CLINICAL STUDY REPORT SYNOPSIS

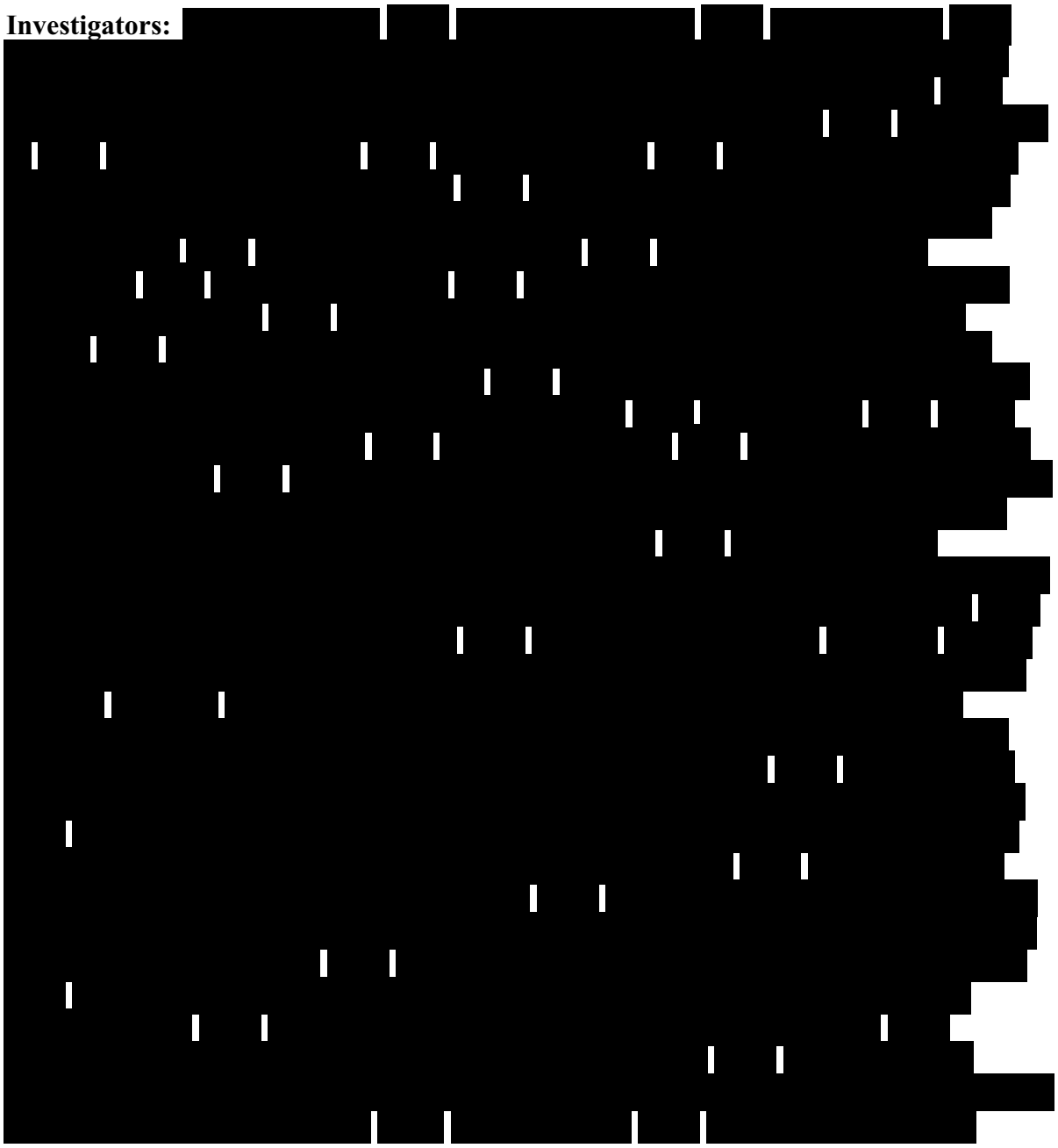
Sponsor: Bristol-Myers Squibb

Investigational Product: Apixaban

Clinical Study Report Synopsis: Protocol CV185056 (B0661001)

Protocol Title: A Safety and Efficacy Trial Evaluating the Use of Apixaban in the Treatment of Symptomatic Deep Vein Thrombosis and Pulmonary Embolism

Investigators:



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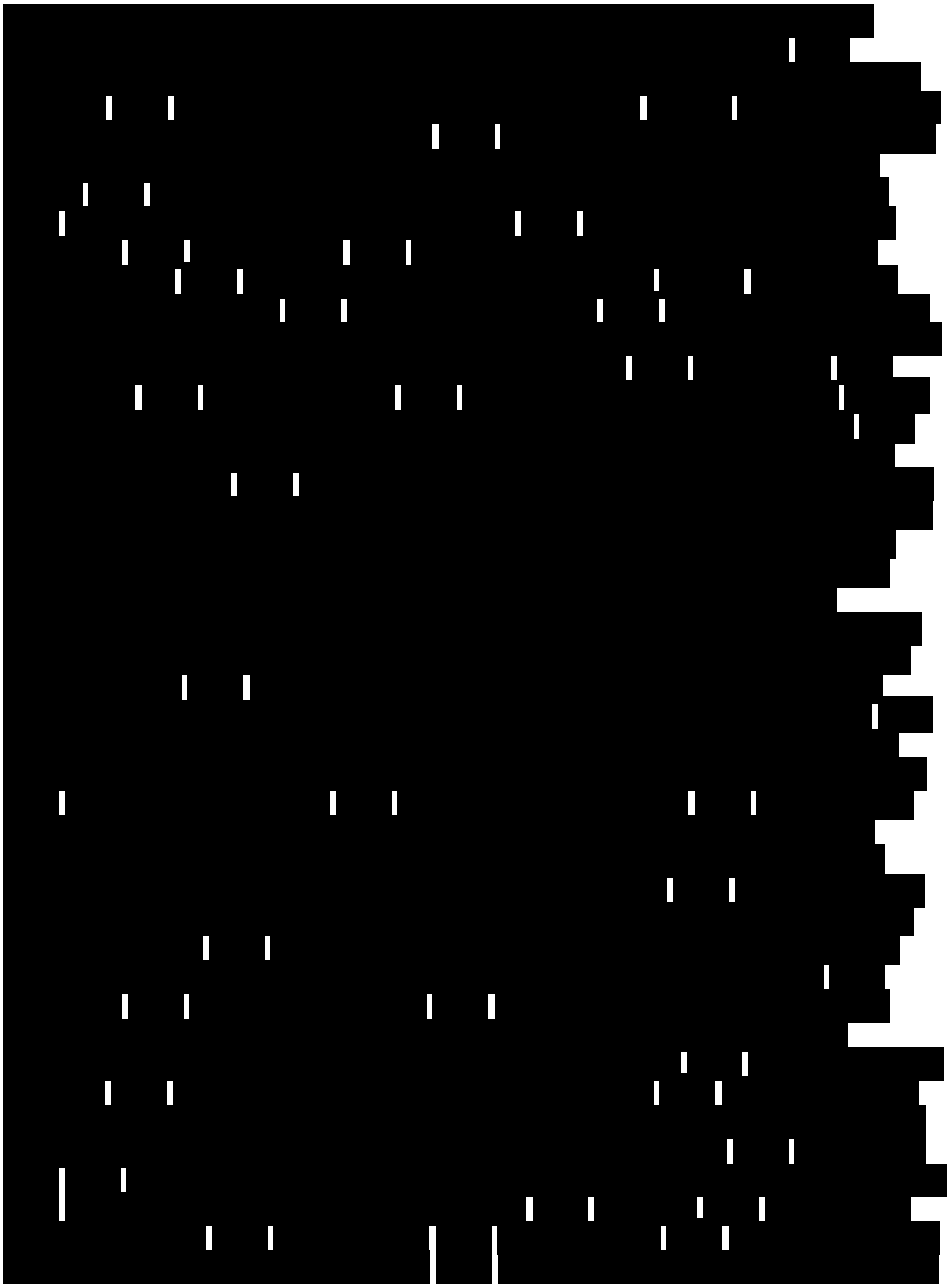

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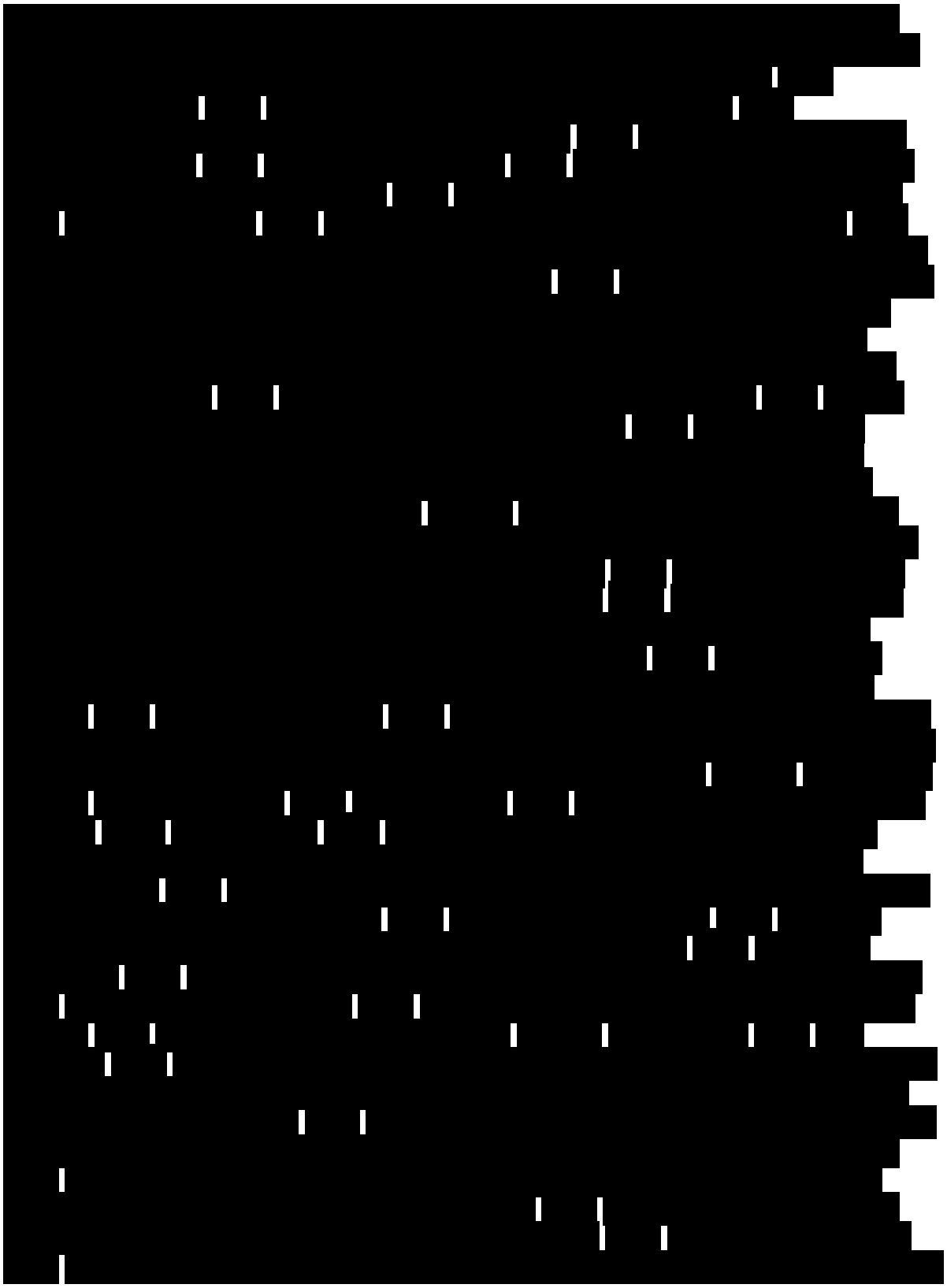

