medical History	X	
Prior/Concomitant Medications	X	
Urine Pregnancy (if clinically indicated)	X	
Cardio-vascular History	X	
Thrombosis Evaluation		X
Bleeding Evaluation		X
Pill Diary Collection		X

Case Report Form

Screening	
Inclusion criteria (all must be checked)	[ ] Age ≥ 18 years [ ] Objectively-confirmed DVT and/or PE [ ] Treated for at least 3 months with standard therapeutic anticoagulant therapy [ ] Has not suffered symptomatic recurrence during prior anticoagulant therapy [ ] Outpatient follow-up at BWH [ ] Willing to provide written informed consent AND have at least one of the following persistent provoking VTE risk factors: [ ] Persistent immobility (defined as paralysis, other inability to ambulate freely, bed-bound, wheelchair-bound) [ ] Obesity (defined as BMI ≥ 30 kg/m2) [ ] Heart failure (systolic, diastolic, or combined) [ ] Chronic lung disease (COPD, asthma, interstitial lung disease) [ ] Chronic kidney disease (eGFR <60 mL/min/1.72m2) [ ] Chronic inflammatory/autoimmune disorder (inflammatory arthritis, vasculitis, inflammatory bowel disease, chronic infection) [ ] Atherosclerotic cardiovascular disease (coronary, cerebrovascular, or peripheral artery disease) (up to 35% in each study group may have atherosclerotic cardiovascular disease as a qualifying persistent risk factor)
Exclusion criteria (NONE must be checked)	[ ] Women who are pregnant or breastfeeding [ ] Women of child-bearing potential who are unwilling or unable to use an acceptable method of birth control (such as oral contraceptives, other hormonal contraceptives [vaginal products, skin patches, or implanted or injectable products], or mechanical products such as an intrauterine device or barrier methods [diaphragm, condoms, spermicides]) to avoid pregnancy for the entire study [ ] Active cancer within the past 5 years [ ] Contraindication to antithrombotic or antiplatelet therapy [ ] Requirement for ongoing anticoagulant therapy (including atrial fibrillation with a CHADSVASC >1, diagnosed antiphospholipid antibody syndrome/deficiency of protein C,

	S, or antithrombin), dual antiplatelet therapy, P2Y12 inhibition, or aspirin at a dose of >81 mg daily [ ] Hemoglobin level < 9 mg/dL, a platelet count < 100,000/mm3, a serum creatinine level > 2.5 mg/dL, an ALT or AST level > 2 times the upper limit of the normal range, or a total bilirubin level > 1.5 times the upper limit of the normal range [ ] History of a platelet disorder such as Von Willebrand Disease [ ] History of bleeding diathesis or have had recent active bleeding [ ] Active hepatobiliary disease [ ] More than 6 months that have elapsed without taking an anticoagulant or low-dose aspirin [ ] Known severe thrombophilia (any increased titer antiphospholipid antibody or positive lupus anticoagulant/DRVVT or deficiency of antithrombin, protein C, or protein S) [ ] Life expectancy < 12 months or hospice care [ ] Prisoners or subjects who are involuntarily incarcerated [ ] Subjects who are compulsorily detained for treatment of either a psychiatric or physical (e.g., infectious disease) illness [ ] Receiving concurrent non-FDA-approved or investigational agents or has received an investigational agent within the past 30 days prior to the first dose of study treatment (with the exception of approved medications being used for an approved indication, e.g., investigating a new dosing regimen for an approved indication). [ ] Any condition, which in the opinion of the investigator, would put the subject at an unacceptable risk from participating in the study [ ] Any other medical, social, logistical, or psychological reason, which in the opinion of the investigator, would preclude compliance with, or successful completion of, the study protocol
STOP HERE AND DO NOT ENROLL PATIENT IF ANY OF THE INCLUSION CRITERIA ARE ABSENT OR ANY EXCLUSION CRITERIA ARE PRESENT	
Eligible	[ ] Yes [ ] No
Written informed consent signed	[ ] Yes [ ] No

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

Venous Thromboembolism Characteristics*** *****Patient may have both PE and DVT; if so complete both fields**	
Deep Vein Thrombosis	DVT confirmed by imaging (ultrasound, CT, MRI, or venogram) [ ] Yes [ ] No
	Date of imaging diagnosis ____/____/_____ MM DD YYYY
	Site of DVT [ ] Upper extremity [ ] Pelvic vein [ ] Leg [ ] Proximal with calf [ ] Proximal without calf [ ] Calf only

	[ ] Other (describe):_____
Pulmonary Embolism	PE confirmed by: [ ] Ventilation perfusion scan [ ] Chest CT [ ] Contrast pulmonary angiogram Hypotension, shock, cardiac arrest or respiratory failure as presenting sign of PE: [ ] Yes [ ] No RV dysfunction [ ] Yes [ ] No Diagnosed by: [ ] CT [ ] Echocardiogram Positive cardiac biomarker (troponin or BNP) [ ] yes [ ] no
	Date of imaging confirmed diagnosis ____/____/_____ MM DD YYYY
Both PE and DVT present	[ ] Yes [ ] No
Symptomatic DVT or PE	[ ] Yes [ ] No
Advanced therapy for VTE	[ ] Inferior vena cava filter [ ] Thrombolytic therapy for PE [ ] Catheter thrombectomy for DVT [ ] Catheter direct therapy for PE [ ] Surgical thrombectomy for DVT [ ] Surgical embolectomy for PE
Outpatient VTE treatment history	[ ] LMWH monotherapy [ ] Fondaparinux [ ] Direct oral anticoagulant [ ] Warfarin Duration of anticoagulation: ___ months (enter number out to the tenth place and round-up; for example 3.48 months would be 3.5 months)

Persistent Provoking VTE Risk Factors	
Persistent provoking VTE risk factors (**patient must have at least one but can have multiple; record all that apply**)	[ ] Persistent immobility (defined as paralysis, other inability to ambulate freely, bed-bound, wheelchair-bound) [ ] Obesity (defined as BMI ≥ 30 kg/m2) [ ] Heart failure (systolic, diastolic, or combined) [ ] Chronic lung disease (COPD, asthma, interstitial lung disease) [ ] Chronic kidney disease (eGRF <60 mL/min/1.72m^2) [ ] Chronic inflammatory/autoimmune disorder (inflammatory arthritis, vasculitis, inflammatory bowel disease, chronic infection) [ ] Atherosclerotic cardiovascular disease (coronary, cerebrovascular, or peripheral artery disease) (up to 35% in each study group may have atherosclerotic cardiovascular disease as a qualifying persistent risk factor)

VTE Risk Factors and Comorbid Conditions	
Cardiovascular disease	[ ] Cardiomyopathy/diminished left ventricular systolic function If yes, EF (%) ____ [ ] Heart failure with reduced EF [ ] Heart failure with preserved EF (EF >50%) [ ] Coronary artery disease If yes, Prior CABG [ ] Prior coronary stent(s) [ ] Prior MI [ ] History of unstable angina [ ] Stable angina [ ] [ ] Valvular heart disease [ ] Atrial fibrillation or atrial flutter [ ] Pulmonary hypertension
Hypertension	[ ] Yes [ ] No
Peripheral artery disease	[ ] Yes [ ] No

Carotid occlusive disease	[ ] Yes [ ] No
Prior cerebrovascular accident (strokes or TIAs)	[ ] Yes [ ] No
Family history of VTE	[ ] Yes [ ] No
Prior personal history of VTE (other than the event that made the patient eligible for this trial)	[ ] Yes [ ] No
Hypercholesterolemia	[ ] Yes [ ] No
Chronic liver disease (as noted in chart)	[ ] Yes [ ] No If yes, cirrhosis [ ] yes [ ] no
Cigarette smoking (check only 1)	[ ] Current smoker [ ] Former smoker [ ] Never smoker
Major surgery within 3 months of VTE diagnosis	[ ] Yes [ ] No If yes, date _____/_____/_____ MM DD YYYY
Prior hospitalization within 30 days of VTE diagnosis	[ ] Yes [ ] No
Chronic lung disease (COPD, asthma, pulmonary fibrosis, interstitial lung disease)	[ ] Yes [ ] No
Diabetes mellitus	[ ] Yes

(Type I or II)	[ ] No
Inflammatory arthritis (rheumatoid arthritis, psoriatic arthritis)	[ ] Yes [ ] No
Inflammatory bowel disease (Crohn's Disease, Ulcerative Colitis)	[ ] Yes [ ] No
Inherited thrombophilia	[ ] Yes [ ] No If yes, indicate: [ ] Factor V Leiden (heterozygous or homozygous) [ ] Prothrombin gene mutation (heterozygous or homozygous)
Active use of oral contraceptive or hormone replacement at time of VTE diagnosis	[ ] Yes [ ] No
Infectious illness requiring antibiotics or antiviral therapy within 3 months of VTE diagnosis	[ ] Yes [ ] No
Serum creatinine >2.5 mg/dL	[ ] Yes [ ] No If yes, is patient on dialysis? [ ] Yes [ ] No **If yes, patient should not be enrolled.**
Concomitant medications	[ ] aspirin If yes, dose = _ _ _ mg/daily **If >81 mg/daily, patient should not be enrolled.** [ ] daily NSAID use

Study Treatment Characteristics	
Randomization	[ ] Oral Apixaban 2.5 mg twice daily [ ] Oral placebo twice daily
Date study drug started	____/____/_____ MM DD YYYY
Date study drug stopped	____/____/_____ MM DD YYYY Completed full 12 months of study drug? [ ] Yes [ ] No If did not stay on drug for 12 months, reason why not? [ ] Fulfilled criteria for a primary study outcome (recurrent VTE or major/clinically relevant non-major bleed) [ ] Patient expired [ ] Adverse drug event or side-effect [ ] Change in clinical status (such as change in goals of care, comfort measures, hospice care) [ ] Patient preference/withdrawal of consent
Medication adherence (via pill count)	Total doses taken/total doses prescribed = (__ / 720) x 100 = _ _ _ %

12-Month Study Outcomes	
Deep vein thrombosis	[ ] Yes [ ] No If yes, date ____/____/_____ MM DD YYYY Confirmed by diagnostic imaging: [ ] Yes [ ] No If yes, by? [ ] Ultrasound [ ] CT [ ] MRI [ ] Venography

	Location: [ ] Upper extremity If checked: [ ] Bilateral or SVC [ ] Lower extremity If checked: [ ] Bilateral or IVC [ ] Proximal (popliteal or higher) [ ] Calf Hospitalized? [ ] Yes [ ] No Treatment: [ ] Anticoagulation [ ] Pharmacomechanical (catheter-based) therapy [ ] Surgery [ ] IVC filter
Superficial vein thrombosis	[ ] Yes [ ] No If yes, date ____/____/_____ MM DD YYYY
Other venous thrombosis (mesenteric, cerebral sinus, gonadal, etc.)	[ ] Yes [ ] No If yes, date ____/____/_____ MM DD YYYY
Pulmonary embolism	[ ] Yes [ ] No If yes, date ____/____/_____ MM DD YYYY Confirmed by diagnostic imaging: [ ] Yes [ ] No If yes, by? [ ] CT [ ] MRI

	[ ] Pulmonary angiography [ ] V/Q scan Location: [ ] Unilateral [ ] Bilateral RV dysfunction on echocardiogram or CT? [ ] Yes [ ] No Positive cardiac biomarker? [ ] Yes [ ] No Associated with hemodynamic or respiratory instability (respiratory failure, shock, hypotension, cardiac arrest)? [ ] Yes [ ] No Fatal? [ ] Yes [ ] No Hospitalized? [ ] Yes [ ] No Treatment: [ ] Anticoagulation [ ] Systemic fibrinolysis [ ] Pharmacomechanical (catheter-based) therapy [ ] Surgical embolectomy [ ] IVC filter
Death	[ ] Yes [ ] No If yes, date ____/____/_____ MM DD YYYY Cause of death: [ ] PE [ ] Myocardial infarction [ ] Stroke

	[ ] Other cardiovascular [ ] Cancer-related [ ] Non-cardiovascular, non-cancer [ ] Unknown [ ] CV Death: includes death due to PE, MI, stroke, other cardiovascular cause, or unknown
Major or clinically relevant non-major bleed	[ ] Yes [ ] No If yes, date ____/____/_____ MM DD YYYY
Major bleed	[ ] Yes [ ] No If yes, date ____/____/_____ MM DD YYYY Location: [ ] Intracranial [ ] Surgical/operative site [ ] Gastrointestinal [ ] Genitourinary [ ] Retroperitoneal [ ] Pericardial [ ] Pulmonary [ ] Other thoracic [ ] Musculoskeletal [ ] Nasopharyngeal [ ] Hematocrit or hemoglobin decrease without clear source [ ] Other Fatal? [ ] Yes [ ] No Hospitalized? [ ] Yes [ ] No Associated with hemodynamically instability? [ ] Yes [ ] No

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

	[ ] Cutaneous (rash, etc.) [ ] Liver function abnormalities [ ] Other: _____ Hospitalized? [ ] Yes [ ] No Study drug discontinuation? [ ] Permanent stop [ ] Temporary stop [ ] Not discontinued
Myocardial infarction (defined as the presence of at least 2 of the 3 following conditions: • The detection of a rise and/or fall of cardiac biomarkers, with at least one of the values being elevated [preferably cardiac troponin (cTn) with at least one value above the 99th percentile upper reference limit] and with at least one of the following: (1) symptoms of myocardial ischemia; (2) new (or presumably new) significant ST-segment/T-wave changes or left bundle branch block; (3) development of pathological	[ ] Yes [ ] No If yes, date ____/____/_____ MM DD YYYY Type: [ ] ST elevation [ ] Non-ST elevation Fatal? [ ] Yes [ ] No Treatment: [ ] Systemic fibrinolysis [ ] Percutaneous coronary intervention (angioplasty, stenting, etc.) [ ] CABG [ ] Medical management

Q waves on ECG; (4) new loss of viable myocardium or regional wall motion abnormality by imaging; (5) identification of intracoronary thrombus by angiography or autopsy)	
Non-MI coronary revascularization	[ ] Yes [ ] No If yes, date ____/____/_____ MM DD YYYY Recascularization: [ ] Percutaneous coronary intervention (angioplasty, stenting, etc.) [ ] CABG
Stroke/TIA (defined as a new, focal neurologic deficit of sudden onset, lasting at least 24 hours, not due to a readily identifiable nonvascular cause (i.e. brain tumor, trauma), as confirmed by a neurologist and neuroimaging.)	[ ] Yes [ ] No If yes, date ____/____/_____ MM DD YYYY Confirmation (both must be present): [ ] By neurologist [ ] By neuroimaging TIA? [ ] Yes [ ] No Stroke? [ ] Yes [ ] No If yes, type of stroke: [ ] Ischemic

	[ ] Hemorrhagic [ ] Other Fatal stroke? [ ] Yes [ ] No Treatment: [ ] Systemic fibrinolysis [ ] Percutaneous thrombectomy [ ] Surgery [ ] Other
Major adverse limb event	[ ] Yes [ ] No Acute limb ischemia [ ] Yes [ ] No (Acute limb ischemia defined as limb-threatening ischemia which is confirmed by limb hemodynamics or imaging and leads to an acute vascular intervention within 30 days of onset of symptoms or absent pedal pulses) Critical limb ischemia (CLI) [ ] Yes [ ] No (CLI is defined as continuing ischemic limb, foot or digit pain leading to hospitalization and intervention and not meeting the definition of ALI, or Fontaine 3 or 4 at baseline with peripheral intervention during the trial) Peripheral intervention [ ] Yes [ ] No (Peripheral vascular intervention is defined as peripheral vascular intervention not meeting the definition for ALI or CLI) Amputation [ ] Yes [ ] No
Admission for heart failure (HFPEF or HFREF)	[ ] Yes [ ] No

Appendix

1. Apixaban Package Insert (Version June 2018)
   https://packageinserts.bms.com/pi/pi_eliquis.pdf

2. Eliquis Medication Guide
   https://packageinserts.bms.com/medguide/medguide_eliquis.pdf

3. Informed Consent Form

Randomized Controlled Trial of Extended-Duration Low-Dose Apixaban to Prevent Recurrence in High-Risk Patients with Provoked Venous Thromboembolism (HI-PRO Trial)

Final version

BMS Protocol #: CV185-745

Protocol Version Date: 11/19/2021

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Protocol Summary

Title: Randomized Controlled Trial of Extended-Duration Low-Dose Apixaban to Prevent Recurrence in High-Risk Patients with Provoked Venous Thromboembolism (HI-PRO Trial)

Design: U.S.-based, single-center, randomized placebo-controlled trial.

Brief Treatment Description: Low-dose apixaban (2.5mg twice daily) for extended-duration secondary prevention of VTE after initial treatment for provoked VTE.

Purpose: To establish the safety and efficacy of low-dose apixaban versus placebo for extended prevention of recurrence after provoked VTE in patients with at least one persistent provoking factor.

Population: Outpatients with provoked VTE with at least one persistent provoking factor.

Enrollment: 600 subjects

Randomization: 1:1

Clinical Site Locations: 1 center (Brigham and Women's Hospital)

Study Duration: 36 months; enrollment period of up to 20 months with 12-month follow-up.

Primary Safety and Efficacy Outcomes:

Primary Safety Outcome: International Society on Thrombosis and Haemostasis (ISTH) major bleeding at 12 months.

Primary Efficacy Outcome: Symptomatic, recurrent VTE, defined as the composite of deep vein thrombosis and/or pulmonary embolism at 12 months.

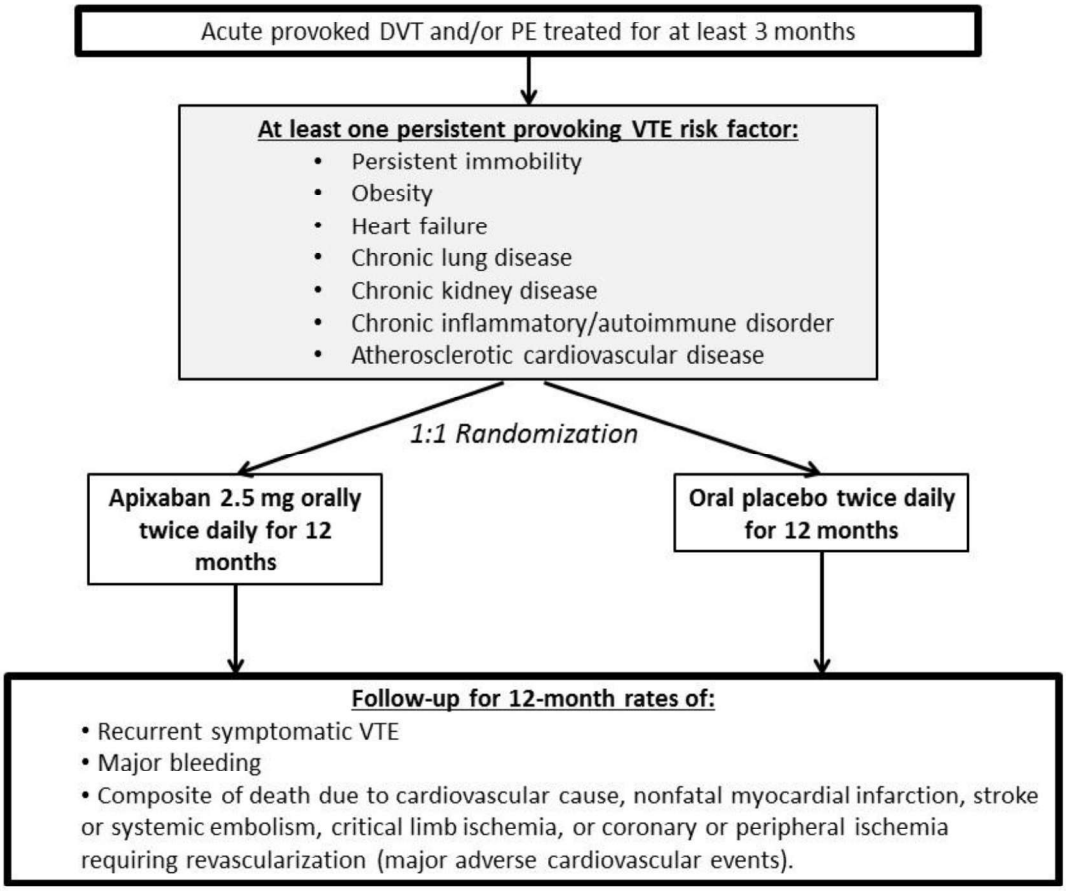
Secondary Safety Outcome: ISTH clinically relevant non-major bleeding at 12 months.