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Site never received drug but was filed to FDA
* No Subjects Randomized

Study Centers: The study was conducted at 358 centers in Argentina, Australia, Austria, Brazil, Canada, Czech Republic, Denmark, France, Germany, Hong Kong, Hungary, India, Israel, Italy, Malaysia, Mexico, Norway, Peoples Republic of China, Poland, Portugal, Romania, Russia, Singapore, South Africa, Korea, Spain, Ukraine, and United States of America.

Publications Based on the Study: Agnelli G, Buller HR, Cohen A, et al. Oral apixaban for the treatment of acute venous thromboembolism. N Engl J Med 2013;1-10.

Study Initiation and Completion Dates: 27 August 2008 to 12 March 2013

Date of Report: 16 September 2013

Phase of Development: Phase 3

Study Objectives:

The primary objective was to determine if apixaban was non-inferior to standard enoxaparin/ warfarin therapy in the combined endpoint of adjudicated recurrent symptomatic venous thromboembolism (VTE) (nonfatal deep vein thrombosis [DVT] or nonfatal pulmonary embolism [PE]) or VTE-related death over 6 months of therapy.

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Secondary Objectives were:

- To determine if apixaban was superior to standard enoxaparin/ warfarin therapy in the combined endpoint of adjudicated recurrent symptomatic VTE (nonfatal DVT or nonfatal PE) or VTE-related death over 6 months of therapy.

- To determine if apixaban was superior to standard enoxaparin/ warfarin therapy in the combined endpoint of adjudicated recurrent symptomatic VTE (nonfatal DVT or nonfatal PE) or all-cause death over 6 months of therapy.

- To characterize apixaban therapy relative to standard enoxaparin/ warfarin therapy in the combined endpoint of adjudicated recurrent symptomatic VTE (nonfatal DVT or nonfatal PE) or cardiovascular (CV) death over 6 months of therapy.

- To characterize apixaban therapy relative to standard enoxaparin/ warfarin therapy in the combined endpoint of adjudicated recurrent symptomatic VTE (nonfatal DVT or nonfatal PE), VTE-related death, or major bleeding over 6 months of therapy.

- To characterize apixaban therapy relative to standard enoxaparin/ warfarin therapy in adjudicated major bleeding during 6 months of therapy.

- To characterize apixaban therapy relative to standard enoxaparin/ warfarin therapy in the composite of adjudicated major bleeding and adjudicated clinically relevant non-major (CRNM) bleeding during 6 months of therapy.

- To characterize the primary efficacy outcome in the subset of subjects with index events of DVT only and in the subset of subjects with index events of PE with or without DVT.

METHODS

Study Design: This was a randomized, active controlled, parallel-group, double-blind, triple-dummy study in subjects with acute symptomatic proximal DVT or acute symptomatic PE. Randomization was stratified by the type of disease (symptomatic proximal DVT only or symptomatic PE with or without DVT) at baseline. If a subject had both symptomatic proximal DVT and symptomatic PE, the subject was stratified to the symptomatic PE group.

Subjects were randomized (1:1 ratio) using a central interactive voice response system (IVRS) and received study treatments for 6 months. Subjects in Group 1 received enoxaparin injections, warfarin tablets, and placebo apixaban tablets. Subjects in Group 2 received placebo enoxaparin injections, placebo warfarin tablets, and apixaban tablets. Total participation in the study for each subject was approximately 7 months (6 months on study treatment followed by a 30-day observation period). Subjects who met eligibility criteria assessed at screening and/or baseline were randomized and dispensed study drug on Day 1. Subjects were requested to return to the study site at Weeks 2, 4, 8, 12, 16, 20, and 24 for study specific activities.

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Diagnosis and Main Criteria for Inclusion:

Men and women aged ≥18 years, who had:

- an unprovoked index event or a provoked index event with a risk for recurrence;
- an acute symptomatic proximal DVT (defined as symptomatic DVT with evidence of proximal thrombosis that involved at least the popliteal vein or a more proximal vein.

Study Treatment: Subjects were randomized (1:1 ratio) to receive enoxaparin injections, warfarin tablets, and placebo apixaban tablets or placebo enoxaparin injections, placebo warfarin tablets, and apixaban tablets. Enoxaparin and placebo enoxaparin were administered for at least 5 days and were to be discontinued after the blinded international normalized ratio (INR) was ≥2, on 1 or more occasions. Subjects initially received an apixaban or placebo apixaban at a dose of 10 mg BID (administered as 2 × 5 mg tablets BID) for initial 7-day treatment, followed by 5 mg BID for 6 months.

Efficacy Evaluations: The primary efficacy endpoint was the incidence of an adjudicated composite of symptomatic, recurrent VTE (nonfatal DVT or nonfatal PE) or VTE-related death. The primary endpoint included events that occurred at any time from randomization until the end of the originally intended treatment period regardless of whether subjects were receiving study medication (using the intent-to-treat principle).

The secondary efficacy endpoints were incidence of adjudicated composite of recurrent symptomatic VTE and all cause death; incidence of adjudicated composite of recurrent symptomatic VTE and CV-related death; incidence of adjudicated composite of recurrent symptomatic VTE, VTE-related death and major bleeding; incidence of adjudicated symptomatic nonfatal DVT; incidence of adjudicated symptomatic nonfatal PE; incidence of adjudicated VTE-related death; incidence of adjudicated CV-related death; incidence of all cause death. These secondary endpoints (with the exception of bleeding which was considered only during the treatment period) included events that occurred at any time from randomization until the end of the intended treatment period regardless of whether subjects were receiving study medication (using the intent-to-treat principle).

Pharmacokinetic, Pharmacodynamic, Outcome Research Evaluations, and INR Monitoring:

Pharmacokinetic (PK) Evaluations: For those sites that participated in PK sample collection, blood specimens from all subjects who consented to participate were collected at the Week 2 and Week 4 visits to maintain the study blind at that site; however, specimens from subjects randomized to active control were not routinely analyzed.

Apixaban samples were assayed using a validated, sensitive and specific high-performance liquid chromatography coupled with atmospheric pressure ionization tandem mass spectrometry method.

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Pharmacodynamic (PD) Evaluations: Anti-coagulation factor Xa activity was measured using an aliquot from the PK plasma sample. Low molecular weight heparin Anti-Xa samples were assayed using a validated, sensitive and specific chromogenic assay method.

Outcomes Research Assessments: Information related to unplanned hospitalizations, rehabilitations, nursing home admissions, and visits to the emergency department or doctor's office was assessed as part of health care utilization. Information related to health care utilization (eg, discharge diagnosis for a hospitalization or the reason or diagnosis of a clinic visit) during the course of the study was collected.

INR Monitoring: This study utilized blinded INR monitoring. The blinded routine consisted of a POC INR device that generated an encrypted code. This code was reported to a centralized IVRS by the investigator. The IVRS decrypted the code and reported back to the investigator either the actual INR result from subjects randomized to warfarin or a sham INR result from subjects randomized to placebo warfarin. Sham INRs were based on a predefined computerized algorithm. Blinded INR testing occurred approximately every month and more frequently during warfarin titration and whenever clinically indicated, to maintain a target blinded INR range between 2 and 3.

Safety Evaluations:

Primary Safety Endpoint: The incidence of adjudicated major bleeding during the treatment period.

Secondary Safety Endpoints: Adjudicated composite of major and CRNM bleeding during the treatment period; adjudicated minor bleeding during the treatment period; and total adjudicated bleeding defined as adjudicated major, CRNM bleeding or minor bleeding during the treatment period.

Safety assessments included adverse event (AE) and serious adverse event (SAE) monitoring at all visits. Vital signs, 12-lead electrocardiogram, physical examinations, and laboratory evaluations were performed at appropriate intervals. In addition to bleeding, thrombocytopenia, elevated liver function tests (LFTs), neurological events, acute myocardial infarction, and acute stroke were prospectively identified as events of special interest for the apixaban clinical program.

Statistical Methods:

The primary efficacy data set used for analyses of event rates consisted of all randomized subjects with a non-missing primary endpoint. Subjects whose outcome for the primary endpoint could not be documented on or after study Day 154 were not included in primary efficacy analysis. Subjects were categorized to the group to which they were assigned by the IVRS, regardless of the treatment actually received (intent-to-treat). The safety data set (as-treated) consisted of all treated subjects (randomized subjects who received at least 1 dose of study drug).