Secondary Efficacy Outcome: The composite of death due to cardiovascular cause, nonfatal myocardial infarction, stroke or systemic embolism, critical limb ischemia, or coronary or peripheral ischemia requiring revascularization (major adverse cardiovascular events, including major adverse limb events) at 12 months.

Follow-Up: Follow-up will consist of Electronic Health Record (EHR) review at 12-months from study enrollment.

Interim Analysis: An interim analysis for the primary safety and efficacy outcomes will be performed when 300 subjects have completed 12-month follow-up.

Study Flow Diagram



DVT, deep vein thrombosis; PE, pulmonary embolism; VTE, venous thromboembolism

Figure 1. Study flow-diagram for a single-center, randomized placebo-controlled trial of extended low-intensity apixaban for high-risk provoked VTE.

Study Subject Contact Calendar:

Date	Event	Study Drug
Enrollment (Month 0)	Subject will be consented by study physician and randomized through the Investigational Drug Service computer randomization program.	3 months of study drug (apixaban or placebo) will be given during this visit or sent to subject within 2 business days of the enrollment visit via mail or courier.
Month 3	Study nurse check-in	First 3 months drug containers and unused drug collected via mail and returned to pharmacy for proper disposal, 3 additional months' worth of medication will be given or sent to subject.
Month 6	Study nurse check-in	Drug containers and unused drug collected via mail and returned to pharmacy for proper disposal, 3 additional months' worth of medication will be given or sent to subject.
Month 9	Study nurse check-in	Drug containers and unused drug collected via mail returned to pharmacy for proper disposal, 3 additional months' worth of medication will be given or sent to subject.
Month 12	End-of-treatment visit	All remaining medications, drug containers, and 12-month drug diary will be collected.

Abbreviations and Definitions

Listed in alphabetical order

ACCP, American College of Chest Physicians

ALI, acute limb ischemia

ALT, alanine transaminase

AST, aspartate aminotransferase

BMI, body mass index

BMS, Bristol-Myers Squibb

BWH, Brigham and Women's Hospital

CEC, clinical endpoints committee

CI, confidence interval

CLI, critical limb ischemia

COPD, chronic obstructive pulmonary disease

CrCl, creatinine clearance

CT, computed tomography

cTn, cardiac troponin

DOAC, direct oral anticoagulant

DRVVT, dilute Russell's viper venom

DSMB, Data Safety Monitoring Board

DVT, deep vein thrombosis

eCRF, electronic case report form

FDA, food and drug administration

FSH, follicle stimulating hormone

GPV&E, Global Pharmacovigilance & Epidemiology

HCG, human chorionic gonadotropin

HRT, hormone replacement therapy

IND, investigational new drug

INR, international normalized ratio

IRB, institutional review board

ISTH, International Society on Thrombosis and Haemostasis

IUD, intrauterine device

LMWH, low-molecular weight heparin

MI, myocardial infarction

MR, magnetic resonance

NOACs, non-vitamin K oral anticoagulants

NSAID, nonsteroidal anti-inflammatory drug

PCC, prothrombin complex concentrate

PE, pulmonary embolism

PI, Proteasome inhibitors

REDCap, Research electronic data capture

SAE, significant adverse event

TRG, thrombosis research group

UADE, unanticipated adverse drug effect

UFH, unfractionated heparin

U.S., United States

VTE, venous thromboembolism

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Specific Aims

Provoked VTE is traditionally considered a transient acute disorder requiring a limited duration of anticoagulant therapy. Patients who suffer deep vein thrombosis (DVT) or pulmonary embolism (PE) following major surgery, major trauma, or periods of immobility are generally treated with time-limited anticoagulation for 3 months. However, provoked VTE patients have recently been recognized as a heterogeneous population comprised of those with transient provoking and persistent provoking risk factors (1). Common risk factors in provoked VTE such as obesity, immobility, atherosclerotic cardiovascular disease, heart failure, chronic lung disease, chronic kidney disease, and inflammatory disorders frequently contribute to an enduring rather than transient risk.

Data from 4,553 patients in the EINSTEIN CHOICE trial and the EINSTEIN VTE Continued Treatment Study demonstrate that provoked VTE patients with persistent provoking factors have a reduction in recurrence with extended duration anticoagulation compared with low-dose aspirin or placebo (1.5% vs. 4.9%) (2,3). Common persistent provoking factors included immobility, obesity, heart failure, and chronic inflammatory disorders, such as Crohn's Disease. Despite being highly prevalent, persistent provoking factors are rarely considered when stopping anticoagulation in patients with provoked VTE who have completed the typical 3- to 6-month duration of therapy. The 2016 American College of Chest Physicians (ACCP) Guidelines on Antithrombotic Therapy for VTE do not distinguish between transient and persistent provoking risk factors and recommend limited-duration anticoagulation for provoked events (4).

However, an emerging opinion is that optimal duration of anticoagulation in provoked VTE patients should be determined based on data from the extended duration rivaroxaban trials (5). Such a strategy breaks from the tradition of dichotomizing VTE as provoked or unprovoked. Rather, persisting risk factors such as heart failure, obesity, family history of VTE, acquired or hereditary thrombophilia, and immobilization are incorporated into the decision-making process for pathways focused on secondary prevention. A suitable long-term strategy for secondary prevention has been recommended in evidence-based clinical practice guidelines for patients with unprovoked VTE (4). Extended-duration anticoagulation with warfarin or the direct oral anticoagulants (DOACs) is validated and recommended for prevention of recurrent unprovoked VTE in patients with a low-risk of bleeding (6). In a landmark extension trial of patients with unprovoked VTE, the AMPLIFY-EXT trial compared two doses of apixaban (2.5 mg and 5 mg, twice daily) with placebo in 2486 patients with VTE who had completed 6 to 12 months of anticoagulation therapy and for whom there was clinical equipoise regarding the need for extended-duration anticoagulant therapy for secondary prevention (7). Symptomatic recurrent VTE or death from VTE occurred in 73 of the 829 patients (8.8%) who were receiving placebo versus 14 of the 840 patients (1.7%) who were receiving 2.5 mg of apixaban and 14 of the 813 patients (1.7%) who were receiving 5 mg of apixaban ($p<0.001$ for both comparisons). In Kaplan-Meier analysis, the apixaban 2.5 mg twice daily

regimen demonstrated a major and clinically-relevant nonmajor bleeding rate similar to that of placebo.

Based on the emerging evidence that provoked VTE patients may require extended-duration anticoagulation for secondary prevention, the apixaban 2.5 mg twice daily dose could be a critical addition to our armamentarium in those at high risk for recurrence at the transition of care from the acute to the chronic treatment phase. However, this hypothesis needs to be tested in a randomized clinical trial. We propose a single-center, randomized placebo-controlled trial conducted at Brigham and Women's Hospital (BWH) to evaluate the impact of low-dose apixaban (2.5 mg twice daily) in a study population exclusively comprised of provoked VTE patients with at least one persistent provoking factor. We have the following study aims:

Specific Aim #1: To compare the 12-month rate of recurrent symptomatic VTE in patients with provoked VTE and at least one persistent provoking factor who are randomized to either apixaban (2.5 mg orally twice daily) as monotherapy or placebo after completing at least 3 months of therapeutic anticoagulation and who have a low risk of bleeding.

Hypothesis #1: Compared with placebo, oral apixaban (2.5 mg twice daily) will reduce the 12-month rate of symptomatic VTE in patients with provoked VTE and at least one persistent provoking factor who have completed at least 3 months of therapeutic anticoagulation and who have a low risk of bleeding.

Specific Aim #2: To compare the 12-month rate of ISTH major bleeding in patients with provoked VTE and at least one persistent provoking factor who are randomized to either apixaban (2.5 mg orally twice daily) as monotherapy or placebo after completing at least 3 months of therapeutic anticoagulation and who have a low risk of bleeding.

Hypothesis #2: Compared with placebo, oral apixaban (2.5 mg twice daily) will be associated with a similar rate of ISTH major bleeding at 12 months in patients with provoked VTE and at least one persistent provoking factor who are randomized to either apixaban (2.5 mg orally twice daily) as monotherapy or placebo after completing at least 3 months of therapeutic anticoagulation and who have a low risk of bleeding.

Introduction and Background

Provoked venous thromboembolism (VTE) is traditionally considered a transient acute disorder requiring a limited duration of anticoagulant therapy. Patients who suffer deep vein thrombosis (DVT) or pulmonary embolism (PE) following major surgery, major trauma, or periods of immobility are generally treated with time-limited anticoagulation for 3 months. However, provoked VTE patients have recently been recognized as a heterogeneous population comprised of those with transient provoking and persistent provoking risk factors (1). Common risk factors in provoked VTE such as obesity, immobility, atherosclerotic cardiovascular disease, heart failure, chronic lung disease, chronic kidney disease, and inflammatory disorders frequently contribute to an enduring rather than transient risk. Furthermore, epidemiological studies (8,9) and the randomized clinical trial EINSTEIN CHOICE (3) suggest that VTE is best characterized as a chronic disorder with periodic relapses. A landmark Danish National Registry analysis demonstrated that patients who suffer provoked or unprovoked VTE have an increased risk of recurrence over the ensuing 30 years and that recurrent PE causes increased mortality (10). While the rate of VTE recurrence ranges 30-50% over 10 years for unprovoked VTE (also termed idiopathic; unprovoked implies that an immediate trigger for the VTE cannot be identified), recurrent events occur in about 20% of patients over 10 years after a provoked event (provoked VTE is defined as post-operative, post-major trauma, post-hospitalization, or related to pregnancy, hormonal contraception/replacement therapy, or immobility) (11–13). Based on these data, provoked VTE patients represent a population vulnerable to VTE recurrence, especially at the transition of care from the initial (acute) treatment phase to the chronic treatment phase, at which point anticoagulation is discontinued in most of these patients.

The EINSTEIN CHOICE trial recently evaluated the safety and efficacy of regimens of full- or lower-intensity anticoagulant therapy versus low-dose aspirin for secondary prevention of VTE after an initial provoked or unprovoked event (2). The EINSTEIN CHOICE Investigators randomly assigned 3396 patients with VTE to receive either once-daily rivaroxaban (at doses of 20 mg or 10 mg) or 100 mg of aspirin. Prior to enrollment in EINSTEIN CHOICE, all study patients completed 6 to 12 months of anticoagulation therapy, and their providers were in equipoise regarding the need for extended anticoagulation. Approximately 60% of patients in EINSTEIN CHOICE had suffered provoked VTE. Symptomatic recurrent VTE occurred in 17 of 1107 patients (1.5%) receiving 20 mg of rivaroxaban and in 13 of 1127 patients (1.2%) receiving 10 mg of rivaroxaban, and in 50 of 1131 patients (4.4%) receiving low-dose aspirin (hazard ratio for 20 mg of rivaroxaban vs. aspirin, 0.34; 95% confidence interval [CI], 0.20 to 0.59; hazard ratio for 10 mg of rivaroxaban vs. aspirin, 0.26; 95% CI, 0.14 to 0.47; $P<0.001$ for both comparisons). Rates of major bleeding were similar (0.5% in the group receiving 20 mg of rivaroxaban, 0.4% in the group receiving 10 mg of rivaroxaban, and 0.3% in the low-dose aspirin group) (2).

Data from 4,553 patients in EINSTEIN CHOICE and the EINSTEIN VTE Continued Treatment Study demonstrate that provoked VTE patients with persistent provoking

factors have a reduction in recurrence with extended duration anticoagulation compared with low-dose aspirin or placebo (1.5% vs. 4.9%) (2,3). Common persistent provoking factors included immobility, obesity, heart failure, and chronic inflammatory disorders, such as Crohn's Disease and rheumatoid arthritis. Despite being highly prevalent, persistent provoking factors are rarely considered when stopping anticoagulation in patients with provoked VTE who have completed the typical 3- to 6-month duration of therapy. The 2016 American College of Chest Physicians (ACCP) Guidelines on Antithrombotic Therapy for VTE do not distinguish between transient and persistent provoking risk factors and recommend limited-duration anticoagulation for provoked events (4).

However, an emerging opinion is that optimal duration of anticoagulation in provoked VTE patients should be determined based on data from the extended duration rivaroxaban trials (5). Such a strategy breaks from the tradition of dichotomizing VTE as provoked or unprovoked. Rather, persisting risk factors such as heart failure, obesity, family history of VTE, acquired or hereditary thrombophilia, and immobilization are incorporated into the decision-making process for pathways focused on secondary prevention.

A suitable long-term strategy for secondary prevention has been recommended in evidence-based clinical practice guidelines for patients with unprovoked VTE (4). Extended-duration anticoagulation with warfarin or the direct oral anticoagulants (DOACs) is validated and recommended for prevention of recurrent unprovoked VTE in patients with a low-risk of bleeding (6). However, current evidence-based clinical practice guidelines are inadequate for secondary prevention in patients with provoked VTE based on several extended-duration anticoagulation trials that included patients with provoked and unprovoked VTE. In a randomized controlled trial of rivaroxaban for extended-duration secondary prevention in patients with either provoked (26%) or unprovoked (74%) DVT, recurrent VTE occurred in 8 patients (1.3%) in the rivaroxaban group compared with 42 patients (7.1%) in the placebo group (hazard ratio, 0.18; 95% CI, 0.09 to 0.39; P<0.001, relative risk reduction, 82%) (3).

In a landmark extension trial of patients with unprovoked VTE, the AMPLIFY-EXT trial compared two doses of apixaban (2.5 mg and 5 mg, twice daily) with placebo in 2486 patients with VTE who had completed 6 to 12 months of anticoagulation therapy and for whom there was clinical equipoise regarding the need for extended-duration anticoagulant therapy for secondary prevention (7). Symptomatic recurrent VTE or death from VTE occurred in 73 of the 829 patients (8.8%) who were receiving placebo versus 14 of the 840 patients (1.7%) who were receiving 2.5 mg of apixaban and 14 of the 813 patients (1.7%) who were receiving 5 mg of apixaban (p<0.001 for both comparisons). In Kaplan-Meier analysis, the apixaban 2.5 mg twice daily regimen demonstrated a major and clinically-relevant nonmajor bleeding rate similar to that of placebo. While approximately 9% of the patients in the AMPLIFY-EXT trial had transient or reversible risk factors for VTE, the provoked VTE population only accounted for approximately 200 patients and precluded a well-powered analysis. Furthermore, the intent of the AMPLIFY-EXT trial was to study unprovoked VTE (7).

Finally, the HI-PRO trial is evaluating a more complex aspect of VTE secondary prevention. Rather than using the simple dichotomized view of VTE as provoked or unprovoked, HI-PRO is focusing on how the risk of recurrence in patients with persisting provoking factors may be modulated by low-dose apixaban. The foundation of this question is based on the current direction in which the field of VTE is moving (5) and supported by the more pathophysiologically-sound ISTH classification of risk factors (1).

Apixaban 2.5 mg twice daily may have additional advantages for extended-duration secondary prevention of VTE compared with rivaroxaban 10 mg daily (which has U.S. FDA approval for extended-duration therapy). Apixaban is a more pharmacokinetically rational regimen, given the half-life of these two DOACs. In trials of stroke prevention of atrial fibrillation, apixaban demonstrated a relatively lower frequency of gastrointestinal bleeding compared with warfarin (14–17). Apixaban has fewer off-target side effects than rivaroxaban, which can cause severe headache (necessitating urgent head CT) and severe rash.

Based on the emerging evidence that provoked VTE patients may require extended-duration anticoagulation for secondary prevention, the apixaban 2.5 mg twice daily dose could be a critical addition to our armamentarium in those at high risk for recurrence at the transition of care from the acute to the chronic treatment phase. However, this hypothesis needs to be tested in a clinical trial. We propose a single-center, randomized controlled trial conducted at Brigham and Women's Hospital (BWH) to evaluate the feasibility of low-dose apixaban (2.5 mg twice daily) in a study population exclusively comprised of provoked VTE patients with persistently provoking risk factors for VTE.

Rationale for the Proposed Study and Trial Design

The rationale for the study design is focused on the lack of data on the safety and efficacy of extended-duration low-dose apixaban for secondary prevention in patients with provoked VTE. A single-center, randomized placebo-controlled trial of extended low-intensity apixaban with a study population enriched for recurrent VTE event rates will be able to provide such data.

The rationale for a single-center study is that Watkins Cardiovascular Clinic at BWH is a Center of Excellence for thrombosis care not only in the New England region but also along the East coast. The BWH Thrombosis Center evaluates an average of 1200 new and follow-up outpatients with VTE per year. In addition, the Vascular Medicine Section at BWH includes 4 additional full-time faculty and 4 full-time Vascular Medicine fellows who also see a high volume of VTE patients. Accordingly, enrollment of 600 patients meeting the entry criteria and none of the exclusion criteria will be accomplished efficiently at our single center.

The rationale behind using a low-dose of apixaban is three-fold. First, low-dose rivaroxaban 10 mg orally daily was effective and safe in the EINSTEIN CHOICE trial (2) for extended-duration anticoagulation in secondary prevention after unprovoked VTE. Second, AMPLIFY-EXT demonstrated efficacy and enhanced safety to a low-dose apixaban regimen (2.5 mg orally twice daily) for extended-duration anticoagulation in secondary prevention after predominantly unprovoked VTE (7). Finally, because the relative risk of recurrence is less (although still unacceptably high) for provoked VTE than unprovoked VTE, a lower dose of apixaban may maintain efficacy while offering a reduction in the risk of major and clinically-relevant non-major bleeding.

The rationale for using low-dose apixaban in a study population that will include obese patients is that an analysis of the AMPLIFY-EXT data by weight demonstrated results for the primary efficacy outcome and the composite outcome of major and clinically relevant nonmajor bleeding were consistent with overall study results (7).

The rationale for using a placebo-control is that current evidence-based guidelines do not recommend any extended thromboprophylactic measures after provoked VTE. Trials of low-dose aspirin for secondary prevention of VTE have largely focused on unprovoked VTE or a mixed population of unprovoked and provoked VTE. In the EINSTEIN CHOICE trial, low-dose aspirin was associated with a bleeding risk similar to anticoagulation with rivaroxaban and a recurrent VTE rate 70% higher than anticoagulation with rivaroxaban (2).

The rationale for inclusion of eligible patients who are already taking ≤ 81 mg of aspirin is based on several factors. First, the HI-PRO trial will include atherosclerotic cardiovascular disease, which will enrich the study population in VTE events because of the strong pathophysiological link between the two (18–21). Many of these patients will be receiving low-dose aspirin (≤ 81 mg). Second, many potentially eligible patients will be receiving low-dose aspirin (≤ 81 mg) for primary prevention of cardiovascular events. Excluding these patients would significantly hinder enrollment. Finally, none of the major landmark trials of low-intensity apixaban (2.5 mg twice daily) excluded patients taking low-dose aspirin (≤ 81 mg). AMPLIFY-EXT and ADOPT allowed up to 165 mg of aspirin daily (7,22).