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This study utilized a hierarchical hypothesis testing plan that was agreed with the Food and Drug Administration on 26 March 2013 as described below and shown in Figure S1.

Figure S1. Hierarchical Statistical Testing for Study CV185056

Non-inferiority for VTE/VTE-related death
↓
Superiority for Major Bleeding
↓
Superiority for VTE/VTE-related death
↓
Superiority for Major Bleeding/CRNM Bleeding

CRNM=Clinically relevant non-major; VTE=Venous thromboembolism.

In this testing sequence, non-inferiority of apixaban relative to comparator was tested at the 1-sided α=0.025 for recurrent VTE/VTE-related death. If non-inferiority was demonstrated then each subsequent endpoint in the testing scheme was tested at 2-sided α=0.05 until failure to reject a null hypothesis at which point all subsequent testing stopped.

Generally, continuous variables were summarized using mean and standard deviation and categorical variables were summarized using relative frequencies. Non-inferiority based on confidence intervals (CIs) was assessed for the primary endpoint only. The estimated relative risk (RR) and the 95% CI about the RR were provided using a stratified analysis. Hypotheses tests (1-sided p-values for non-inferiority) were based on the Yanagawa, Tango and Hiejima test. Hypotheses test of superiority for efficacy endpoints were based on the Cochran-Mantel-Haenszel (CMH) test stratified by the type of index event (DVT or PE with/without DVT). Descriptive statistics for binary endpoints included event rate in each group, the estimated RR with 95% CI about the RR. The 95% CI for the RR was computed based on CMH's method stratified by index event. Summaries of time-to-event data were displayed in graphical format using Kaplan-Meier estimates.

All efficacy analyses were performed on efficacy outcomes confirmed by adjudication using the intent-to-treat population, where subjects were grouped by the treatment assigned at randomization. Sensitivity analyses were performed using the intent-to-treat population to assess robustness of the results of the primary efficacy analysis to missing data.

Major bleeding was included in the inferential hierarchical testing scheme. Superiority for major bleeding was tested only following successful testing of the primary endpoint that required significance for non-inferiority for both RR and risk difference (RD) (Figure S1). Adjudicated minor bleeding, CRNM bleeding, and total adjudicated bleeding were also analyzed to support the characterization of bleeding risk. Incidence of these endpoints was analyzed using the methods described above for analysis of major bleeding.

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AEs and marked abnormalities in clinical laboratory tests were summarized by treatment group.

RESULTS

Subject Disposition and Demography:

A total of 5395 subjects were randomized to treatment and 5365 (99.4%) subjects received at least 1 dose of study medication (this is excluding data from Site CV185056-[redacted] which was excluded due to audit findings). A total of 3491 subjects were aged <65 years, 1130 subjects were aged 65 years to 75 years and 774 subjects were aged ≥75 years. The overall mean age was 56.9 years and 58.7% of the overall subjects were male. Most subjects were white (82.7%, overall). A total of 544 (10.1%) subjects were diagnosed with provoked VTE with additional risk factors for recurrence and 4845 (89.8%) subjects were diagnosed with unprovoked VTE.

Of the 5365 subjects treated, 2676 received apixaban, and 2689 received enoxaparin/warfarin. A similar proportion of subjects completed 6 months of treatment in both groups (86.0% and 84.7% in the apixaban treatment group and the enoxaparin/warfarin treatment group, respectively). A total of 790 (14.6%) subjects discontinued study drug during the intended treatment period; 377 (14.0%) subjects were in the apixaban treatment group, and 413 (15.3%) subjects were in the enoxaparin/warfarin treatment group. The most frequent reason for discontinuation was AEs (332 [6.2%] subjects). The proportion of subjects who discontinued due to AEs was lower in the apixaban treatment group (5.6%) than the enoxaparin/warfarin treatment group (6.7%). The lower proportion of subjects who discontinued due to AEs in the apixaban group was due to less bleeding related AEs in the apixaban treatment group (0.7%) compared to the enoxaparin/warfarin treatment group (1.7% subjects). A total of 5244 subjects (2609 and 2635 subjects in the apixaban treatment group and the enoxaparin/warfarin treatment group, respectively) were included in primary efficacy analysis and 5365 subjects (2676 and 2689 subjects in the apixaban treatment group and the enoxaparin/warfarin treatment group, respectively) were included in safety analysis.

Efficacy Results:

Primary: The results of the primary efficacy analysis are presented in Table S1. The proportion of subjects with an adjudicated composite of symptomatic, recurrent VTE (nonfatal DVT or nonfatal PE) or VTE-related death was 0.0226 in the apixaban treatment group compared to 0.0269 in the enoxaparin/warfarin treatment group. Non-inferiority of apixaban to enoxaparin/warfarin was achieved for both RR and RD with high confidence ($p<0.0001$) which permitted inferential testing for a reduction in major bleeding versus warfarin. Following rejection of the null hypothesis for major bleeding (superiority achieved for major bleeding), superiority was not achieved for VTE/VTE-related death resulting in further inferential testing being halted.