Atherosclerosis is associated with an increased risk of VTE. A link between atherosclerotic cardiovascular disease and VTE was first suggested by Prandoni and colleagues, who observed that the presence of carotid plaque was associated with a doubling in VTE risk (23). Many risk factors for VTE, such as obesity, hypertension, dyslipidemia, diabetes, and smoking, overlap with those for atherosclerosis (21,24). The link between VTE and atherosclerotic cardiovascular disease also appears to be reciprocal. A recent analysis of TRA2P-TIMI 50 (Thrombin Receptor Antagonist in Secondary Prevention of Atherothrombotic Ischemic Events-Thrombolysis in Myocardial Infarction) and PEGASUS-TIMI 54 (Prevention of Cardiovascular Events in Patients With Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin-Thrombolysis in Myocardial Infarction 54) demonstrated the

risk of VTE increased with the number of symptomatic vascular territories affected by atherosclerosis (18). A recent editorial in Circulation called for medicine to abandon the dichotomized view of VTE as provoked or unprovoked and called for the basis of the optimal duration of anticoagulation to be determined by persisting risk factors, including cardiovascular disease (5). Because of the potential for a majority of patients in the study to have atherosclerotic cardiovascular disease limiting the generalizability of the results, up to 35% in each study group may have atherosclerotic cardiovascular disease as a qualifying persistent risk factor.

The rationale for enrollment at 3-months is derived from the 2016 American College of Chest Physicians (ACCP) evidence-based clinical practice document entitled "Antithrombotic Therapy for VTE Disease: CHEST Guideline and Expert Panel Report, "In patients with proximal DVT or pulmonary embolism (PE), we recommend long-term (3 months) anticoagulant therapy over no such therapy (Grade 1B)" (Kearon C, Akl EA, Ornelas J, et al. Antithrombotic Therapy for VTE Disease: CHEST Guideline and Expert Panel Report. Chest 2016;149:315-52). This statement supports the 3-month timepoint as an appropriate juncture to determine whether extended duration anticoagulation or discontinuation of antithrombotic therapy is appropriate.

The 2016 ACCP evidence-based clinical practice guidelines rely upon a more traditional classification for determining the risk of VTE recurrence after 3 months, a dichotomous approach distinguishing "provoked" from "unprovoked" (idiopathic) VTE, that has subsequently fallen out of favor. The 2016 ACCP guidance document states the following regarding extended-duration antithrombotic therapy for prevention of recurrent VTE:

"In patients with a proximal DVT of the leg or PE provoked by surgery, we recommend treatment with anticoagulation for 3 months over (i) treatment of a shorter period (Grade 1B), (ii) treatment of a longer time-limited period (eg, 6, 12, or 24 months) (Grade 1B), or (iii) extended therapy (no scheduled stop date) (Grade 1B).

In patients with a proximal DVT of the leg or PE provoked by a nonsurgical transient risk factor, we recommend treatment with anticoagulation for 3 months over (i) treatment of a shorter period (Grade 1B) and (ii) treatment of a longer time-limited period (eg, 6, 12, or 24 months) (Grade 1B). We suggest treatment with anticoagulation for 3 months over extended therapy if there is a low or moderate bleeding risk (Grade 2B), and recommend treatment for 3 months over extended therapy if there is a high risk of bleeding (Grade 1B)."

These guidelines fail to address the large population of patients with VTE who may have had a provoking factor but also have enduring risk factors for recurrence, such as those with persistent immobility, obesity, heart failure, chronic lung disease, chronic kidney disease, chronic inflammatory/autoimmune disorder, and atherosclerotic cardiovascular disease (Albertsen IE, Piazza G, Goldhaber SZ. Let's

Stop Dichotomizing Venous Thromboembolism as Provoked or Unprovoked. Circulation. 2018 Dec 4;138(23):2591-2593 and Albertsen IE, Piazza G, Søgaard M, Nielsen PB, Larsen TB. Extended oral anticoagulation after incident venous thromboembolism - a paradigm shift? Expert Rev Cardiovasc Ther. 2020 Apr;18(4):201-208).

More recently, the 2019 European Society of Cardiology Guidelines for the Diagnosis and Management of Acute Pulmonary Embolism, developed in collaboration with the European Respiratory Society (ERS), have recognized the importance of identifying persistent, or enduring, risk factors for VTE recurrence (Konstantinides SV, Meyer G, Becattini C, et al. 2019 ESC Guidelines for the diagnosis and management of acute pulmonary embolism developed in collaboration with the European Respiratory Society (ERS). Eur Heart J 2019). This paradigm shift away from the previous practice of dichotomizing VTE into “provoked” and “unprovoked” has also been endorsed by the International Society on Thrombosis and Haemostasis (ISTH), which recommends that clinicians consider persistent predisposing factors when determining whether to extend anticoagulation beyond 3 months (Kearon, C, Ageno, W, Cannegieter, SC, Cosmi, B, Geersing, G-J and Kyrle, PA, for the Subcommittees on Control of Anticoagulation, and Predictive and Diagnostic Variables in Thrombotic Disease. Categorization of patients as having provoked or unprovoked venous thromboembolism: guidance from the SSC of ISTH. J Thromb Haemost 2016; 14: 1480-3).

Accordingly, the 2019 European Society of Cardiology Guidelines state that the decision to pursue extended-duration anticoagulation should rest upon recognition of both transient risk factors for VTE but also the presence of persistent, or enduring, conditions that result in a prolonged risk of VTE recurrence after an initial event. These include chronic medical disorders like inflammatory bowel disease, connective tissue disease, and other hypercoagulable states. Rather than dichotomizing VTE patients into “unprovoked” or “provoked”, the 2019 European Society of Cardiology Guidelines recommend assessment of persistent predisposing factors and an estimated long-term recurrence risk (if anticoagulation is discontinued after 3 months). The Guidelines suggest that only patients with an estimated recurrence risk of less than 3% per year should receive time-limited treatment (see figure below). Patients with greater than 8% risk of recurrence per year (for example, those with cancer-related VTE) are mandated to receive indefinite duration anticoagulation. There is clinical and research equipoise for the patient population that has an intermediate risk for recurrence (3-8% risk of recurrence per year).

The inclusion and exclusion criteria for the current study follows the evidence-based clinical practice guideline recommendations from the ESC and ISTH and identify a population of patients with VTE who have a 3-8% of VTE recurrence per year. We have estimated a 12-month VTE recurrence rate of 6% in our proposed study population, exactly within this range of clinical and research equipoise.

Study Objectives

Primary Safety Objective: To quantitatively assess the International Society on Thrombosis and Haemostasis (ISTH) major bleeding at 12 months.

Primary Efficacy Objective: To quantitatively assess the 12-month rate of symptomatic, recurrent VTE, defined as the composite of deep vein thrombosis and/or pulmonary embolism.

Secondary Safety Objective: To quantitatively assess the 12-month rate of ISTH clinically relevant non-major bleeding.

Secondary Efficacy Objective: To quantitatively assess the composite of death due to cardiovascular cause, nonfatal myocardial infarction, stroke or systemic embolism, critical limb ischemia, or coronary or peripheral ischemia requiring revascularization (major adverse cardiovascular events, including major adverse limb events) at 12 months.

Study Design

600-patient U.S.-based, single-center, randomized, double-blinded, placebo-controlled study of apixaban 2.5 mg orally twice daily for extended prevention of recurrence after provoked VTE in patients with at least one persistent provoking factor who have completed at least 3 months of standard therapeutic anticoagulation and who have a low risk of bleeding.

Study Duration

The study will be completed in 36 months: 2 months for start-up (including Human Research Committee/Institutional Review Board [IRB] approval and finalizing the Case Report Form), 32 months for patient enrollment, follow-up, and data collection, and 2 months for data analysis and writing up the results (**Table 1**).

Table 1. Study timeline.

Milestone	**Duration (months)**
Start-up	2
Patient enrollment	20
Completion of data collection	12
Data analysis and completion of study report	2
TOTAL	**36**

Study Population

Patients who are 18 years of age or older with provoked deep vein thrombosis and/or pulmonary embolism, have completed at least 3 months of therapeutic anticoagulation, have a low risk of bleeding, and have at least one persistent provoking risk factor.

Low risk of bleeding is defined by several of the exclusion criteria:

- have contraindications to antithrombotic or antiplatelet therapy
- have a requirement for ongoing anticoagulant therapy, dual antiplatelet therapy, or aspirin at a dose of > 81 mg daily
- have a hemoglobin level < 9 mg/dL, a platelet count < 100,000/mm^3, a serum creatinine level > 2.5 mg/dL, an ALT or AST level > 2 times the upper limit of the normal range, or a total bilirubin level > 1.5 times the upper limit of the normal range
- have history of bleeding diathesis or have had recent active bleeding
- have active hepatobiliary disease

In a recent propensity score-matched analysis of data from 15,254 “all-comers” newly diagnosed VTE patients in the Truven Health MarketScan commercial and Medicare Supplement claims databases in the U.S., apixaban compared with rivaroxaban was associated with an optimal balance of decreased risk of recurrent VTE (HR 0.37 [95% CI 0.24–0.55]; p<0·0001) and major bleeding events (0·54 [0·37–0·82]; p=0.0031) (25). Based on these data, we believe that apixaban will provide superb efficacy and safety compared with placebo in the prespecified high-risk for VTE recurrence and low-risk for bleeding patient population of HI-PRO.

Study Inclusion Criteria

- Man or woman
- Age ≥ 18 years
- Objectively-confirmed provoked DVT and/or PE
  (Note: including post COVID-19 infection and post COVID-19 vaccination)
- Treated for at least 3 months with standard therapeutic anticoagulant therapy
- Has not suffered symptomatic recurrence during prior anticoagulant therapy
- Outpatient follow-up at BWH
- AND have at least one of the following persistent provoking VTE risk factors:
  - Persistent immobility (defined as paralysis, other inability to ambulate freely, bed-bound, wheelchair-bound)
  - Obesity (defined as BMI ≥ 30 kg/m2)
  - Heart failure (systolic, diastolic, or combined)
  - Chronic lung disease (COPD, asthma, interstitial lung disease)
  - Chronic kidney disease (eGFR <60 mL/min/1.73m2)
  - Chronic inflammatory/autoimmune disorder (inflammatory arthritis, vasculitis, inflammatory bowel disease, chronic infection)
  - Atherosclerotic cardiovascular disease (coronary, cerebrovascular, or peripheral artery disease) (up to 35% in each study group may have

atherosclerotic cardiovascular disease as a qualifying persistent risk factor)
    - **NOTE:** Eligible patients will be allowed to have multiple risk factors, and there will not be a limit as to how many of the above risk factors a subject may have. In addition, we will place no limit on the number of patients included with multiple risk factors. A study population with multiple risk factors is highly representative of the provoked VTE population and will provide the greatest generalizability of the study results to real-world clinical practice. Including patients with single and multiple persistent provoking risk factors will also facilitate enrollment. As noted, there is clinical and research equipoise regarding whether patients with a single or multiple persistent provoking VTE risk factors should receive extended duration thromboprophylaxis for secondary prevention.
- Willing to provide written informed consent

Study Exclusion Criteria

- Women who are pregnant or breastfeeding
- Women of child-bearing potential who are unwilling or unable to use an acceptable method of birth control (such as oral contraceptives, other hormonal contraceptives [vaginal products, skin patches, or implanted or injectable products], or mechanical products such as an intrauterine device or barrier methods [diaphragm, condoms, spermicides]) to avoid pregnancy for the entire study
- Active cancer within the past 5 years
- Contraindication to antithrombotic or antiplatelet therapy
- Requirement for ongoing anticoagulant therapy, dual antiplatelet therapy, P2Y12 inhibition, or aspirin at a dose of > 81 mg daily
- Hemoglobin level < 9 mg/dL, a platelet count < 100,000/mm3, a serum creatinine level > 2.5 mg/dL or CrCl <25 mL/minute (as determined by Cockcroft-Gault equation), an ALT or AST level > 2 times the upper limit of the normal range, or a total bilirubin level > 1.5 times the upper limit of the normal range
- History of a platelet disorder such as Von Willebrand Disease
- History of bleeding diathesis or have had recent active bleeding
- Active severe hepatobiliary disease
- More than 6 months that have elapsed without taking an anticoagulant or low-dose aspirin
    - **NOTE:** The risk of recurrent VTE following cessation of anticoagulation rises slowly over the first 3-6 months (26). After this initial period, the cumulative risk of recurrent VTE steepens. Using a limit of no greater than 6 months of interruption in anticoagulation before potential re-initiation of anticoagulation as part of this trial will safely facilitate

enrollment as opposed to restricting the population to no greater than 3 months of interruption.

- Known severe thrombophilia (any increased titer antiphospholipid antibody or positive lupus anticoagulant/DRVVT or deficiency of antithrombin, protein C, or protein S) which would indicate long-term full therapeutic anticoagulation with a vitamin K antagonist
- Life expectancy < 12 months or hospice care
- Prisoners or subjects who are involuntarily incarcerated
- Subjects who are compulsorily detained for treatment of either a psychiatric or physical (e.g., infectious disease) illness
- Receiving concurrent non-FDA-approved or investigational agents or has received an investigational agent within the past 30 days prior to the first dose of study treatment (with the exception of approved medications being used for an approved indication, e.g., investigating a new dosing regimen for an approved indication)
- Any condition, which in the opinion of the investigator, would put the subject at an unacceptable risk from participating in the study
- Any other medical, social, logistical, or psychological reason, which in the opinion of the investigator, would preclude compliance with, or successful completion of, the study protocol
- History of a severe hypersensitivity reaction to apixaban
- Required prescription of a medication that is contraindicated to be co-administered with apixaban

Enrollment of Women of Childbearing Potential and Partners

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

Investigators will counsel women of childbearing potential and male subjects who are sexually active with women of childbearing potential on the importance of pregnancy

prevention and the implications of an unexpected pregnancy Investigators will advise women of childbearing potential and male subjects who are sexually active with women of childbearing potential on the use of highly effective methods of contraception. Highly effective methods of contraception have a failure rate of < 1% when used consistently and correctly.

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

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

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

A woman of childbearing potential is defined as any female who has experienced menarche and who has not undergone surgical sterilization (hysterectomy or bilateral oophorectomy) and is not postmenopausal. Menopause is defined as 12 months of amenorrhea in a woman over age 45 years, in the absence of other biological or physiological causes. In addition, females under the age of 55 years must have a serum follicle stimulating hormone (FSH) level > 40mIU/mL to confirm menopause.

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

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

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

Screening Procedures

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

1. The Principal Investigator or designee will be contacted by the responsible provider to initiate screening.

2. The Principal Investigator or designee will confirm that patient is ≥ 18 years of age or older.

3. The Principal Investigator or designee will confirm fulfillment of the study inclusion criteria and the absence of **all** exclusion criteria.

4. The Principal Investigator or designee will provide the potential study subject with the study Informed Consent Form to review, sign, and date. Informed consent must be obtained from a subject with the capacity for medical decision-making. The process for obtaining informed consent must be in compliance with the Partners IRB guidelines and policies. Informed consent may be obtained by the Principal Investigator or Co-Investigators. Potential study subjects will not be enrolled if Informed Consent cannot be obtained. A copy of the signed Informed Consent Form must be provided to the subject. Signed Informed Consent Forms must remain in each subject's study file and must always be available for verification.

5. A research staff member will enter the patient demographic data into the screening portion of the electronic case report form (eCRF).

6. Subjects who agree to participate in the study and sign the Informed Consent Form will be considered for enrollment in the study and should have baseline data which includes:
    a. History and physical examination within the past 6 months
    b. Review of relevant laboratory data from within the past three months. If laboratory data for a complete blood count, basic chemistry panel, and coagulation (prothrombin time and activated partial thromboplastin time) are not available from the past three months, these will be drawn at the initial study visit and paid for by the study.
    c. Serum (β-HCG) or urine pregnancy test (u-HCG) for women of child-bearing potential

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

Assessment of Enrollment

After 10 months of study recruitment, an assessment of enrollment will be conducted. If 300 study subjects have not been recruited by 10 months, activation of second study site, Brigham and Women's Faulkner Hospital, will be considered by the Study Investigators. Activation of the Brigham and Women's Faulkner Hospital as a study site will require submission to and approval by the Partners Human Research Committee/IRB.

Treatment Description

Subjects will begin anticoagulation within 3 weeks of passing the screening procedure. Subjects who are 18 years of age or older with provoked DVT and/or PE, have completed at least 3 months of therapeutic anticoagulation, have a low risk of bleeding, and have at least one persistent provoking risk factor will be randomly assigned to receive apixaban 2.5 mg orally twice daily or oral placebo for extended secondary prevention of VTE for a duration of 12 months.

If during the study period the patient requires an invasive procedure or surgery that necessitates the discontinuation of anticoagulation (study drug), apixaban should be held as per the prescribing guidelines (**Appendix**, http://packageinserts.bms.com/pi/pi_eliquis.pdf). If appropriate based on the judgment of the responsible clinician, apixaban should be restarted when safe to do so postoperatively.

Patients and providers will be blinded as to the study group assignment.

Both study drug and placebo will be dispensed by the BWH Investigation Drug Service in 3-month allotments either in person at the screening visit, other non-study related office visit at BWH, or directly to the patient within 2 business days of the enrollment visit via mail or courier in accordance with BWH Investigation Drug Service policy. Subsequent allotments will be dispensed via mail or courier in accordance with BWH Investigation Drug Service policy. Our Research Nurse will communicate with study subjects by telephone at 3 months intervals in advance of releasing a 3-month allotment of study drug or placebo to ensure that treatment is not interrupted due to the subjects' supplies running out.

Randomization

Subjects who are 18 years of age or older with provoked DVT and/or PE, have completed at least 3 months of therapeutic anticoagulation, have a low risk of bleeding, and have at least one persistent provoking risk factor will be randomly assigned by computer in a 1:1 ratio to receive apixaban 2.5 mg orally twice daily or oral placebo for extended secondary prevention of VTE for a duration of 12 months.

Safety Outcomes

Primary Safety Outcome

The primary safety outcome will be major bleeding at 12 months. Major bleeding is defined as overt bleeding that is associated with a decrease in the hemoglobin level ≥ 2 g/dL, leads to transfusion ≥ 2 units of packed red blood cells, occurs in a critical site, or contributes to death (27). The primary safety outcome will be independently adjudicated by a blinded Clinical Endpoints Committee (CEC) review.

Secondary Safety Outcome

Clinically relevant non-major bleeding at 12 months will be evaluated (please see below) and is defined as overt bleeding that does not meet the criteria for major bleeding but that is associated with the need for medical intervention, unscheduled contact with a physician, interruption or discontinuation of the study drug, or discomfort or impairment of activities of daily living (28).

Efficacy Outcomes

Primary Efficacy Outcome

The primary efficacy outcome will be symptomatic, recurrent VTE, defined as the composite of deep vein thrombosis and/or pulmonary embolism at 12 months. The primary efficacy outcome will be independently adjudicated by a blinded CEC review.

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

PE is diagnosed based on new mismatched perfusion defect(s) on ventilation perfusion scan, the presence of a new pulmonary artery filling defect on contrast-enhanced chest CT, a new finding of intraluminal filling defect on invasive pulmonary angiography, or evidence of PE at autopsy.

Secondary Efficacy Outcome

A secondary efficacy outcome will be the composite of death due to cardiovascular cause, nonfatal myocardial infarction (MI), stroke or systemic embolism, critical limb ischemia (CLI), or coronary or peripheral ischemia requiring revascularization (major adverse cardiovascular events, including major adverse limb events) at 12 months. The secondary efficacy outcome will be independently adjudicated by a blinded CEC review.

An acute MI is defined as the presence of at least 2 of the 3 following conditions (29):

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

An acute stroke is defined as a new, focal neurologic deficit of sudden onset, lasting at least 24 hours, not due to a readily identifiable nonvascular cause (i.e. brain tumor, trauma), as confirmed by a neurologist and neuroimaging (7). All strokes during the study will be assessed by imaging or autopsy, and classified as primary hemorrhagic, non-hemorrhagic, infarction with hemorrhagic conversion, or unknown, as defined by the American College of Cardiology.

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

Cardiovascular death is defined as a death for which a definite non-cardiovascular cause (e.g. cancer) has not been identified. Uncertain causes of deaths are presumed to be cardiovascular unless proven otherwise.

Major adverse limb events include acute limb ischemia (ALI) and critical limb ischemia (CLI) (30). Acute limb ischemia is defined as limb-threatening ischemia which is confirmed by limb hemodynamics or imaging and leads to an acute vascular intervention (i.e. pharmacologic [heparin, thrombolysis], peripheral arterial surgery/reconstruction, peripheral angioplasty/stent, or amputation) within 30 days of onset of symptoms. In the absence of confirmation by limb hemodynamics or imaging, absent pedal pulses is acceptable as hemodynamic criterion for acute limb ischemia. If the event does not meet the definition for ALI it may be classified as

chronic limb ischemia, peripheral vascular intervention or other peripheral vascular hospitalization.

CLI is defined as continuing ischemic limb, foot or digit pain leading to hospitalization and intervention and not meeting the definition of ALI, or Fontaine 3 or 4 at baseline with peripheral intervention during the trial.

Peripheral vascular intervention is defined as peripheral vascular intervention not meeting the definition for ALI or CLI.

Additional Study Outcomes: Admission for heart failure will also be assessed at 12 months. Adherence to the twice-daily regimen of apixaban (and placebo) will be recorded as the total number of doses taken divided by the total number of doses prescribed. Adherence data will be recorded on patient-maintained drug diaries.

Clinical Endpoints Committee Adjudication of Study Outcomes

Primary and secondary safety and efficacy outcome will be independently adjudicated by a Clinical Endpoints Committee (CEC) that is blinded with regards to the subject's treatment allocation (randomization). The CEC will include a chairperson and independent reviewers who are physicians with experience in vascular medicine and thrombosis. The CEC will adjudicate all index events (proximal DVT and/or PE). During the study period and the post-treatment observation period, the CEC will adjudicate all suspected occurrences/recurrences of venous or arterial thromboembolic events, deaths, and the following events of special interest: acute myocardial infarction, acute stroke, and thrombocytopenia. The CEC will also review all suspected episodes of bleeding, and categorize adjudicated bleeding as major, clinically relevant non-major, or minor bleeding. The Committee will be provided with all relevant documentation related to the events but will be blinded as to the subject's treatment allocation. The criteria and definitions of the study outcomes as well as the procedures followed by the Committee are described in this protocol.

Drug Accountability

Study drug and placebo will be physically stored at BWH in our Investigational Drug Pharmacy. Drug handling and dispensing will be accomplished through our BWH Investigational Drug Service. The Director of Pharmacy at BWH will oversee the Investigational Drug Service in this regard for the purposes of the clinical trial. Documentation of administration will by accomplished by our Electronic Health Record (EHR; EPIC) in addition to a patient drug diary, which is being kept to assess medication adherence. The Investigational Drug Service will collect empty study drug containers and unused drug via mail using prepaid labels that will be provided to the patient or courier as per Investigational Drug Service policy. We will perform drug accountability assessment when the drug containers are collected at each 3-month interval.

Follow-Up

Follow-Up Evaluation

Routine laboratory testing is neither recommended nor required in patients receiving extended duration apixaban, including the 2.5 mg twice daily dosing regimen. Patients enrolled in the study will either have been identified from one of the practices of our Vascular Medicine faculty or will be assigned to one of our faculty for long-term management of VTE. Accordingly, every patient enrolled in the study will have ongoing medical care with a dedicated Vascular Medicine provider. Study patients will be encouraged to follow-up with their primary care, , and other appropriate clinicians. Specifically, at the end of the treatment visit, every patient will be reminded to follow-up with a PCP as dictated by routine care and best clinical practice. Demographic, clinical characteristics, medication records, and outcomes will be abstracted from the BWH Electronic Health Record (EPIC).

When our Research Nurse conducts the every 3-month telephone call in advance of releasing a 3-month allotment of study drug or placebo the subject will be queried for any issues with the study or adverse events.

We will conduct an end-of-treatment visit to obtain data relevant to the study end points.

We will assess medication adherence via pill count. Medication adherence will be calculated in three month intervals as the total number of doses taken divided by the total number of doses prescribed for that time period ([x / 180] x 100 = medication adherence [%]) and also for the total 360-day study period ([x / 720] x 100 = medication adherence [%]). Subjects will be given a study drug diary to fill out at home each day. Subjects will write down the time they take their study drug and any side effects. The study drug diary will be collected at a regularly scheduled office visit or the end-of-treatment visit at conclusion of the study period.

Subject Retention, Withdrawal, and Termination

Continued participation of study subjects will be encouraged at the time of outpatient evaluation through the 12-month follow-up interval. However, study subjects will be informed that they retain the right to withdraw from the study at any time without compromise to their current or subsequent medical care. Subjects will be terminated from the study if they expire or elect to withdraw.

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

1. Be contacted by telephone **AND**
2. Have their physicians contacted

Withdrawal criteria will include:

1. Patient requests to withdraw
2. Reasons related to SAE:
    a. Initiating or continuing study drug places the subject at undue hazard as determined by the Investigator;
    b. SAE or other safety concern that is related to study drug treatment;
    c. Major or life-threatening bleeding (as defined in the protocol)
    d. ALT or AST ≥ 3 ULN, if suspected to be due to the study drug
    e. Calculated CrCL decreased to < 30 mL/min confirmed by repeat testing at least one week later, or need for dialysis
3. Pregnancy
4. Patient develops severe hepatic impairment (Child-Pugh class C) during the trial
5. Death
6. Lost to follow-up (every attempt will be made by the Investigator not to have subjects "lost to follow-up")
7. Study terminated by sponsor (termination of all or part of the study by the sponsor, in concert with the study leadership)

Safety Monitor

An independent Safety Monitor has been selected for this study. The Safety Monitor is an expert in VTE and is distinct from the DMSB and Study Staff and will be available throughout the study to assess patient safety issues that may arise, objectively. The Safety Monitor will have the ability to break the blind of a study patient as the need arises (immediately, in real-time). If the Safety Monitor is unavailable because of travel, one of the Physician Study Investigators will serve as back-up. The Safety Monitor will attend DSMB meetings, although will be non-voting. The Safety Monitor will have the ability to request an ad hoc DSMB meeting should a safety issue arise that warrants further review.

Assessment and Reporting of Adverse Events

Definitions

Adverse events

An adverse event (AE) is defined as any new untoward medical occurrence or worsening of a pre-existing medical condition in a patient or clinical investigation subject administered an investigational (medicinal) product and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of investigational product, whether or not considered related to the investigational product. The causal relationship to study drug is determined by a physician and should be used to assess all AEs.

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

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

Serious Adverse Events

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

- results in death
- is life-threatening (defined as an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- requires inpatient hospitalization or causes prolongation of existing hospitalization
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect
- is an important medical event, defined as a medical event that may not be immediately life-threatening or result in death or hospitalization but, based on appropriate medical and scientific judgment, may jeopardize the subject or may require intervention (e.g., medical, surgical) to prevent one of the other serious outcomes listed above. Examples of such events include but are not limited to intensive treatment in an emergency department or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization.

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

The following hospitalizations are not considered SAEs:

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

lack of housing, economic inadequacy, caregiver respite, family circumstances, administrative reason)

Adverse Events of Special Interest

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

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

Pre-Existing Medical Conditions

A pre-existing medical condition is one that is present at the start of the study. Pre-existing medical conditions should be recorded in the baseline and demographic data section of the electronic case report form (eCRF). Pre-existing medical conditions should be reassessed during the trial and reported as an adverse event or severe adverse event only if the frequency, severity, or character of the conditions worsens significantly or unexpectedly during the study. When reporting such adverse events, the description should convey that the pre-existing condition has changed by including applicable descriptors (e.g., "more frequent" headaches). Previously scheduled hospitalizations and hospitalizations required for diagnostic or elective surgical procedures for the management of unchanged pre-existing medical condition should not be considered adverse events.

Serious Adverse Event Collecting and Reporting

Following the subject's written consent to participate in the study, all SAEs, whether related or not related to study drug, must be collected, including those thought to be associated with protocol-specified procedures. All SAEs must be collected that occur during the screening period and within 30 days of discontinuing dosing. If applicable, SAEs must be collected that relate to any later protocol-specific procedure.

When our Research Nurse conducts the every 3 month telephone call in advance of releasing a 3-month allotment of study drug or placebo the subject will be queried for any issues with the study or adverse events. The Electronic Health Record, Epic, will notify study staff when a study subject is admitted to the hospital or presents to the Emergency Department. This notification will be an additional avenue for detection of SAEs. Providers will also be able to see that the patient is enrolled in the study and how to contact study staff through the EHR.

SAEs will be detected via report from the study subject, the subject's care providers, a study physician or staff member, or identification from the EHR during data collection. Patients that report AEs to the study staff will be contacted by a study physician and triaged to the appropriate setting for care depending on the nature and severity of the AE and in accordance with best clinical practices.

The investigator should report any SAE occurring after these time periods that is believed to be related to study drug or protocol-specified procedure. An SAE report should be completed for any event where doubt exists regarding its status of seriousness. If the investigator believes that an SAE is not related to study drug, but is potentially related to the conditions of the study (such as withdrawal of previous therapy, or a complication of a study procedure), the relationship should be specified in the narrative section of the SAE Report Form.

SAEs, whether related or unrelated to the study drug, and pregnancies must be reported to BMS within 1 business day of becoming aware of the event:

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

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

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

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

SAE Reconciliation

The Sponsor will reconcile the clinical database AE cases (**case level only**) transmitted to BMS Global Pharmacovigilance (GPV&E) (Worldwide.Safety@bms.com).

- The Investigator will request from BMS GPV&E, aepbusinessprocess@bms.com the SAE reconciliation report and include the BMS protocol number every 3 months and prior to data base lock or final data summary
- GPV&E will send the investigator the report to verify and confirm all SAEs have been transmitted to BMS GPV&E.
- 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 should be sent immediately to BMS (Worldwide.Safety@bms.com).

Health Authority Reporting (U.S. FDA IND)

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

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

MedWatch SAE forms should be sent to the FDA at:

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

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

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

In addition to the Sponsor Investigator's responsibility to report events to their local Health Authority (HA), suspected serious adverse reactions (whether expected or unexpected) shall be reported by BMS to the relevant competent health authorities in all concerned countries according to local regulations (either as expedited and/or in aggregate reports).

- In accordance with local regulations, BMS will notify sponsor investigators of all reported SAEs that are suspected (related to the investigational product) and unexpected (ie, not previously described in the Investigator's Brochure (IB)). An event meeting these criteria is termed a Suspected, Unexpected Serious Adverse Reaction (SUSAR). Sponsor investigator notification of these events will be in the form of either a SUSAR Report or a Semi-Annual SUSAR Report.
  - ✓ Other important findings which may be reported by BMS as an Expedited Safety Report (ESR) include: increased frequency of a clinically significant expected SAE, an SAE considered associated with study procedures that could modify the conduct of the study, lack of efficacy that poses significant hazard to study subjects, clinically significant safety finding from a nonclinical (eg, animal) study, important safety recommendations from a

study data monitoring committee, or sponsor or BMS decision to end or temporarily halt a clinical study for safety reasons.

- ✓ Upon receiving an ESR from BMS, the investigator must review and retain the ESR with the IB. Where required by local regulations or when there is a central IRB/Independent Ethics Committee (IEC) for the study, the sponsor will submit the ESR to the appropriate IRB/IEC. The investigator and IRB/IEC will determine if the informed consent requires revision. The investigator should also comply with the IRB/IEC procedures for reporting any other safety information.

Non-Serious Adverse Events

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

Non-Serious Event Collecting and Reporting

The collection of non-serious AE information should begin following the subject's written consent to participate in the study. 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.

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.

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 captured and reported as appropriate:

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

- Any laboratory test result abnormality that required the subject to receive specific corrective therapy.

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

Pregnancy

If, following initiation of apixaban, it is subsequently discovered that a study subject is pregnant or may have been pregnant at the time of apixaban exposure, including during at least 5 half-lives after product administration, the investigational product will be permanently discontinued in an appropriate manner. The investigator must immediately notify WorldwideSafety@BMS.com of this event via the Pregnancy Surveillance Form within 24 hours and in accordance with SAE reporting procedures.

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

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

Protocol-required procedures for study discontinuation and follow-up must be performed on the subject unless contraindicated by pregnancy. Other appropriate pregnancy follow-up procedures should be considered if indicated.

Other Safety Considerations

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

Documentation of Adverse Events

Information about potential adverse events should be reviewed during the 6-month follow-up period. Subjects should be encouraged to report adverse events spontaneously or in response to non-directed questioning by their usual healthcare providers. If it is determined that an adverse event has occurred, the study staff

member entering data into the eCRF should obtain all of the information necessary to complete the Adverse Event section. All observed or reported adverse events, regardless of the suspected causal relationship to study treatment must be recorded in the Adverse Event section of the eCRF. The Sponsor will be notified when an event has been entered into the database.

Duration of Adverse Event Reporting Period

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

Specific Adverse Event Reporting Guidelines

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

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

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

Categorization of Adverse Events

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

Intensity or Severity

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

Mild	Awareness of a symptom or sign that does not interfere with the patient's usual activity or is transient and resolves without treatment and without sequelae
Moderate	Interferes with the patient's usual daily activities, but he or she is still able to function
Severe	Interrupts a patient's usual daily activities and generally requires medication, surgery, or other intervention for treatment

Expectedness

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

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

Relatedness

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

Definite	An adverse event is clearly related to apixaban

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

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

Outcome

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

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

Treatment or Action Taken

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

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

Expedited Reporting of Serious Adverse Events (SAE)

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

1. Report any serious adverse event that occurs to the Sponsor within 24 hours of knowledge of the event (Monday through Friday). If the investigator does

not have all information regarding the SAE, ***he/she will not wait to receive additional information before notifying the Sponsor*** of the event and completing the eCRF. The investigator shall provide an event update when additional information is received.

NOTE: The Sponsor will automatically be notified when an adverse event or serious adverse event has been entered into the database when the investigator fills in an eCRF.

2. In the reporting of serious adverse events, the study investigator shall provide any potentially relevant information including:
    a. Subject demographics
    b. Pre-existing conditions
    c. The complete description of the adverse event.
    d. Date and time of adverse event onset
    e. Severity
    f. Treatment
    g. Results of diagnostic testing
    h. Duration of sequelae
    i. Outcome (if known)
    j. Date and time of adverse event resolution.
    k. Information on suspected medications including dose, route of administration, frequency, dates, lot number, expiration date, and concomitant medications

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

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

Sponsor Unanticipated Adverse Drug Effects (UADEs) Reporting Responsibilities

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

<u>Data Reporting, Processing, and Quality Control</u>

Data Acquisition, Monitoring, and Quality Control

Subject data will be collected using a web-based electronic case report form (eCRF) called REDCap. Database monitoring and quality control will be performed by the Data Safety Monitoring Board (DSMB).

Monitoring Plan

Monitoring procedures will consist of the following:

During the study, the study staff shall perform monthly random reviews of data with checks for accuracy and completeness, and document that corrective actions have been taken in response to protocol deviations or other forms of non-compliance. These reports will be provided to the Data Safety Monitoring Board.

Data Safety Monitoring Board

Three independent individuals with relevant expertise in VTE and anticoagulation will be appointed to a data safety monitoring board (DSMB) whose primary responsibility is to protect the safety of study subjects and to provide ongoing, critical, and unbiased evaluation of the progress of the study. The DSMB will be comprised of two independent physicians and an independent statistician. To further ensure idependence of the DSMB, the DSMB Chair has been selected and is an expert in VTE AND comes from outside the Mass General Brigham Network.

The DSMB will:

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

The DSMB will meet virtually via Zoom under the restrictions imposed by the COVID-19 pandemic. The DSMB will meet once before the initiation of the trial and then at least once every three months for the duration of the trial in addition to prespecified meetings at 10 months and 50% of enrollment (Table). In addition, the DSMB may be convened on an *ad hoc* basis at the request of the study investigators if the need (for example, due to a study-related concern) arises in between regularly scheduled meetings. The DSMB chair may call an emergency meeting at any time should questions of patient safety arise or at the request of the Study Safety Monitor. The exact dates and times of the DSMB meetings will be determined based on the availability of all three members to meet and will take place within the first two weeks of the given month.

1. Prior to the first meeting, the DSMB will be provided with FDA- and IRB-approved protocol, DSMB Charter, and DSMB Adjudication Report Form to allow for review and charter revisions prior to the first meeting called the DSMB Kick-off meeting.
2. The DSMB Kick-Off meeting will provide formal training on the protocol provided by the Thrombosis Research Group staff. During the first meeting, the DSMB will review and approve the final Charter. The DSMB will determine reports needed for safety review and establish stopping rules.
3. Planned DSMB meetings will take place every three months. The DSMB will review all safety data collected to date on the initial subjects enrolled. The DSMB will also assess whether the study is on-track to meet its enrollment goal. Once the review is complete and no safety or enrollment concerns are raised, the trial will continue.
4. A DSMB meeting will be held at the halfway point through the enrollment period (10 months). At this point the DSMB will assess whether the study is on-track to meet its enrollment goal. The DSMB will also assess any safety concerns at that time. Once the review is complete and no safety or enrollment concerns are raised, the trial will continue.
5. A DSMB meeting will also occur when 50% of the planned enrollment population has completed 12-month follow-up as part of the prespecified interim analysis. This planned interim analysis will inform the DSMB on whether the study should be stopped early due to efficacy, safety concerns, or futility or continue to enroll the full 600-patient cohort.
6. A final DSMB meeting will take place after follow-up completion of the last subject. The DSMB will review all remaining safety data collected on the subjects enrolled.
7. The DSMB chair may call an emergency meeting at any time should questions of patient safety arise or at the request of the independent Study Safety Monitor. All materials, discussions, and proceedings of the DSMB are completely confidential. The Chair and other participants present at DSMB meetings are expected to maintain confidentiality.

Table. Schedule of Planned DSMB Assessments.

Milestone-Based Meetings	Timing
Kick-Off	1 month before enrollment of first patient
Halfway Point of Enrollment Period	10 months after first patient enrolled
300th Patient Interim Analysis	After follow-up completion in the 300th patient
Final Meeting	After follow-up completion in last patient

Recurring Meetings	
#2	3 months after first patient enrolled
#3	6 months after first patient enrolled
#4	9 months after first patient enrolled
#5	12 months after first patient enrolled
#6	15 months from first patient enrolled
#7	18 months from first patient enrolled
#8	21 months from first patient enrolled

Interim Safety and Efficacy Analysis

The DSMB will meet to review the safety and efficacy outcomes for the first 300 patients enrolled in the study when they have completed 12-month follow up. Whether to continue, amend, suspend, or terminate the study will be made based in this interim analysis. The DSMB will review the safety and efficacy outcomes again at the completion of follow up completion of the last patient enrolled in the study.