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Sensitivity analyses were performed that repeated the primary analysis by varying a hypothetical event rate in the missing data and using all randomized subjects as opposed to the efficacy evaluable population. Results of the sensitivity analyses supported the robustness of the primary analysis. The results of primary efficacy analysis were also consistent across DVT and PE strata. In addition, no subgroup by treatment interactions of clinical relevance were noted, which further supported the primary analysis.

Per-protocol analysis was performed and demonstrated that the overall efficacy results are consistent with the primary efficacy analysis with the RR of 0.66 ($p < 0.0001$ for non-inferiority). The proportion of subjects with the primary efficacy endpoint in the per-protocol analysis was 0.0142 in the apixaban treatment group compared to 0.0215 in the enoxaparin/warfarin treatment group. Reasons for subjects excluded from per-protocol population were similar in both treatment arms as outlined in Table S1. The most common exclusions from per-protocol analysis were discontinuation of treatment before the end of the intended treatment period without having had an incidence of the primary efficacy endpoint and <80% compliance with study medications.

Overall time in therapeutic range (TTR; INR between 2.0 to 3.0) for subjects treated with enoxaparin/warfarin was 60.9%, INR was <2.0 for 22.9% of the time and >3.0 for 16.1% of the time. The effects of apixaban relative to warfarin in preventing VTE recurrence were maintained across study sites regardless of TTR quartiles as evidenced by the lack of center TTR quartile by treatment interaction.

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Table S1. Analysis of Adjudicated VTE (Nonfatal DVT or Nonfatal PE)/VTE-Related Death

Symptomatic VTE (Nonfatal DVT or Nonfatal PE)/ VTE-Related Death	Apixaban	Enoxaparin/ Warfarin
Primary Analysis (Primary Efficacy Subjects)		
n/N1[a]	59/2609	71/2635
Event rate (95% CI)*	0.0226 (0.0169, 0.0283)	0.0269 (0.0208, 0.0331)
Relative risk (95% CI)†	0.8390 (0.5965, 1.1802)	
p-value for non-inferiority‡	<0.0001	
p-value for superiority†	0.3128	
Risk difference (95% CI)§	-0.0044 (-0.0128, 0.0040)	
p-value for non-inferiority‡	<0.0001	
p-value for superiority§	0.3090	
Primary Analysis (Per-Protocol Subjects)		
n/N2	32/2257	48/2235
Event rate (95% CI)*	0.0142 (0.0093, 0.0191)	0.0215 (0.0155, 0.0275)
Relative risk (95% CI)†	0.6611 (0.4243, 1.0301)	
p-value for non-inferiority‡	<0.0001	
Risk difference (95% CI)§	-0.0072 (-0.0150, 0.0005)	
p-value for non-inferiority‡	<0.0001	

* CI for single event rate was calculated based on the Wald asymptotic confidence limits.
† Relative risk, CI, and p-value were calculated based on CMH test stratified by index event strata.
‡ p-value was calculated based on the Yanagawa-Tango-Hiejima test stratified by index event strata for non-inferiority.
§ Risk difference, CI, and p-value were calculated based on the inverse variance method when there was at least 1 event of interest per treatment group and index event stratum, otherwise they were calculated based on the harmonic means method when there was at least 1 event of interest per index event stratum.
CI=Confidence interval; CMH=Cochran–Mantel–Haenszel; DVT=Deep vein thrombosis; n=Number of subjects with observation; N1=Total number of efficacy evaluable subjects in respective groups (Primary Efficacy Subjects); N2=Total number of per-protocol subjects in respective group; PE=Pulmonary embolism; VTE=Venous thromboembolism.
a. Subjects with missing endpoint information were excluded from the analysis.

Secondary: The rates for the adjudicated composite of recurrent symptomatic VTE (nonfatal DVT or nonfatal PE)/all-cause death and symptomatic VTE (nonfatal DVT or nonfatal PE)/CV-related death were not significantly different between the treatment arms. The rates for the adjudicated composite of recurrent symptomatic VTE (nonfatal DVT or nonfatal PE)/VTE-related death/major bleeding, and VTE (nonfatal DVT or nonfatal PE)/CV-related death/myocardial infarction/stroke/major bleeding/CRNM bleeding were significantly different between the treatment arms ($p<0.05$).

Other adjudicated efficacy endpoints included nonfatal DVT, nonfatal PE, VTE-related death, CV-related death, and all-cause death; results were similar for both treatment groups.

Pharmacokinetic, Pharmacodynamic, and Outcome Research Results:

PK/PD data were combined with data from other studies for the population PK PD analyses and the results will be presented in a separate population PK/PD report.

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Outcome Research Results: There were more numbers of hospitalizations in the enoxaparin/warfarin group compared to the apixaban groups. The reason for the majority of hospitalizations were VTE, bleeding and "other".