The DSMB will be responsible for:

1. Assessing study enrollment and likelihood of completion of 600 patients randomized
2. Assessing the study event rate in the placebo group and likelihood of obtaining enough events to satisfy the requirements for the primary efficacy analysis
3. Assessing the event rates in the treatment and placebo groups
4. Assessing the accumulated SAEs to determine whether the safety stopping criteria have been meet

Actions taken by the DSMB will include the following recommendations:

1. Study termination if stopping criteria for safety or futility have been met
2. Study modification if the DSMB deems that remediation measures have a reasonable probability of successful completion of the study
3. Continuation of the study as is

Blinding/Unblinding

This study will be conducted in a blinded fashion. To maintain blinding of study treatment, study medications will be prepared using placebo matching the active treatments. Subjects, Investigators, members of any of the administrative and adjudicating committees, and the Sponsor's staff conducting the study, will not have access to individual subject treatment assignments.

Blinding is critical to the integrity of this clinical study. However, in the event of a medical emergency or pregnancy in an individual subject, in which knowledge of the investigational product is critical to the subject's management, the blind for that

subject may be broken by the Safety Monitor (or if unavailable, the treating investigator). Before breaking the blind of an individual subject's treatment, the Safety Monitor should have determined that the information is necessary, i.e., that it will alter the subject's immediate management. In many cases, particularly when the emergency is clearly not investigational product-related, the problem may be properly managed by assuming that the subject is receiving active product without the need for unblinding.

The Safety Monitor should ensure that health care professionals who may provide any elective, urgent or emergent medical or surgical care for a subject after randomization are informed that:

1. The subject is enrolled in a clinical study and is receiving blinded oral study treatment, consisting of:
    a. Factor Xa inhibitor, OR
    b. Placebo
2. The factor Xa inhibitor is an anticoagulant, with a half-life of approximately 12 hours, which cannot be monitored using standard laboratory tests, such as PT, PTT, ACT, and INR
3. In the event of an emergency, this person should be treated symptomatically as would any other person being treated with anticoagulants. Treatment in an emergency may include discontinuation of all study treatment, and the use of standard resuscitative management and hemostatic agents such as prothrombin complex concentrate or andexanet alfa, if appropriate.

When knowledge of the subject's randomized treatment assignment would have a meaningful impact on individual management, for example in many cases of clinically significant bleeding or the need for urgent invasive procedures, the subject's treatment assignment should be unblinded. This information should be provided to those who are caring for the subject and as few other people as possible. In these cases, we will minimize bias by assuring that the clinical events committee remains blinded to treatment assignment, even if the investigator has been unblinded. Every subject will be provided with an alert card.

The alert card:

- Will indicate that the subject is participating in a double-blind clinical trial.
- Provides the sponsor's name and trial number.
- Will note that the subject may be receiving either placebo or an investigational anticoagulant drug (a factor Xa inhibitor).
- Provides the Study Safety Monitor's name and emergency contact information to provide information to emergency medical personnel

The need to break the blind must first be discussed with the responsible Safety Monitor who will be available to page at all times by the responsible care provider. The Safety Monitor will have electronic access to the subject's study allocation and can thereby break the blind.

Invasive Procedures and Surgery

Several factors govern the management of anticoagulation in this study with respect to surgery and invasive procedures, as well as the management of bleeding that may occur in subjects on study drugs. These are:

- The risk of thromboembolism in an individual subject (low, intermediate or high).
- The risk of bleeding associated with the procedure or surgery.
- Whether the surgery or invasive procedure is elective or emergent in nature.
- The desirability of maintaining blinding, if at all possible, without creating risk for the subject.
- The times of onset and offset of anticoagulant effect for apixaban

Elective Procedures

In general, local standards of care for discontinuation of anticoagulation prior to elective procedures/surgery should be employed; these may be informed by current guidelines.

These are summarized below:

- Stop apixaban/apixaban-placebo 2-4 days before the planned procedure.
- If the procedure is associated with an increased risk of thrombosis, brief postoperative protection with UFH or LMWH may be considered.
- Restart apixaban/apixaban-placebo postoperatively (usually the day after surgery) when it is deemed safe to do so. If UFH/LMWH is used in the postoperative period, it is recommended that apixaban/apixaban-placebo begin:
    - ≥ 2 hours after the last dose of UFH;
    - ≥ 6 hours after the last dose of LMWH indicated for twice daily administration; or
    - ≥ 12 hours after the last dose of LMWH indicated for once daily administration (or fondaparinux).

Emergency Procedures

For urgent or emergent invasive procedures, when waiting 4 - 5 days is not an option, management will in part depend on the randomized treatment assignment (placebo or apixaban) and unblinding may be necessary (see Section on Blinding/Unblinding). Regardless of treatment, study drugs should be discontinued and standard laboratory coagulation tests (PT/INR, aPTT, platelet count, etc.) performed. The procedure should be carried out and in such a way to minimize the risk of bleeding. For subjects receiving apixaban, the risk of bleeding with invasive procedures is unknown. At therapeutic doses, the anticoagulant effects of apixaban will not be reflected in standard coagulation tests. Given its half-life (12 hours), however, the anticoagulant effect of apixaban abates in 24 - 48 hours. Depending on the subject's risk of

bleeding with the procedure, subjects receiving apixaban who require an invasive or surgical procedure within 24 hours of their last dose may be treated with prothrombin complex concentrate or andexanet alfa. If treatment with an alternative open label anticoagulant/antithrombotic is indicated for the procedure, it should be used at the lowest therapeutic dose (if at all) in the 12 hours following last dose of apixaban.

Treatment Guidelines for Bleeding/Suspected Bleeding

Subjects with bleeding or suspected bleeding will undergo confirmatory laboratory or other testing (e.g., US, CT, MRI) and a (S)AE CRF must be completed. The date and time of the onset of the bleeding event will be recorded on the CRF.

For subjects with minor bleeding, study drug may or may not be held at the discretion of the local physician and investigator. A risk/benefit determination should be made weighing the subject's risk of further bleeding against the subject's risk of thromboembolism and benefit from continued anticoagulation. Minor bleeding should otherwise be managed according to local standard of care.

For subjects with clinically significant bleeding, the study drugs should generally be held. Bleeding should be managed according to local standard of care and may include measures such as:

- Local measures to stop the bleeding
- Volume resuscitation, and transfusion of blood products as appropriate
- Standard laboratory tests (e.g., hemoglobin, hematocrit, platelet count, etc.)

Note: Neither apixaban nor the comparator affects standard coagulation tests.

The management of clinically significant bleeding will in part depend on the randomized treatment assignment (placebo or apixaban) so unblinding may be necessary (see Section on Blinding/Unblinding). Should unblinding occur, subjects receiving placebo should be managed according to the local standard of care. Given its half-life (12 - 15 hours), however, the anticoagulant effect of apixaban abates in 24 - 48 hours. Subjects receiving apixaban with clinically significant bleeding that does not respond to local measures may be treated with prothrombin complex concentrate (PCC) or andexanet alfa as per Good Clinical Practice and local anticoagulant reversal protocols.

Management of Recurrent Venous Thromboembolic Events

If a subject has a confirmed recurrent symptomatic VTE (DVT or PE), as deemed by the primary investigator, then the patient must discontinue study treatment and transition to the appropriate standard of care. The subject should remain in the study and should be followed in the same manner as a subject who has discontinued study treatment as described in the protocol.

Prohibited and/or Restricted Treatments

Prohibited Treatments:

The following medications or therapies are prohibited during the study treatment period:

- Potent inhibitors of CYP3A4 (e.g., azole antifungals [itraconazole and ketoconazole], macrolide antibiotics [clarithromycin and telithromycin], protease inhibitors [ritonavir, indinavir, nelfinavir, atazanavir, and saquinavir], and nefazadone)
- Aspirin > 81 mg/day
- Dual antiplatelet therapy such as concomitant (simultaneous) use of both aspirin and a thienopyridine (e.g., clopidogrel, ticlopidine)
- Other antithrombotic agents (e.g., UFH, LMWH, direct thrombin inhibitors, fondaparinux)
- GP IIb/IIIa inhibitors (e.g., abciximab, eptifibatide, tirofiban)

If treatment with a prohibited agent becomes necessary, study drug should be temporarily interrupted, and restarted as soon as possible following discontinuation of the prohibited medication or therapy.

Restricted Treatments:

The administration of the following agents in subjects on study drug should be done cautiously given the increased risk of bleeding. In such cases, consideration of interruption of the study drug may be warranted; this decision should be made after a careful assessment of the risks and potential benefits.

Examples:

- Chronic (> 3 months) daily NSAIDs. NSAIDs should not be administered in doses that exceed those in the approved label
- Cytotoxic/myelosuppressive therapy

In addition, if a subject is currently receiving an agent that is a potent inducer of CYP3A4 (e.g., rifampin), the investigator should carefully evaluate that subject's risk of thromboembolism, as the plasma concentration of apixaban may be lower than that in subjects not receiving a potent inducer of CYP3A4

Stopping Criteria

The DSMB will consider efficacy events, in addition to safety events, before making any study stopping recommendations to the principal investigator.

1. General Stopping Rules

A. The DSMB, IRBs, regulatory authorities, or the Investigator may make recommendations to terminate the study if the safety and well-being of the subjects is in jeopardy.
B. If the study is terminated or suspended, prompt notification will be provided to all parties of the study.
C. Patient enrollment may be paused or terminated early if the DSMB determines that the potential benefits of continuing the trial are unlikely to outweigh the risks. For example, if the probability of achieving the target primary endpoints falls below a certain threshold, the trial will be stopped or paused for re-evaluation.

2. Safety Stopping Rules

   The study will be terminated by the DSMB and principal investigator at any point if the following stopping criterion is met:

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

3. Stopping Rules for Futility

   The study will be terminated by the DSMB and principal investigator if any of the following stopping criteria is met:

   a. Fewer than 36 events are observed in the placebo group at the time of the 300th patient interim statistical analysis
   b. Enrollment progress has been limited such that the study does not have a reasonable chance of randomizing 600 patients even after efforts to remediate recruitment

Protocol Violations

The study staff will rapidly and firmly address any protocol violations with the DSMB. If a protocol violation is detected or suspected, the investigator(s) will first be asked to provide a written explanation. After reviewing the available information, the study staff will categorize protocol violations as either major (eligibility or

primary/secondary endpoint determination compromised or indefinite) or minor (data still able to be used for endpoint determination), and will record and track them. Protocol violations with be reviewed by the DSMB. Major protocol deviations will be reported to the Partners Human Research Committee within five working days of the date the investigator becomes aware of the unapproved deviation. Minor deviations will be recorded in a Minor Deviation Log and this will be submitted to the Partners IRB with the continuing review.

Data Confidentiality

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

Compliance with Laws and Regulations

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

Statistical Methods

Sample Size Calculation

This study is a 600-patient single-center, randomized controlled trial utilizing an enriched population. Based on the contemporary (within the last 10 years) large pivotal trials of extended duration anticoagulation (2,3,7) and a large meta-analysis of low-dose aspirin (31) for prevention of recurrent events in patients with initial unprovoked VTE or clinically suspected to have a high risk of recurrence, we conservatively estimate an average 12-month VTE recurrence rate in patients not treated with extended-duration anticoagulation (placebo group) of 6% (Table 2).

VTE Recurrence Rates in the Control Arm in Major Extended Duration Secondary Prevention Trials including Provoked Events

Trial	% Provoked	Control	Rate	Follow-Up Period
EINSTEIN CHOICE	60%	Aspirin 81 mg QD	**3.6%**	<12 months (follow-up shorter than planned in

				subset of patients)
EINSTEIN VTE Continued Treatment	25%	Placebo	**7.1%**	12 months
AMPLIFY EXT	9%	Placebo	**8.8%**	12 months

In EINSTEIN CHOICE which randomized 60% of patients with provoked VTE, the control group received low-dose aspirin (which based on a meta-analysis in unprovoked VTE patients confers about a 33% relative risk reduction) had a recurrence rate of 3.6% (2,31). Accordingly, we would expect the 12-month VTE recurrence rate to be at least 33% higher in patients assigned to placebo in the proposed study and therefore approximately 5-6%. The recurrent VTE rate among placebo patients in the AMPLIFY-EXT trial of apixaban was quite a bit higher at 8.8% (7). By requiring that at least one additional persistent provoking VTE risk factor be present (persistent immobility, obesity, heart failure, chronic lung disease, chronic kidney disease, inflammatory disorder, or atherosclerotic cardiovascular disease), we will expect an "enriched" event rate in the population of the proposed study by at least 2-fold (all of these persistent provoking risk factors increase the risk of VTE by 2-4-fold; Table 3) (32). Many patients enrolled in the study will have multiple persistent provoking VTE risk factors (for example, heart failure, obesity, and atherosclerotic cardiovascular disease) and thereby have an even higher risk for recurrence. In an effort to be ultra-conservative, we kept the multiplier for this enriched study population to 2-fold (while in reality for many study patients it could be 4-fold or even higher). Accordingly, our estimate of a 12-month VTE recurrence rate of 6% is very conservative and still below the VTE recurrence rates reported in EINSTEIN VTE Continued Treatment and AMPLIFY EXT (neither of which included an enriched population).

Table 3. Relative risk of VTE by persistent provoking risk factor.

Persistent Provoking Risk Factor	**Relative Risk**
Persistent immobility	4-fold
Obesity (BMI ≥ 30)	2-3-fold
Heart failure	2-fold
Chronic lung disease	2-fold
Chronic kidney disease	2-fold
Inflammatory/autoimmune disorder	3-fold
Atherosclerotic cardiovascular disease	4-fold

Based on the data from EINSTEIN CHOICE, we conservatively estimate that low-intensity apixaban (2.5 mg twice daily) compared with placebo will provide a similar

reduction (75%) in recurrent VTE as low-intensity rivaroxaban (10 mg daily) compared with low-dose aspirin (2). The 75% relative risk reduction was reported specifically for recurrent VTE and in the provoked VTE patient population, comparing rivaroxaban 10 mg daily versus low-dose aspirin. This relative risk reduction specifically pertains to our primary study outcome and our exact patient population and comes from a robust randomized controlled trial analysis. If anything, the reduction in the proposed study should be even greater since we propose a placebo-control instead of active (aspirin) control and we will be following our patients for 12 months, instead of allowing shorter follow-up as was reported in EINSTEIN CHOICE. Accordingly, assuming an estimated incidence in the placebo group of 6% at 12 months and a decrease in the primary outcome of 75% with apixaban 2.5 mg twice daily as compared with placebo, we calculated that we would need to enroll 279 patients in each group for the study to have 80% power to show the superiority of low-intensity apixaban over placebo, at a two-sided alpha level of 0.05. To account for patients who may be lost to follow-up or withdraw from the study, we will recruit 300 in each arm and 600 total.

EINSTEIN-CHOICE enrolled patients after a required 6 to 12 months of anticoagulant therapy. Our study requires that patients complete at least 3 months of anticoagulant therapy in accordance with current and widely-accepted evidence-based clinical practice guidelines (Eur Heart J. 2020; 41: 543–603, Chest. 2016;149:315-352, and Circulation. 2011;123:1788–1830). Data from the PADIS-PE study showed that the rate of VTE recurrence is higher closer in temporal proximity to the initial event, such that the recurrence rate is higher at 3-6 months after diagnosis than it is at 6-12 months (Couturaud F, et al. Six Months vs Extended Oral Anticoagulation After a First Episode of Pulmonary Embolism. JAMA. 2015;314(1):31-40). Accordingly, the anticipated event rate should be higher in our study than EINSTEIN-CHOICE and the resultant observed relative risk reduction is likely to be higher.

Sensitivity analyses performed for the comparison between apixaban 2.5 mg twice daily and placebo (Tables 4 - 6) show that our sample size is most sensitive to change in the impact of the extended duration anticoagulation. However, we have been very conservative in our effect size calculation and baseline recurrent VTE rate (for example, we have not taken into account the increase in event rates of an enriched population with persistent immobility, obesity, heart failure, chronic lung disease, chronic kidney disease, inflammatory disorder, or atherosclerotic cardiovascular disease), as above.

Table 4. Sensitivity of sample size to changes in power.

Power	Total Sample Size
60%	350
70%	440
80%	**558**
90%	746
99%	1300

(assuming event rate of 6%; 75% risk reduction attributed to low-dose apixaban)

Table 5. Sensitivity of sample size to changes in VTE event rate.

VTE Event Rate	Total Sample Size
3%	1140
4%	848
6%	**558**
8%	412
10%	326

(assuming 80% power; 75% risk reduction attributed to low-dose apixaban)

Table 6. Sensitivity of sample size to changes in impact of extended duration anticoagulation with low-intensity apixaban (effect size).

Relative Risk Reduction	Total Sample Size
45%	1908
55%	1198
65%	800
75%	**558**
80%	472

(assuming 80% power; event rate of 6%)

The sample size calculation for the trial was calculated based upon 12-month rates of recurrent VTE from pivotal randomized controlled trials (2,3,7,33) and a large meta-analysis of low-dose aspirin vs. placebo (31). Accordingly, assuming an estimated incidence in the placebo group of 6% at 12 months and a decrease in the primary outcome of 75% with apixaban 2.5 mg twice daily as compared with placebo, we calculate that we will need to enroll 279 patients in each group for the study to have 80% power to show the superiority of low-intensity apixaban over placebo, at a two-sided alpha level of 0.05. If the trial utilized 6-month follow-up instead of 12-month, we would observe fewer recurrent VTE events and would require an increase in the sample size, which would require a longer enrollment period and would incur greater cost. As such, we have determined 12-month follow-up to facilitate the most efficient and cost-effective trial.

We have conducted a retrospective analysis using an ongoing BWH registry of 405 patients with pulmonary embolism/deep vein thrombosis. We identified 83 patients without active cancer and with at least one provoking risk factor. Among those who received 3-6 months of anticoagulation, 11.1% developed symptomatic recurrent venous thromboembolism in the ensuing year after stopping anticoagulation. If we utilize this baseline rate of recurrent VTE in our sample size calculation, we will require 212 patients in each study group, assuming a 75% relative risk reduction with apixaban 2.5 mg twice daily compared with placebo and 90% power to show the superiority of low-intensity apixaban over placebo, at a two-sided alpha level of 0.05.

We have also consulted with an independent biostatistician from the Harvard Catalyst Biostatistics Program (Shelley Hurwitz, PhD) to review our sample size requirement. She confirmed our sample size calculation using a recurrent VTE rate in the placebo

group of 6% from the best available literature and also using the rate of 11.1% from our observational cohort of patients that would be eligible for this study (see Table 7. below).

Table 7. Harvard Catalyst Biostatistics Program Consultant Sample Size Calculations (performed by Dr. Hurwitz using STATA).

Anticipated Event Rate = 6%	Anticipated Event Rate = 11.1%
. power twoproportions .06 .015, test(chi2) n(558) Estimated power for a two-sample proportions test Pearson's chi-squared test Ho: p2 = p1 versus Ha: p2 != p1 Study parameters: alpha = 0.0500 N per group = 279 p1 = 0.0600 p2 = 0.0150 Estimated power: power = 0.8005	. power twoproportions .111 .0278, test(chi2) n(424) Estimated power for a two-sample proportions test Pearson's chi-squared test Ho: p2 = p1 versus Ha: p2 != p1 Study parameters: alpha = 0.050 N per group = 212 p1 = 0.1110 p2 = 0.0278 Estimated power: power = 0.9236
Required N = 279 per group	Required N = 212 per group

It was also suggested that we consider using the lower limit of the 95% confidence interval around our estimate of 11.1%, which would be 8.2%. The statistician suggested that this would also provide a conservative estimate of the frequency of recurrent VTE for the sample size calculation (see Table 8 below).

Table. 8 Harvard Catalyst Biostatistics Program Consultant Sample Size Calculation Using Lower Limit of 95% Confidence Interval of Our Observational Cohort Estimate (performed by Dr. Hurwitz using STATA).

Anticipated Event Rate = 8.2%
. power twoproportions .082 .0205, test(chi2) n(558) Estimated power for a two-sample proportions test Pearson's chi-squared test Ho: p2 = p1 versus Ha: p2 != p1 Study parameters: alpha = 0.0500 N = 558 N per group = 279 p1 = 0.0820 p2 = 0.0205 Estimated power: power = 0.9111
Required N = 279 per group

Using this more conservative sample size calculation, we would aim to enroll 300 patients in each arm for a total trial population of 600.

Statistical Analysis Plan

For this study, we will calculate:

1) the 12-month frequency of major and clinically relevant non-major bleeding
2) the 12-month frequency of symptomatic recurrent VTE

The primary efficacy objective of this trial is to determine whether apixaban 2.5 mg twice daily is superior to placebo for the primary endpoint of symptomatic, recurrent VTE after 12 months of extended therapy. The analysis will include descriptive statistics of event rates and 95% CI, and risk difference and 95% CI. The Mantel-Haenszel statistic will be used to test this hypothesis formally. Superiority over placebo will be claimed for a dose if the Hochberg adjusted p-value is ≤ 0.05 and the RR is < 1. The analysis will be supported by Kaplan-Meier curves. The primary efficacy outcome analysis will be intention-to-treat. We will also perform an on-treatment analysis.

The primary safety objective will be to determine whether apixaban 2.5 mg twice daily results in a statistically significant difference in major bleeding at 12 months (during the treatment period) compared with placebo. Analysis of incidence of these endpoints will be based on the safety analysis set. The analysis will include descriptive statistics of event rates and 95% CI, and risk difference and 95% CI. Hypotheses will be tested using Mantel-Haenszel statistic. The analysis will be supported by Kaplan-Meier curves of the time to first adjudicated major bleeding event. All bleeding analyses will be conducted on the safety dataset.

Baseline characteristics will be summarized by group. Any imbalances between the treatment groups for any demographic or baseline characteristic will be assessed based on clinical relevance in reviewing the summaries. For any differences deemed clinically relevant to the efficacy comparisons, exploratory analyses that include the imbalanced factor as a categorized covariate will be performed.

To account for the effect of baseline low-dose aspirin use in the study population on the rate of recurrent VTE after an initial provoked event, we will perform a pre-specified stratified efficacy analysis of patients receiving low-dose apixaban or placebo with low-dose aspirin compared with patients just receiving low-dose apixaban or placebo. We will calculate stratum-specific risk ratios (RR). Comparing the “crude” (overall or unadjusted) and stratum-specific risk ratios will enable us to determine whether aspirin modifies the effect of low-dose apixaban and to what extent. If the stratum-specific risk ratio is similar to the crude risk ratio, then there is minimal impact of low-dose aspirin. However, if the stratum-specific risk ratio differs from the unadjusted estimate by 10% or more, then low-dose aspirin modifies the effect of low-dose apixaban. We will conduct a similar analysis for the safety outcome of major bleeding.

We will also pre-specify subgroup analyses focused on the safety and efficacy of major populations of interest, in particular, elderly patients (age ≥ 65 years), women, and those with persistent provoking factors of immobility, obesity, heart failure, chronic lung disease, chronic kidney disease, hemodialysis, chronic inflammatory/autoimmune disorder, and atherosclerotic cardiovascular disease.

Means, medians, and frequency distributions will be calculated for continuous variables. Number and percentages will be reported for binary and categorical variables. Differences between subgroups of interest will be examined using the chi-square or Fisher's exact test for binary and categorical variables and t-test or Wilcoxon Rank Sum for continuous variables (if the subgroups are of sufficient size for statistical comparison).

Safety outcome analyses will be performed among patients who received one or more doses of a study drug (Safety Population). All p-values reported will be two-sided. A p-value < 0.05 will be considered significant. All analyses will be performed using SAS software.

Interim Analysis

We will conduct a pre-specified interim analysis to assess the primary safety and efficacy outcomes after 50% of the planned enrollment population has completed 12-month follow-up. This planned interim analysis will inform the Data Safety Monitoring Board on whether the study should be stopped early due to efficacy, safety concerns, or futility or continue to enroll the full 600-patient cohort.

The DSMB will be responsible for:

5. Assessing study enrollment and likelihood of completion of 600 patients randomized
6. Assessing the study event rate in the placebo group and likelihood of obtaining enough events to satisfy the requirements for the primary efficacy analysis
7. Assessing the event rates in the treatment and placebo groups
8. Assessing the accumulated SAEs to determine whether the safety stopping criteria have been meet

Actions taken by the DSMB will include the following recommendations:

4. Study termination if stopping criteria for safety or futility have been met
5. Study modification if the DSMB deems that remediation measures have a reasonable probability of successful completion of the study
6. Continuation of the study as is

Investigator Responsibilities

Study Initiation

Before enrollment of the first subject at the study site, the following documents must be on file with the funding provider (BMS/Pfizer):

1. Current *curriculum vitae* of the principal investigator and all co-investigators
2. Current, dated Institutional Review Board (IRB) membership list
3. Written documentation of IRB protocol approval (protocol number/title and approval date) and Informed Consent Form (protocol number/title and approval date)
4. A copy of the IRB-approved Informed Consent Form (The Informed Consent Form must be reviewed by the study Principal Investigator prior to IRB submission.)

Study Completion

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

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

Informed Consent

The Informed Consent Form must be signed by the subject before enrollment into the study. A hardcopy of the Informed Consent Form must be provided to the subject. If applicable, informed consent should be obtained using Interpreter Services. If an interpreter is required to explain the study, the informed consent form will be reviewed with translation in the patient's native tongue, and a short consent document will presented to the patient for signature in the language in which the patient is literate.

Signed Informed Consent Forms must remain in each subject's study file and be available for verification by the Study Sponsor at all times. Documentation of the date informed consent was obtained and a notation that a signed copy of the Informed Consent Form was provided to the study subject should be recorded. The informed consent process must always be conducted in a non-coercive manner.

Disclosure of Data

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

Retention of Records

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

Feasibility

Brigham and Women's Hospital

Brigham and Women's Hospital (BWH) is a 793-bed acute tertiary care facility providing medical and surgical care for patients with general medical, cardiothoracic, orthopedic, oncologic, neurologic, obstetric, gynecologic, and gastrointestinal conditions. With the opening of the Heart and Vascular Center in 2014, BWH has solidified its position as a world leader in cardiovascular care and research, supporting an integrated care model in a single location. The Watkins Cardiovascular Clinic provides care to a large a growing outpatient population from the metropolitan Boston area, surrounding suburbs, and New England region. Dr. Piazza's cardiovascular medicine outpatient practice in the Watkin Cardiovascular Clinic, which is based in the Heart and Vascular Center, includes a large number of referrals for VTE and determination of the optimal duration of anticoagulation. The Watkin Cardiovascular Clinic also houses the outpatient practices of an additional seven Vascular Medicine faculty members and four Vascular Medicine fellows. These providers will serve as an important additional source of eligible study patients. The Vascular Medicine Section at BWH also staffs the Cardiovascular Medicine Consultation Service which evaluates and treats several hundred patients with VTE each year. The vast majority of these patients follow up in our outpatient clinics.

The BWH Thrombosis Research Group

The Thrombosis Research Group (TRG), directed by Dr. Goldhaber, Professor of Medicine, Harvard Medical School and Interim Chief of the Division of Cardiovascular Medicine and Section Head of Vascular Medicine, is based at BWH and Harvard Medical School. The Thrombosis Research Group has a decades-long commitment to VTE prevention and a dedication to improving the outcomes of all patients at risk for VTE. Dr. Piazza, Associate Professor of Medicine, Harvard Medical School, is the Associate Director of the Thrombosis Research Group and Assistant Section Head of Vascular Medicine at BWH as well as the Director of the Vascular Medicine Training Program. Dr. Piazza is the Chair of the ACC PVD Section Leadership Council and serves on the Scientific Session Planning Committees for the AHA and SVM. Dr. Piazza appreciates the national and global burden of recurrent VTE from his roles leading the Vascular Medicine educational initiatives for the ACC and AHA and from his perspective as a Co-Investigator on a number of VTE-related clinical trials (34–36) and observational studies (37). Dr. Piazza is currently leading a clinical trial evaluating the safety and efficacy of apixaban for primary prevention of VTE in multiple myeloma patients on immunomodulatory regimens known to increase the risk of thrombosis (38). Drs. Piazza and Goldhaber's dedication to and expertise in subject recruitment is clearly highlighted in their participation in the 7000-patient, multi-center, National Heart Lung and Blood Institute-sponsored Cardiovascular Inflammation Reduction Trial (CIRT) (39). Drs. Piazza and Goldhaber's efforts have made BWH the top enrolling site for CIRT. Dr. Goldhaber was the Principal Investigator of the ADOPT Trial of apixaban 2.5 mg twice daily for prevention of VTE in acutely ill medical patients during hospitalization and in the extended period after their discharge from the hospital (22).

The Thrombosis Research Group has an infrastructure of experienced leadership, with trained personnel in a multidisciplinary academic team (research pharmacists, cardiology fellows, research nurses, research coordinators, biostatisticians, administrators, and medical informatics specialists). Data storage and computing resources, as well as a network of regional, national, and international collaborating investigators, facilitate our execution of ongoing research projects and our planning of future research projects. The Thrombosis Research Group has studied all aspects of VTE, including epidemiology, diagnosis, treatment, and prevention. According to www.pubmed.gov, the group has authored more than 100 Original Reports since 2010.

Drs. Piazza and Goldhaber have extensive experience leading randomized controlled trials focused on prevention and treatment of thromboembolic disease. Examples of major Thrombosis Research Group-lead trials in this area include the 2500-patient multicenter Electronic Alert Trial (40), the 2500-patient multicenter Physician Alert Trial (41), the 2500-patient Discharge Alert Trial (42), and the 85-patient multicenter eTRIS trial (35).

Vascular Medicine at BWH is a regional Center of Excellence for VTE care. An EPIC Electronic Health Record query of the outpatient clinic volume of the five Vascular Medicine faculty providers and the 4 full-time Vascular Medicine fellows

demonstrated a provoked VTE volume of approximately 1500 new and follow-up patients.

Table 7. EPIC query estimate of new and follow-up provoked VTE patient volume in 2018.

Provider	Provoked VTE Volume (patients/year)
Piazza	300
Goldhaber	400
Campia	400
Gerhard-Herman	100
Sobieszczyk	100
4 Full-Time Vascular Medicine Fellows	200
TOTAL	**1500**

Since running this EPIC analysis, we have also added two additional full-time Vascular Medicine faculty, Dr. Arvind Pandey and Dr. Laurel Lee. Both specialize in the care of patients with VTE and see frequent referrals for determination of optimal duration of anticoagulation and long-term secondary prevention of recurrent events. Furthermore, we will recruit from our inpatient cardiovascular medicine consult service and cardiovascular medicine ward service which receive a high volume of provoked VTE referrals. Accordingly, we anticipate having the ability to draw on these additional sources of provoked VTE patients for at least another 100 provoked VTE patients per year.

Even without the added VTE patient volumes of Dr. Pandey and Dr. Lee, we calculate 1600 new and follow-up provoked VTE patients who present for outpatient visits at BWH per year and we conservatively estimate that 25% will fail to meet all the inclusion criteria or will meet at least one exclusion criterion. Therefore, an estimated 1200 patients will be eligible for enrollment in the trial in the first year.

We will also have our research nurse run reports from EPIC to identify other patients in our non-Vascular Medicine cardiology practices that will be eligible but may not be scheduled to see us. We will also aggressively communicate the launch of the study to our non-Vascular Medicine cardiology colleagues. Furthermore, we will recruit from our inpatient cardiovascular medicine consult service and cardiovascular medicine ward service which receive a high volume of provoked VTE. Accordingly, we anticipate having the ability to draw on these additional sources of provoked VTE patients for at least another 100 provoked VTE patients per year.

As the trial will enroll over 20 months, we estimate that we will be able to draw from 1200 patients in the first year and 800 patients in the 8 months that comprise the second year of enrollment. This will yield 2000 patients from which to enroll 600 subjects for the trial.

Based on our prior clinical trial experience at the BWH Thrombosis Research Group, we conservatively estimate that 50% of the patients who are screened and found to be eligible for the trial will consent to participate. Therefore, an estimated 1000 eligible patients would be willing to provide informed consent to participate in the HI-PRO trial. Accordingly, enrollment of the planned 600-patient study population should be feasible and efficiently accomplished at BWH.

Additionally, the BWH Thrombosis Research Group has the infrastructure to operationalize this enrollment plan. The Thrombosis Research Group has two full-time dedicated research assistants, a research intern, a research nurse, three faculty physicians, a full-time advanced Vascular Medicine fellow, and a number of general Cardiovascular Medicine fellows who participate in our research studies. We have coordinated our ongoing research projects to accommodate the percent efforts required by our research staff and physician team members to maximize our success at enrollment for this trial. Accordingly, we have adequate staffing and physician support to add to the research personnel for this trial, identify eligible patients, and maintain our enrollment on track. We also have an adequate reserve in staffing and flexibility to augment our effort should enrollment require it.

TRG led the patient recruitment effort for the Cardiovascular Inflammation Reduction Trial (CIRT), a randomized, double-blind trial of low-dose methotrexate in 4786 patients with previous myocardial infarction or multivessel coronary disease who additionally had either type 2 diabetes or the metabolic syndrome (39). CIRT was a landmark study which involved a novel application of a challenging anti-inflammatory drug, serial laboratory evaluations, and a high number of follow-up phone calls and in-person office visits, which required patients to travel from as far as California to Boston. Despite these challenges, TRG made BWH the overall top enrolling site in the CIRT trial.

We anticipate rapid enrollment in the HI-PRO trial. First, all the patients in the study will be familiar with anticoagulation and many will have received apixaban. Second, there are no study-mandated laboratory tests or office visits. Third, many patients with provoked VTE are reluctant to discontinue anticoagulation after the acute treatment phase because of the fear of recurrent events. We anticipate that many patients with provoked VTE will be highly interested in participating in a clinical trial of extended secondary prevention thromboprophylaxis, especially with the favorable safety and efficacy profile of low-intensity apixaban. It is quite possible that greater than 50% of eligible patients will want to participate and provide informed consent. In such a scenario, we would expect to enroll more quickly.

Potential Risks and Benefits

Potential benefits to the subject

The potential benefit of treatment with low-dose apixaban in patients with provoked VTE is secondary prevention of VTE, including fatal PE.

Potential Benefits to Society

The major potential benefit to society of the proposed trial of apixaban for secondary prevention of VTE in patients with provoked VTE is that if successful, the study will provide the foundation for a new indication for extended-duration anticoagulation for VTE prevention. The data acquired from this randomized, placebo-controlled trial will establish the safety and efficacy of low-dose apixaban versus placebo for extended prevention of recurrence after provoked VTE in patients with at least one persistent provoking factor. The study will draw widespread interest for apixaban in the extended prevention of recurrence after provoked VTE and will most certainly be of interest to high-impact peer-reviewed journals and to a broad spectrum of clinicians who will be better able to care for their VTE patients using these data.

Potential Risks to the Subject

The foreseeable risk of apixaban for secondary prevention of VTE in patients with provoked VTE is major bleeding.

Risks of Research Procedures Performed on Subjects

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

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

Anticipated Risks of Drug

Adverse reactions occurring in ≥1% of patients treated for DVT and PE in the AMPLIFY study (source table 6 USPI)

- Epistaxis
- Contusion
- Hematuria
- Menorrhagia
- Hematoma
- Hemoptysis
- Rectal hemorrhage
- Gingival bleeding

Less common adverse reactions occurring in Eliquis-treated patients in AMPLIFY or AMPLIFY-EXT studies occurring with a frequency of ≥0.1% to <1%:

- Blood and lymphatic system disorders: hemorrhagic anemia
- Gastrointestinal disorders: hematochezia, hemorrhoidal hemorrhage, gastrointestinal hemorrhage, hematemesis, melena, anal hemorrhage
- Injury, poisoning, and procedural complications: wound hemorrhage, postprocedural hemorrhage, traumatic hematoma, periorbital hematoma
- Musculoskeletal and connective tissue disorders: muscle hemorrhage
- Reproductive system and breast disorders: vaginal hemorrhage, metrorrhagia, menometrorrhagia, genital hemorrhage
- Vascular disorders: hemorrhage
- Skin and subcutaneous tissue disorders: ecchymosis, skin hemorrhage, petechiae
- Eye disorders: conjunctival hemorrhage, retinal hemorrhage, eye hemorrhage
- Investigations: blood urine present, occult blood positive, occult blood, red blood cells urine positive
- General disorders and administration-site conditions: injection-site hematoma, vessel puncture-site hematoma

Additional information about the risks of apixaban can be found in the Apixaban Med Guide (see Appendix).

Protection of Subjects against the Risks of Research Procedures

Before Study Enrollment

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

During Follow-Up

Changes in health status during the 12-month follow-up period will be evaluated by the patient's primary physician, and other routine providers. All subjects enrolled will also have ongoing medical care with a dedicated Vascular Medicine provider. As apixaban is an FDA-approved drug commonly used for thromboprophylaxis and does not require routine follow-up clinical or laboratory monitoring for toxicity, the study will not mandate any follow-up visits or procedures other than those required for the patient's routine care.

Protection against Loss of Confidentiality

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

Use of Information and Publication

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

Ethical Considerations

In this prospective, single-center randomized placebo-controlled study, we will be evaluating the impact of apixaban for secondary prevention of VTE in patients with provoked VTE with at least one persistent provoking factor. The benefits of apixaban for secondary prevention of VTE in patients with provoked VTE have not been assessed. The risk of bleeding in provoked VTE patients receiving apixaban has not been determined.