Safety Results:

Primary and Secondary Safety Endpoint Results: Results of adjudicated major bleeding during the treatment periods are presented in Table S2. Superiority (RR=0.3070; 95% CI: 0.1728 to 0.5452; p <0.0001) in adjudicated major bleeding was observed for the apixaban treatment group compared to the enoxaparin/warfarin treatment group. Overall, a total of 15 subjects (6 gastrointestinal, 2 rectal [of this, fatal bleeding in 1 subject], 3 intracranial, 1 retroperitoneal, 1 nasal, 1 skin, and 1 urogenital) in the apixaban treatment group and 49 subjects (18 gastrointestinal [of this, fatal bleeding in 1 subject], 6 intracranial, 6 intramuscular [of this, fatal bleeding in 1 subject], 5 skin, 1 nasal, 3 retroperitoneal, 4 urogenital, 2 intra-articular, 2 intraocular, 2 other, 1 rectal, and 1 other critical organ) in the enoxaparin/warfarin treatment group experienced major bleeding events.

Table S2. Analysis of Adjudicated Major Bleeding During the Treatment Period (Treated Subjects)

	Apixaban N=2676	Enoxaparin/Warfarin N=2689
Major bleeding, n	15	49
Event rate (95% CI)*	0.0056 (0.0028, 0.0084)	0.0182 (0.0132, 0.0233)
Relative risk (95% CI)†	0.3070 (0.1728, 0.5452)	
p-value for superiority†	<0.0001	
Risk difference (95% CI)‡	-0.0113 (-0.0170, -0.0056)	

* CI for single event rate was calculated based on the Wald asymptotic confidence limits.
† Relative risk, CI, and p-value were calculated based on CMH test stratified by index event strata.
‡ Risk difference, CI, and p-value were calculated based on the inverse variance method when there was at least 1 event of interest per treatment group and index event stratum, otherwise they were calculated based on the harmonic means method when there was at least 1 event of interest per index event stratum.
CI=Confidence interval; CMH=Cochran–Mantel–Haenszel; n=Number of subjects with observation; N=Total number of subjects in respective group.

The secondary adjudicated bleeding endpoints assessed were: major/CRNM bleeding, CRNM bleeding, minor bleeding, and total bleeding. Statistically significant lower rates of bleeding were observed all components of bleeding; adjudicated major/CRNM bleeding, CRNM bleeding, minor bleeding, and total bleeding for the apixaban treatment group compared to the enoxaparin/warfarin treatment group (p <0.0001).

Adverse Events and Serious Adverse Events:

The proportion of subjects with any AE with onset during the treatment period was similar across in both treatment groups (67.1% of subjects in the apixaban treatment group and

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71.5% of subjects in the enoxaparin/warfarin treatment group). Results were generally consistent in each index event strata (DVT and PE) with the overall findings.

The most common AEs (>5% in any treatment group) with onset during the treatment period were headache (6.3% and 6.2% in the apixaban treatment group and enoxaparin/warfarin treatment group, respectively), and epistaxis (2.9% and 5.4% in the apixaban treatment group and enoxaparin/warfarin treatment group, respectively).

The majority of AEs in each treatment group were mild or moderate in severity. Severity was comparable in both treatment groups. Overall, 6.6% subjects in the apixaban treatment group and 7.5% in the enoxaparin/warfarin treatment group experienced severe AEs. Overall, 2.2% subjects in the apixaban treatment group and 2.5% in the enoxaparin/warfarin treatment group experienced very severe AEs.

The number of treated subjects who discontinued due to AEs was similar in the apixaban treatment group (6.1%) and the enoxaparin/warfarin treatment group (7.4%). However, a lower proportion of subjects discontinued due to bleeding related AEs in the apixaban treatment group (0.7%) compared to the enoxaparin/warfarin treatment group (1.7% subjects).

Similar proportions of subjects in both treatment groups experienced an SAE with onset during the treatment period (15.6% and 15.2% in the apixaban treatment group and the enoxaparin/warfarin treatment group, respectively). The most frequently reported SAEs (>1% in any treatment group) with onset during the treatment period were DVT and PE. The proportion of subjects who experienced an SAE considered related to treatment was lower in the apixaban treatment group (1.8%) compared with the enoxaparin/warfarin group (3.3%).

A summary of SAEs with an outcome of death that occurred during the treatment period is presented in Table S3.

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Table S3. Summary of Serious Adverse Events With Outcome of Death During the Treatment Period (Treated Subjects)