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

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Table 8. Study Calendar

Procedure	Screening	12-Month Follow-Up
Informed Consent	X	
Inclusion/Exclusion	X	
Demographics	X	
Medical History	X	
Prior/Concomitant Medications	X	
Urine Pregnancy (if clinically indicated)	X	
Cardio-vascular History	X	
Thrombosis Evaluation		X
Bleeding Evaluation		X
Pill Diary Collection		X

Case Report Form

Screening	
Inclusion criteria (all must be checked)	[ ] Age ≥ 18 years [ ] Objectively-confirmed DVT and/or PE [ ] Treated for at least 3 months with standard therapeutic anticoagulant therapy [ ] Has not suffered symptomatic recurrence during prior anticoagulant therapy [ ] Outpatient follow-up at BWH [ ] Willing to provide written informed consent AND have at least one of the following persistent provoking VTE risk factors: [ ] Persistent immobility (defined as paralysis, other inability to ambulate freely, bed-bound, wheelchair-bound) [ ] Obesity (defined as BMI ≥ 30 kg/m2) [ ] Heart failure (systolic, diastolic, or combined) [ ] Chronic lung disease (COPD, asthma, interstitial lung disease) [ ] Chronic kidney disease (eGFR <60 mL/min/1.72m2) [ ] Chronic inflammatory/autoimmune disorder (inflammatory arthritis, vasculitis, inflammatory bowel disease, chronic infection) [ ] Atherosclerotic cardiovascular disease (coronary, cerebrovascular, or peripheral artery disease) (up to 35% in each study group may have atherosclerotic cardiovascular disease as a qualifying persistent risk factor)
Exclusion criteria (NONE must be checked)	[ ] Women who are pregnant or breastfeeding [ ] Women of child-bearing potential who are unwilling or unable to use an acceptable method of birth control (such as oral contraceptives, other hormonal contraceptives [vaginal products, skin patches, or implanted or injectable products], or mechanical products such as an intrauterine device or barrier methods [diaphragm, condoms, spermicides]) to avoid pregnancy for the entire study [ ] Active cancer within the past 5 years [ ] Contraindication to antithrombotic or antiplatelet therapy [ ] Requirement for ongoing anticoagulant therapy (including atrial fibrillation with a CHADSVASC >1, diagnosed antiphospholipid antibody syndrome/deficiency of protein C,

	S, or antithrombin), dual antiplatelet therapy, P2Y12 inhibition, or aspirin at a dose of >81 mg daily [ ] Hemoglobin level < 9 mg/dL, a platelet count < 100,000/mm3, a serum creatinine level > 2.5 mg/dL, an ALT or AST level > 2 times the upper limit of the normal range, or a total bilirubin level > 1.5 times the upper limit of the normal range [ ] History of a platelet disorder such as Von Willebrand Disease [ ] History of bleeding diathesis or have had recent active bleeding [ ] Active hepatobiliary disease [ ] More than 6 months that have elapsed without taking an anticoagulant or low-dose aspirin [ ] Known severe thrombophilia (any increased titer antiphospholipid antibody or positive lupus anticoagulant/DRVVT or deficiency of antithrombin, protein C, or protein S) [ ] Life expectancy < 12 months or hospice care [ ] Prisoners or subjects who are involuntarily incarcerated [ ] Subjects who are compulsorily detained for treatment of either a psychiatric or physical (e.g., infectious disease) illness [ ] Receiving concurrent non-FDA-approved or investigational agents or has received an investigational agent within the past 30 days prior to the first dose of study treatment (with the exception of approved medications being used for an approved indication, e.g., investigating a new dosing regimen for an approved indication). [ ] Any condition, which in the opinion of the investigator, would put the subject at an unacceptable risk from participating in the study [ ] Any other medical, social, logistical, or psychological reason, which in the opinion of the investigator, would preclude compliance with, or successful completion of, the study protocol
STOP HERE AND DO NOT ENROLL PATIENT IF ANY OF THE INCLUSION CRITERIA ARE ABSENT OR ANY EXCLUSION CRITERIA ARE PRESENT	
Eligible	[ ] Yes [ ] No
Written informed consent signed	[ ] Yes [ ] No

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

Venous Thromboembolism Characteristics*** *****Patient may have both PE and DVT; if so complete both fields**	
Deep Vein Thrombosis	DVT confirmed by imaging (ultrasound, CT, MRI, or venogram) [ ] Yes [ ] No
	Date of imaging diagnosis ____/____/_____ MM DD YYYY
	Site of DVT [ ] Upper extremity [ ] Pelvic vein [ ] Leg [ ] Proximal with calf [ ] Proximal without calf [ ] Calf only

	[ ] Other (describe):_____
Pulmonary Embolism	PE confirmed by: [ ] Ventilation perfusion scan [ ] Chest CT [ ] Contrast pulmonary angiogram Hypotension, shock, cardiac arrest or respiratory failure as presenting sign of PE: [ ] Yes [ ] No RV dysfunction [ ] Yes [ ] No Diagnosed by: [ ] CT [ ] Echocardiogram Positive cardiac biomarker (troponin or BNP) [ ] yes [ ] no
	Date of imaging confirmed diagnosis ____/____/_____ MM DD YYYY
Both PE and DVT present	[ ] Yes [ ] No
Symptomatic DVT or PE	[ ] Yes [ ] No
Advanced therapy for VTE	[ ] Inferior vena cava filter [ ] Thrombolytic therapy for PE [ ] Catheter thrombectomy for DVT [ ] Catheter direct therapy for PE [ ] Surgical thrombectomy for DVT [ ] Surgical embolectomy for PE
Outpatient VTE treatment history	[ ] LMWH monotherapy [ ] Fondaparinux [ ] Direct oral anticoagulant [ ] Warfarin Duration of anticoagulation: ___ months (enter number out to the tenth place and round-up; for example 3.48 months would be 3.5 months)

Persistent Provoking VTE Risk Factors	
Persistent provoking VTE risk factors (**patient must have at least one but can have multiple; record all that apply**)	[ ] Persistent immobility (defined as paralysis, other inability to ambulate freely, bed-bound, wheelchair-bound) [ ] Obesity (defined as BMI ≥ 30 kg/m2) [ ] Heart failure (systolic, diastolic, or combined) [ ] Chronic lung disease (COPD, asthma, interstitial lung disease) [ ] Chronic kidney disease (eGRF <60 mL/min/1.72m^2) [ ] Chronic inflammatory/autoimmune disorder (inflammatory arthritis, vasculitis, inflammatory bowel disease, chronic infection) [ ] Atherosclerotic cardiovascular disease (coronary, cerebrovascular, or peripheral artery disease) (up to 35% in each study group may have atherosclerotic cardiovascular disease as a qualifying persistent risk factor)

VTE Risk Factors and Comorbid Conditions	
Cardiovascular disease	[ ] Cardiomyopathy/diminished left ventricular systolic function If yes, EF (%) ____ [ ] Heart failure with reduced EF [ ] Heart failure with preserved EF (EF >50%) [ ] Coronary artery disease If yes, Prior CABG [ ] Prior coronary stent(s) [ ] Prior MI [ ] History of unstable angina [ ] Stable angina [ ] [ ] Valvular heart disease [ ] Atrial fibrillation or atrial flutter [ ] Pulmonary hypertension
Hypertension	[ ] Yes [ ] No
Peripheral artery disease	[ ] Yes [ ] No

Carotid occlusive disease	[ ] Yes [ ] No
Prior cerebrovascular accident (strokes or TIAs)	[ ] Yes [ ] No
Family history of VTE	[ ] Yes [ ] No
Prior personal history of VTE (other than the event that made the patient eligible for this trial)	[ ] Yes [ ] No
Hypercholesterolemia	[ ] Yes [ ] No
Chronic liver disease (as noted in chart)	[ ] Yes [ ] No If yes, cirrhosis [ ] yes [ ] no
Cigarette smoking (check only 1)	[ ] Current smoker [ ] Former smoker [ ] Never smoker
Major surgery within 3 months of VTE diagnosis	[ ] Yes [ ] No If yes, date _____/_____/_____ MM DD YYYY
Prior hospitalization within 30 days of VTE diagnosis	[ ] Yes [ ] No
Chronic lung disease (COPD, asthma, pulmonary fibrosis, interstitial lung disease)	[ ] Yes [ ] No
Diabetes mellitus	[ ] Yes

(Type I or II)	[ ] No
Inflammatory arthritis (rheumatoid arthritis, psoriatic arthritis)	[ ] Yes [ ] No
Inflammatory bowel disease (Crohn's Disease, Ulcerative Colitis)	[ ] Yes [ ] No
Inherited thrombophilia	[ ] Yes [ ] No If yes, indicate: [ ] Factor V Leiden (heterozygous or homozygous) [ ] Prothrombin gene mutation (heterozygous or homozygous)
Active use of oral contraceptive or hormone replacement at time of VTE diagnosis	[ ] Yes [ ] No
Infectious illness requiring antibiotics or antiviral therapy within 3 months of VTE diagnosis	[ ] Yes [ ] No
Serum creatinine >2.5 mg/dL	[ ] Yes [ ] No If yes, is patient on dialysis? [ ] Yes [ ] No **If yes, patient should not be enrolled.**
Concomitant medications	[ ] aspirin If yes, dose = _ _ _ mg/daily **If >81 mg/daily, patient should not be enrolled.** [ ] daily NSAID use

Study Treatment Characteristics	
Randomization	[ ] Oral Apixaban 2.5 mg twice daily [ ] Oral placebo twice daily
Date study drug started	____/____/_____ MM DD YYYY
Date study drug stopped	____/____/_____ MM DD YYYY Completed full 12 months of study drug? [ ] Yes [ ] No If did not stay on drug for 12 months, reason why not? [ ] Fulfilled criteria for a primary study outcome (recurrent VTE or major/clinically relevant non-major bleed) [ ] Patient expired [ ] Adverse drug event or side-effect [ ] Change in clinical status (such as change in goals of care, comfort measures, hospice care) [ ] Patient preference/withdrawal of consent
Medication adherence (via pill count)	Total doses taken/total doses prescribed = (__ / 720) x 100 = _ _ _ %

12-Month Study Outcomes	
Deep vein thrombosis	[ ] Yes [ ] No If yes, date ____/____/_____ MM DD YYYY Confirmed by diagnostic imaging: [ ] Yes [ ] No If yes, by? [ ] Ultrasound [ ] CT [ ] MRI [ ] Venography

	Location: [ ] Upper extremity If checked: [ ] Bilateral or SVC [ ] Lower extremity If checked: [ ] Bilateral or IVC [ ] Proximal (popliteal or higher) [ ] Calf Hospitalized? [ ] Yes [ ] No Treatment: [ ] Anticoagulation [ ] Pharmacomechanical (catheter-based) therapy [ ] Surgery [ ] IVC filter
Superficial vein thrombosis	[ ] Yes [ ] No If yes, date ____/____/_____ MM DD YYYY
Other venous thrombosis (mesenteric, cerebral sinus, gonadal, etc.)	[ ] Yes [ ] No If yes, date ____/____/_____ MM DD YYYY
Pulmonary embolism	[ ] Yes [ ] No If yes, date ____/____/_____ MM DD YYYY Confirmed by diagnostic imaging: [ ] Yes [ ] No If yes, by? [ ] CT [ ] MRI

	[ ] Pulmonary angiography [ ] V/Q scan Location: [ ] Unilateral [ ] Bilateral RV dysfunction on echocardiogram or CT? [ ] Yes [ ] No Positive cardiac biomarker? [ ] Yes [ ] No Associated with hemodynamic or respiratory instability (respiratory failure, shock, hypotension, cardiac arrest)? [ ] Yes [ ] No Fatal? [ ] Yes [ ] No Hospitalized? [ ] Yes [ ] No Treatment: [ ] Anticoagulation [ ] Systemic fibrinolysis [ ] Pharmacomechanical (catheter-based) therapy [ ] Surgical embolectomy [ ] IVC filter
Death	[ ] Yes [ ] No If yes, date ____/____/_____ MM DD YYYY Cause of death: [ ] PE [ ] Myocardial infarction [ ] Stroke

	[ ] Other cardiovascular [ ] Cancer-related [ ] Non-cardiovascular, non-cancer [ ] Unknown [ ] CV Death: includes death due to PE, MI, stroke, other cardiovascular cause, or unknown
Major or clinically relevant non-major bleed	[ ] Yes [ ] No If yes, date ____/____/_____ MM DD YYYY
Major bleed	[ ] Yes [ ] No If yes, date ____/____/_____ MM DD YYYY Location: [ ] Intracranial [ ] Surgical/operative site [ ] Gastrointestinal [ ] Genitourinary [ ] Retroperitoneal [ ] Pericardial [ ] Pulmonary [ ] Other thoracic [ ] Musculoskeletal [ ] Nasopharyngeal [ ] Hematocrit or hemoglobin decrease without clear source [ ] Other Fatal? [ ] Yes [ ] No Hospitalized? [ ] Yes [ ] No Associated with hemodynamically instability? [ ] Yes [ ] No

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

	[ ] Cutaneous (rash, etc.) [ ] Liver function abnormalities [ ] Other: _____ Hospitalized? [ ] Yes [ ] No Study drug discontinuation? [ ] Permanent stop [ ] Temporary stop [ ] Not discontinued
Myocardial infarction (defined as the presence of at least 2 of the 3 following conditions: • The detection of a rise and/or fall of cardiac biomarkers, with at least one of the values being elevated [preferably cardiac troponin (cTn) with at least one value above the 99th percentile upper reference limit] and with at least one of the following: (1) symptoms of myocardial ischemia; (2) new (or presumably new) significant ST-segment/T-wave changes or left bundle branch block; (3) development of pathological	[ ] Yes [ ] No If yes, date ____/____/_____ MM DD YYYY Type: [ ] ST elevation [ ] Non-ST elevation Fatal? [ ] Yes [ ] No Treatment: [ ] Systemic fibrinolysis [ ] Percutaneous coronary intervention (angioplasty, stenting, etc.) [ ] CABG [ ] Medical management

Q waves on ECG; (4) new loss of viable myocardium or regional wall motion abnormality by imaging; (5) identification of intracoronary thrombus by angiography or autopsy)	
Non-MI coronary revascularization	[ ] Yes [ ] No If yes, date ____/____/_____ MM DD YYYY Recascularization: [ ] Percutaneous coronary intervention (angioplasty, stenting, etc.) [ ] CABG
Stroke/TIA (defined as a new, focal neurologic deficit of sudden onset, lasting at least 24 hours, not due to a readily identifiable nonvascular cause (i.e. brain tumor, trauma), as confirmed by a neurologist and neuroimaging.)	[ ] Yes [ ] No If yes, date ____/____/_____ MM DD YYYY Confirmation (both must be present): [ ] By neurologist [ ] By neuroimaging TIA? [ ] Yes [ ] No Stroke? [ ] Yes [ ] No If yes, type of stroke: [ ] Ischemic

	[ ] Hemorrhagic [ ] Other Fatal stroke? [ ] Yes [ ] No Treatment: [ ] Systemic fibrinolysis [ ] Percutaneous thrombectomy [ ] Surgery [ ] Other
Major adverse limb event	[ ] Yes [ ] No Acute limb ischemia [ ] Yes [ ] No (Acute limb ischemia defined as limb-threatening ischemia which is confirmed by limb hemodynamics or imaging and leads to an acute vascular intervention within 30 days of onset of symptoms or absent pedal pulses) Critical limb ischemia (CLI) [ ] Yes [ ] No (CLI is defined as continuing ischemic limb, foot or digit pain leading to hospitalization and intervention and not meeting the definition of ALI, or Fontaine 3 or 4 at baseline with peripheral intervention during the trial) Peripheral intervention [ ] Yes [ ] No (Peripheral vascular intervention is defined as peripheral vascular intervention not meeting the definition for ALI or CLI) Amputation [ ] Yes [ ] No
Admission for heart failure (HFPEF or HFREF)	[ ] Yes [ ] No

Appendix

1. Apixaban Package Insert (Version June 2018)
   https://packageinserts.bms.com/pi/pi_eliquis.pdf

2. Eliquis Medication Guide
   https://packageinserts.bms.com/medguide/medguide_eliquis.pdf

3. Informed Consent Form

Table. Amendments between original and final versions of the protocol				
Section	**Location in Protocol**	**Change from original to final version**	**Rationale for Change**	**IRB Approval Date**
Study Inclusion criteria	Page 20	Added the following: “(Note: including post COVID-19 infection and post COVID-19 vaccination)”	We have clarified that COVID-19 and/or vaccination for COVID-19 may be considered as provoking factors for VTE.	December 20, 2021

Statistical Analysis Plan (SAP)

Randomized Controlled Trial of Extended-Duration Low-Dose Apixaban to Prevent Recurrence in High-Risk Patients with Provoked Venous Thromboembolism (HI-PRO Trial)

Date: 03/24/2025

(First and final version)

Study PI: Gregory Piazza, MD, MS

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1. Study Overview

Patients who have experienced at least one persistent provoking factor following an initial provoked venous thromboembolism (VTE) are suspected to be at an increased risk of recurrence. However, it is still unclear whether extended-duration anticoagulation is beneficial for such patients. The HI-PRO randomized controlled trial conducted at Brigham and Women's Hospital (BWH) has been designed to investigate the safety and efficacy of extended-duration low-dose apixaban 2.5 mg twice daily for preventing recurrence in high-risk patients after initial provoked VTE.

2. Specific Aims

In this section, we provide an overview of the trial's specific aims. Based on the emerging evidence that provoked VTE patients may require extended-duration anticoagulation for secondary prevention, the apixaban 2.5 mg twice daily dose could be a critical addition to our armamentarium in those at high risk for recurrence at the transition of care from the acute to the chronic treatment phase. However, this hypothesis needs to be tested in a randomized clinical trial. We propose a single-center (BWH), randomized placebo-controlled trial conducted at to evaluate the impact of low-dose apixaban (2.5 mg twice daily) in a study population exclusively comprised of provoked VTE patients with at least one persistent provoking factor. We have the following study aims:

Specific Aim #1: To compare the 12-month recurrent symptomatic VTE in patients with provoked VTE and at least one enduring factor who are randomized to either apixaban (2.5 mg orally twice daily) as monotherapy or placebo after completing at least 3 months of therapeutic anticoagulation and who have a low risk of bleeding.

Specific Aim #2: To compare the 12-month ISTH major bleeding in patients with provoked VTE and at least one enduring factor who are randomized to either apixaban (2.5 mg orally twice daily) as monotherapy or placebo after completing at least 3 months of therapeutic anticoagulation and who have a low risk of bleeding.

3. Definitions

3.1 Target Population

The study is planned to enroll a total of 600 subjects at Brigham and Women's Hospital (BWH). The study design is a single center randomized controlled trial that will take place at BWH. The allocation ratio for the study is 1:1, meaning that half of the participants will be assigned to apixaban 2.5 mg twice daily, and the other half will be assigned to placebo for a duration of one year.

To ensure that the study enrolls the most appropriate participants, a set of detailed inclusion and exclusion criteria have been developed. These criteria are intended to identify individuals who are at high risk of recurrent VTE and are likely to benefit from extended-duration anticoagulation therapy without incurring a prohibitive risk of bleeding.

The allocation of treatments will be conducted by randomization procedures, ensuring that each participant has an equal chance of being assigned to the apixaban or placebo group. The study will be closely monitored for safety, and participants will be closely followed up throughout the study period to assess the efficacy and safety of the treatment. Below, we provide the detailed inclusion and exclusion criteria, which has been described.

3.2 Study Inclusion Criteria

The study is looking for men and women aged 18 years or older who have been objectively confirmed with provoked DVT and/or PE, and have been treated with standard therapeutic anticoagulant therapy for at least three months without symptomatic recurrence. Participants must have at least one enduring VTE risk factor, such as obesity, heart failure, chronic lung disease, chronic kidney disease, pregnancy, or use of hormonal therapies such as oral contraceptives, or chronic inflammatory/autoimmune disorder. They must be willing to provide written informed consent and have outpatient follow-up at BWH. Participants who have atherosclerotic cardiovascular disease may also be eligible for the study, with up to 35% in each study group having this condition as a qualifying persistent risk factor. The study also includes individuals who have experienced VTE post-COVID-19 infection and post-COVID-19 vaccination.

Eligible patients will be allowed to have multiple risk factors, and there will not be a limit as to how many of the above risk factors a subject may have. In addition, we will place no limit on the number of patients included with multiple risk factors. A study population with multiple risk factors is highly representative of the provoked VTE population and will provide the greatest generalizability of the study results to real-world clinical practice. Including patients with single and multiple persistent provoking risk factors will also facilitate enrollment. As noted, there is clinical and research equipoise regarding whether patients with a single or multiple persistent provoking VTE risk factors should receive extended duration thromboprophylaxis for secondary prevention.

3.3 Study Exclusion Criteria

The study excludes pregnant or breastfeeding women, women who are of child-bearing potential and unwilling or unable to use an acceptable method of birth control, and individuals with active cancer within the past 5 years or a contraindication to antithrombotic or antiplatelet therapy. The study also excludes those who require ongoing anticoagulant therapy, dual antiplatelet therapy, P2Y12 inhibition, or aspirin at a dose of > 81 mg daily. Other exclusion criteria include various medical conditions, such as severe thrombophilia, hemoglobin level < 9 mg/dL, platelet count < 100,000/mm3, serum creatinine level > 2.5 mg/dL, ALT or AST level > 2 times the upper limit of the normal range, or a total bilirubin level > 1.5 times the upper limit of the normal range. Additionally, individuals with a history of a platelet disorder, bleeding diathesis, or recent active bleeding, active severe hepatobiliary disease, or more than 6 months that have elapsed without taking an anticoagulant or low-dose aspirin are excluded. The study also excludes individuals with a known severe thrombophilia, life expectancy < 12 months or hospice care, prisoners, and individuals who are compulsorily detained for treatment of either a psychiatric or physical illness. Finally, individuals who are receiving concurrent non-FDA-approved or investigational agents or have received an investigational agent within the past 30 days prior to the first dose of study treatment are also excluded, as well as those who have a history of a severe hypersensitivity reaction to apixaban or require a medication that is contraindicated to be co-administered with apixaban.

4. Outcomes

Both safety and efficacy will be assessed in this trial. Outcome definitions are as follows:

4.1 Efficacy Outcomes

4.1.1 Primary Efficacy Outcomes

The primary efficacy outcome will be the time to first symptomatic, recurrent VTE, defined as the composite of fatal or nonfatal deep vein thrombosis and/or pulmonary embolism within 12 months from randomization. The primary efficacy outcome will be independently adjudicated by a Clinical Events Committee (CEC) blinded to assigned treatments. DVT is diagnosed as a newly non-compressible venous segment or segments on ultrasonography or a filling defect on computed tomographic (CT) venography, magnetic resonance (MR) venography, or contrast venography. PE is diagnosed based on new mismatched perfusion defect(s) on ventilation-perfusion scan, the presence of a new pulmonary artery filling defect on contrast-enhanced chest CT, a new finding of intraluminal filling defect on invasive pulmonary angiography, or evidence of PE at autopsy. Death due to causes other than DVT or PE will be considered a competing risk for this outcome.

4.1.2 Secondary Efficacy Outcomes

Secondary efficacy outcomes include the time to first occurrence of a composite of death due to cardiovascular causes, nonfatal myocardial infarction (MI), stroke or systemic embolism, chronic limb-threatening ischemia (CLTI), or coronary or peripheral ischemia requiring revascularization (major adverse cardiovascular events, including major adverse limb events) within 12 months, and the individual components of this outcome. An additional composite outcome will include all the components of the above composite of major adverse cardiovascular events as well as symptomatic VTE. A composite thrombotic outcome will be analyzed and will include symptomatic VTE, fatal or nonfatal myocardial infarction (MI), stroke/TIA or systemic embolism. The secondary efficacy outcomes will be independently adjudicated by a CEC blinded to assigned treatments. Non-cardiovascular death will be considered a competing risk.

4.2 Safety Outcomes

4.2.1 Principal Safety Outcome

The principal safety outcome will be the time to first major bleeding within 12 months from randomization. Major bleeding is defined according to the International Society on Thrombosis and Haemostasis (ISTH) as overt bleeding that is associated with a decrease in the hemoglobin level ≥ 2 g/dL, leads to transfusion ≥ 2 units of packed red blood cells, occurs in a critical site, or contributes to death 1. The principal safety outcome will be independently adjudicated by a blinded CEC review. Non-hemorrhagic death will be considered a competing risk for this outcome.

4.2.2 Secondary Safety Outcome

The time to first clinically relevant non-major bleeding within 12 months will be evaluated and is defined per the ISTH as overt bleeding that does not meet the criteria for major bleeding but that is associated with the need for medical intervention, unscheduled contact with a physician, interruption or discontinuation of the study drug, or discomfort or impairment of activities of daily living 2. Like the primary safety outcome, this outcome will be assessed by the CEC, blinded to assigned treatments. All-cause death will be considered a competing risk for this outcome. We will also assess a composite outcome of major bleeding and clinically-relevant nonmajor bleeding. Non-hemorrhagic death will be considered a competing risk for these outcomes.

For all the outcomes, the last time contact date will be used for determining censoring.

5. Details of Randomization and Blinding

Subjects who are 18 years of age or older with provoked DVT and/or PE, have completed at least 3 months of therapeutic anticoagulation, have a low risk of bleeding, and have at least one enduring risk factor will be randomly assigned by computer in a 1:1 ratio to receive apixaban 2.5 mg orally twice daily or oral placebo for extended secondary prevention of VTE for a duration of 12 months.

This study will be conducted in a blinded fashion. To maintain blinding of study treatment, the active study drug and placebo will be matched for color, size and box. Subjects, investigators, members of any of the administrative and adjudicating committees, and the Sponsor's staff conducting the study, will not have access to individual subject treatment assignments.

An independent Safety Monitor has been selected for this study. The Safety Monitor is an expert in VTE and is distinct from the DMSB and Study Staff and will be available throughout the study to assess patient safety issues that may arise, objectively. The Safety Monitor will have the ability to break the blind of a study patient as the need arises (immediately, in real-time). If the Safety Monitor is unavailable because of travel, one of the Physician Study Investigators will serve as back-up.

6. Statistical Plan

6.1 Power Calculation

Our power calculation accommodates efficacy outcomes. This is an implementation of the power calculation method described in Section 14.12 (page 807) of Rosner (2006). The equitation of power calculation based on 1:1 randomization is expressed as below:

$$Power = \Phi\left(\frac{\sqrt{m}|\lambda - 1|}{\lambda + 1} - Z_{1-\frac{\alpha}{2}}\right),$$

where is the expected total number of events over both groups, n is the total sample size, p_E and p_c are the probabilities of event in treatment group and placebo group over the maximum time of the study, λ is postulated hazard ratios for the treatment over placebo.

We postulated the following anticipated parameters for the power calculation: a) by the end of follow up, the event rate of the placebo arm is 6% and there is 75% reduction rate with active treatment (low-intensity apixaban), i.e., the event rate of the placebo arm is 1.5%; b) the postulated hazard ratios for the treatment over placebo by 1-year follow-up ranges from 0.2-0.24. These anticipated parameters are based on previous studies [3,4]. In Figure 1, we provide the power analysis given certain sample size. The power under the significance of 0.05 is given for the total sample with 1:1 randomization ranging from 500-700. To achieve sufficient sample sizes needed for reach the power of 80%, we conservatively choose 600 patients to ensure the enough power.

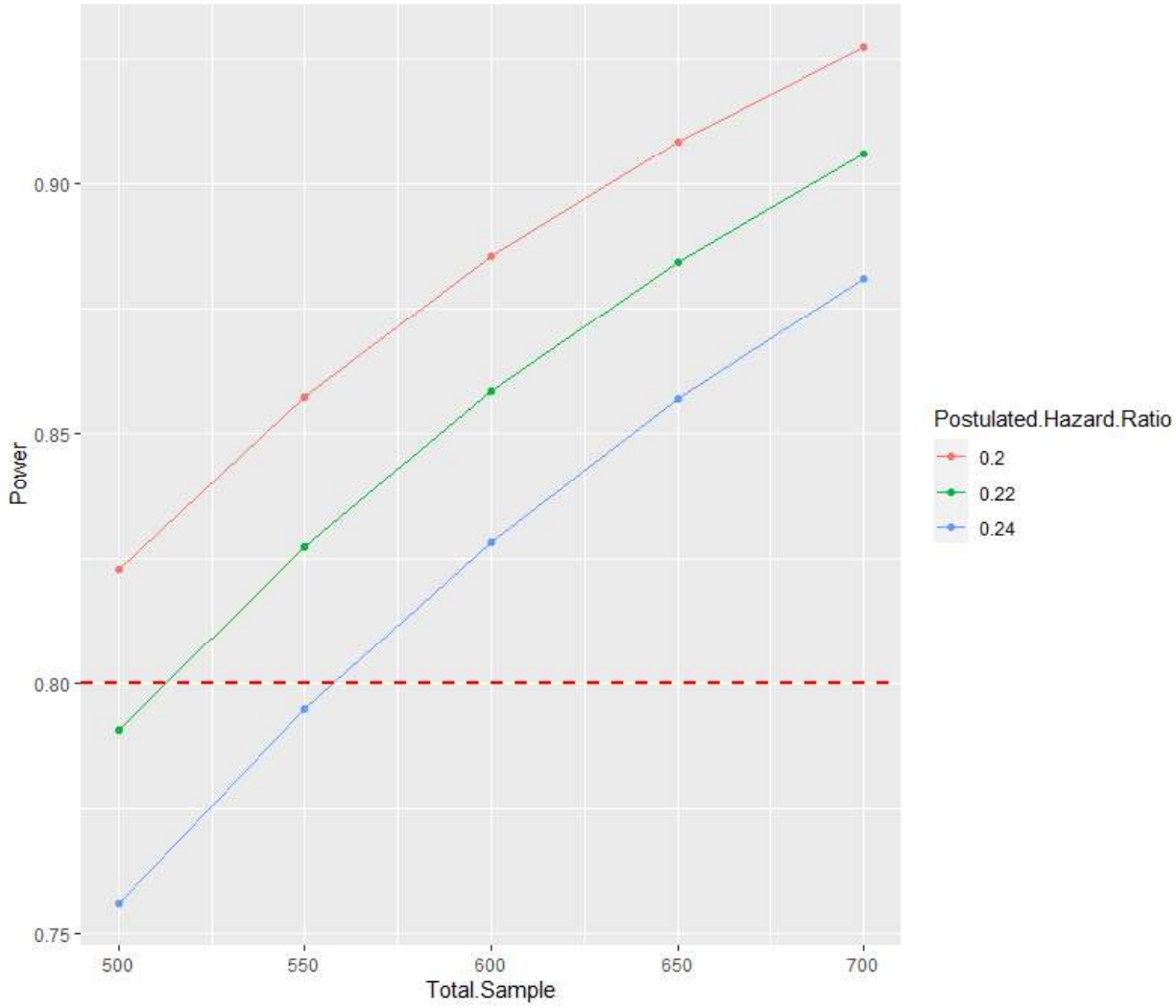

Figure 1. The power calculation given the postulated hazard ratios and with 1:1 randomization. The red curve indicates the power of 80%.

6.2 Cohort Definition

In this section, we define a main cohort and four confirmatory cohorts for the analysis of efficacy and safety (**Table**).

Main Cohort (ITT): we will use the intention-to-treat (ITT) cohort since it maintains the original randomization scheme ("as randomized") [5].

Confirmatory Cohort (MITT): the modified intention-to-treat (MITT) cohort consisting of all randomized patients who took at least one dose of the assigned treatment and did not undergo post-randomization exclusion.

Confirmatory Cohort (PP-1): Additional analyses will include a per-protocol (PP) population for subjects who took 80% of the study drug (or placebo).

Confirmatory Cohort (PP-2): Additional analyses will include a per-protocol (PP) population for subjects who took 80% of the study drug (or placebo) with censoring for either ISTH major bleeding or clinically relevant nonmajor bleeding event.

Confirmatory Cohort (Safety Cohort): In this cohort, we will only consider bleeding events (major bleed or clinically relevant non-major bleed) that occurred within 96 hours of taking a dose of the study drug (or placebo). The follow-up duration will be considered until the occurrence of a bleeding event or 96 hours after taking the last dose of the study drug (or placebo), whichever comes first.

6.2.1 Table. Analysis cohorts.

Analysis Set	**Definition**	**Primary Efficacy-12-month recurrent symptomatic VTE**	**Primary Safety-12-month ISTH major bleeding**
ITT	All randomized	Number of events Proportion Cumulative incidence Hazard ratio 95% confidence interval **P-value**	Number of events Proportion Cumulative incidence Hazard ratio 95% confidence interval
mITT	All randomized who took at least one dose of assigned treatment (apixaban or placebo) and did not undergo post-randomization exclusion	Number of events Proportion Cumulative incidence Hazard ratio 95% confidence interval	Number of events Proportion Cumulative incidence Hazard ratio 95% confidence interval
Per protocol without censoring for bleeding events	Subjects who took 80% of assigned treatment doses (apixaban or placebo)	Number of events Proportion Cumulative incidence Hazard ratio 95% confidence interval	Number of events Proportion Cumulative incidence Hazard ratio 95% confidence interval
Per protocol with censoring for bleeding events	Subjects who took 80% of assigned treatment doses (apixaban or placebo) with censoring for either ISTH major bleeding or clinically relevant nonmajor bleeding event	Number of events Proportion Cumulative incidence Hazard ratio 95% confidence interval	Number of events Proportion Cumulative incidence Hazard ratio 95% confidence interval
Safety set	Subjects who took at least one dose of the study drug (or placebo) until	Number of events Proportion Cumulative incidence Hazard ratio	Number of events Proportion Cumulative incidence Hazard ratio

	96 hours after the administration of the last dose of the study drug.	95% confidence interval	95% confidence interval **P-value**

6.3 Baseline Demographics and Clinical Comorbidities Description

Understanding the baseline demographics and clinical comorbidities of a cohort is crucial for interpreting study results and drawing conclusions about the generalizability of findings. In the HI-PRO trial, a table of descriptive statistics will be provided to summarize the baseline demographics of the intention-to-treat cohort. The table will include information on logical and categorical variables, such as age, sex, race, and comorbidities. The numbers and percentages will be provided for these variables, allowing for an assessment of the distribution and prevalence of different characteristics among the study population. In addition to logical and categorical variables, the table will also provide information on continuous variables, such as body mass index, hemoglobin level, and serum creatinine level. For these variables, the mean and standard deviation (SD) will be provided to summarize the central tendency and variability of the data.

According to the recent statistical reporting guideline from some experts [6], we will not provide p-values for testing the differences in baseline characteristics of the two assigned groups. However, the balances should be checked to see the quality of randomization by inspecting the standardized difference. We will consider the ones with a standardized difference >0.1 as clinically different. For a certain category whose observations are smaller than five counts, we may consider regrouping the categories.

6.4 Survival Analysis

6.4.1 Principal Analysis

We first provide analysis without adjustment of baseline demographics. For both the primary and secondary efficacy outcomes and principal and secondary safety outcomes, we use the Kaplan-Meier curve to estimate the survival functions of each group. If there is a presence of competing risks, cumulative incidence functions (CIFs) will be used to estimate the survival function[7]. The two-side log-rank test is used to measure if the apixaban 2.5 mg twice a day has a better survival chance than placebo (i.e., better chance of meeting the primary outcome). If there is a presence of competing risk, the log-rank based on cause-specific hazards [8] will be used. The corresponding hazard ratio of treatment effect and its confidence interval will be reported.

While our analysis is based on randomization, we also provide confirmatory analyses with the adjustment of baseline demographics and clinical comorbidities since it may capture any potential variations to make the statistical analysis more powerful. We use Cox regression to assess both the primary and secondary efficacy outcomes, while with adjustment of baseline demographics and clinical comorbidities. No interaction effects will be added. If there are competing risks, a cause-specific hazard model [7] will be used. The hazard ratio for be being treatment with the apixaban 2.5 mg twice a day will be used to test the treatment effect. The hazard ratio of other baseline demographics will be reported as supplementary information.

If the trial has a good randomization, we expect that the hazard ratio of treatment in analysis with the adjustment of baseline demographics and its p-value implies the same conclusion as in analysis without adjustment of baseline demographics. However, if they are not consistent in

clinical interpretation, i.e., a) the interpretation directions are different; b) p-values indicate different conclusion of significance, we will use the hazard ratio of treatment in analysis with the adjustment of baseline demographics as the main results to report, and the results of unadjusted one is treated as supplementary materials.

6.4.2 Subgroup Analysis

The study will conduct subgroup analyses based on certain predetermined factors such as whether the patient has PE versus non-PE, age (65 years or older versus younger), sex (male versus female), chronic kidney disease (defined as presence or absence of eGFR<60 mL/min/1.72m2), atherosclerotic cardiovascular disease (present versus absent), baseline low-dose aspirin use (present versus absent), the number of provoking risk factors (2 or more versus less than 2), provoking factor of travel, and baseline aspirin use. The survival analysis within each subgroup will be repeated using the main cohort and tested in confirmatory cohorts, as needed. The p-value of the additive interaction effect between treatment and subgroup will be reported.

In case the subgroup analysis of baseline aspirin use indicates a relevant modification effect (the p-value for the additive interaction effect <0.05), the study will repeat the primary analysis by reporting the treatment effect of apixaban vs placebo with the adjustments for a) the use of aspirin and b) the interaction term.

6.5 Back-Up Methods if Proportional Hazard Assumption is Violated

The Cox regression relies on the assumption of proportional hazards over time. The hazard proportionality test[9] is used to check the assumption. If the assumption of proportional hazard is violated. We will use the following backup methods. The log-rank test will be replaced by Kaplan–Meier curve-based tests (including weighted Kaplan–Meier and restricted mean survival time) [10]. Survival analysis based on restricted mean survival time will be implemented and restricted mean time lost (RMTL) ratios will replace the hazard ratio for reporting.

6.6 Interim Analysis

We will conduct a pre-specified interim analysis to assess the primary safety and efficacy outcomes after 50% of the planned enrollment population has completed 12-month follow-up. This planned interim analysis will inform the Data Safety Monitoring Board on whether the study should be stopped early due to efficacy, safety concerns, or futility or continue to enroll the full 600-patient cohort. The following three elements are used in considering the interim analysis:

6.7 Stopping for safety:

In the event that three distinct occurrences of unprovoked intracranial hemorrhages or major bleeding episodes are observed within the group of patients receiving apixaban, a thorough investigation will be conducted. This investigation will involve a review by an adjudication committee to confirm the authenticity of these incidents, ensuring that there have been no breaches of the study protocol that could have contributed to the adverse events. If the committee determines that these incidents are indeed linked to the apixaban treatment, specific measures will be implemented in response to these findings.

The decision to take action upon the confirmation of three such events is rooted in the clinical expertise of the researchers involved in the study. This threshold was established after extensive deliberation and consultation with the Mass General-Brigham Institutional Review Board (IRB).

The IRB is an independent body responsible for protecting the rights and welfare of human subjects involved in research, and their guidance plays a crucial role in maintaining the ethical standards of the study.

6.8 Stopping for futility:

The futility stopping rule is in place to prevent the unnecessary continuation of a clinical trial if there is a high likelihood that the primary efficacy outcome rate in the placebo arm falls below 6%. This threshold is considered clinically safe and is set to ensure that resources are not wasted on a trial that is unlikely to produce meaningful results. The problem is framed as a hypothesis testing scenario, where the null hypothesis states that the primary efficacy rate is greater than or equal to 0.06, and the alternative hypothesis suggests that it is less than 0.06.

If the null hypothesis is rejected, it indicates that the actual event rates in the placebo arm are less than 6%. To reject the null hypothesis, fewer than 4 events must be observed. In this context, the trial's progress will be assessed during an interim statistical analysis when the 12-month follow-up is completed for the 300th patient. At this point, if there are fewer than 4 events observed in the placebo group, the decision to terminate the trial will be considered.

6.9 Stopping for efficacy (superiority):

The efficacy stopping rule is a guideline used to determine whether a clinical trial should be terminated early based on the observed results. This rule is applied in situations where the data collected from the trial's participants, in this case, 300 patients, clearly demonstrates that the treatment being studied has a significantly higher efficacy than the placebo. The objective is to avoid exposing more patients to an inferior treatment (placebo) and to expedite the process of bringing a highly effective treatment to the market.

In this specific scenario, the efficacy stopping rule is based on the unadjusted hazard ratio, which is a measure of the relative risk of an event occurring in the treatment group compared to the placebo group. A hazard ratio of less than 0.1 is considered as "overwhelmingly superior efficacy," indicating that the treatment group has a much lower risk of the event than the placebo group.

To determine whether the trial should be stopped, a hypothesis test is conducted. The null hypothesis (H0) states that the hazard ratio is larger than or equal to 0.1, while the alternative hypothesis (H1) states that the hazard ratio is smaller than 0.1. If the null hypothesis is rejected based on the data collected from the enrolled patients, it would be concluded that the treatment has overwhelmingly superior efficacy compared to the placebo. As a result, the trial would be terminated early, allowing for a more rapid progression towards making the effective treatment available to patients who could benefit from it.

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