System Organ Class Preferred Term	Apixaban N=2676	Enoxaparin/Warfarin N=2689
	n (%)	n (%)
Total subjects with an event	37 (1.4)	44 (1.6)
Cardiac disorders	10 (0.4)	7 (0.3)
Acute myocardial infarction	3 (0.1)	0
Cardiac arrest	1 (<0.1)	1 (<0.1)
Cardiac failure	1 (<0.1)	2 (<0.1)
Cardio-respiratory arrest	1 (<0.1)	0
Cardiopulmonary failure	1 (<0.1)	0
Myocardial infarction	1 (<0.1)	2 (<0.1)
Pericardial haemorrhage	1 (<0.1)	0
Ventricular fibrillation	1 (<0.1)	0
Cardiogenic shock	0	2 (<0.1)
General disorders and administration site conditions	8 (0.3)	4 (0.1)
Death	4 (0.1)	2 (<0.1)
Multi-organ failure	3 (0.1)	1 (<0.1)
Multi-organ disorder	1 (<0.1)	0
Asthenia	0	1 (<0.1)
Infections and infestations	8 (0.3)	6 (0.2)
Sepsis	2 (<0.1)	3 (0.1)
Infection	1 (<0.1)	0
Lung infection	1 (<0.1)	0
Peritonitis	1 (<0.1)	0
Pneumonia	1 (<0.1)	2 (<0.1)
Septic shock	1 (<0.1)	1 (<0.1)
Urosepsis	1 (<0.1)	0
Purulent pericarditis	0	1 (<0.1)
Respiratory, thoracic and mediastinal disorders	8 (0.3)	10 (0.4)
Pulmonary embolism	4 (0.1)	6 (0.2)
Acute respiratory failure	2 (<0.1)	0
Pneumonia aspiration	1 (<0.1)	0
Respiratory distress	1 (<0.1)	0
Chronic obstructive pulmonary disease	0	1 (<0.1)
Interstitial lung disease	0	1 (<0.1)
Pneumothorax	0	2 (<0.1)
Neoplasms benign, malignant and unspecified (including cysts and polyps)	5 (0.2)	12 (0.4)
Colon cancer	1 (<0.1)	0
Gallbladder cancer	1 (<0.1)	0
Malignant neoplasm progression	1 (<0.1)	1 (<0.1)
Metastatic neoplasm	1 (<0.1)	1 (<0.1)
Neoplasm malignant	1 (<0.1)	0
Adenocarcinoma	0	1 (<0.1)
Cervix carcinoma	0	1 (<0.1)
Gastrointestinal cancer metastatic	0	1 (<0.1)
Lung cancer metastatic	0	1 (<0.1)

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Table S3. Summary of Serious Adverse Events With Outcome of Death During the Treatment Period (Treated Subjects)

System Organ Class Preferred Term	Apixaban N=2676	Enoxaparin/Warfarin N=2689
	n (%)	n (%)
Lung neoplasm malignant	0	1 (<0.1)
Oesophageal cancer metastatic	0	1 (<0.1)
Ovarian cancer metastatic	0	1 (<0.1)
Pancreatic carcinoma	0	1 (<0.1)
Pancreatic carcinoma stage IV	0	1 (<0.1)
Small cell lung cancer metastatic	0	1 (<0.1)
Vascular disorders	1 (<0.1)	2 (<0.1)
Arterial thrombosis	1 (<0.1)	0
Aortic rupture	0	1 (<0.1)
Shock haemorrhagic	0	1 (<0.1)
Blood and lymphatic system disorders	0	2 (<0.1)
Anaemia	0	1 (<0.1)
Disseminated intravascular coagulation	0	1 (<0.1)
Gastrointestinal disorders	0	4 (0.1)
Gastrointestinal haemorrhage	0	3 (0.1)
Neutropenic colitis	0	1 (<0.1)
Hepatobiliary disorders	0	2 (<0.1)
Hepatic failure	0	2 (<0.1)
Metabolism and nutrition disorders	0	1 (<0.1)
Failure to thrive	0	1 (<0.1)

The denominator to calculate each percentage was the total number of treated subjects within each treatment group.
Deaths: included all deaths that occurred from first dose through 30 days after the last dose of blinded study drug.
Subject could have multiple adverse events with outcome of death.
n=Number of subjects with adverse event; N=Total number of subjects in respective group.

Adverse Events Related to Bleeding:

The proportion of subjects who experienced an AE related to bleeding was lower in the apixaban treatment group (15.5%) compared with the enoxaparin/warfarin group (25.8%). The proportion of subjects experiencing bleeding related AEs was consistent with overall result across DVT and PE strata.

Adjudicated Adverse Events of Special Interest:

Adjudicated AEs of special interest included myocardial infarction, acute stroke (hemorrhagic, non-hemorrhagic, hemorrhagic stroke or major bleeding, infarction with hemorrhagic conversion, and unknown type), and thrombocytopenia. Overall, the occurrence of all adjudicated events of special interest was low.

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Clinical Laboratory Evaluation:

Most frequently reported laboratory abnormalities were the presence of red blood cells, white blood cells and leucocyte esterase in urine, decreased hemoglobin and absolute lymphocyte count, increased alanine aminotransferase (ALT) and absolute eosinophils count.

- Liver Function Tests: LFTs included aspartate aminotransferase, ALT, total bilirubin, and alkaline phosphatase (ALP). The proportion of subjects experiencing elevations in LFTs during the treatment period were lower in the apixaban treatment group (3.9%) compared with the enoxaparin/warfarin treatment group (7.4%). This was primarily driven by ALT elevation (2.0% versus 5.6% in the apixaban treatment group and the enoxaparin/warfarin treatment group, respectively).

- Platelet Count: No subjects experienced a decreased platelet count ($<50 \times 10^9$ c/L) during the treatment period. A total of 31 subjects experienced a decreased platelet count ($<100 \times 10^9$ c/L) during treatment (22 subjects versus 9 subjects in the apixaban treatment group and the enoxaparin/warfarin treatment group, respectively).

- Creatine Kinase: A total of 44 subjects experienced elevated creatine kinase (CK) (>5 × ULN) during the treatment period (20 subjects in the apixaban treatment group and 24 subjects in the enoxaparin/warfarin treatment group). A total of 10 subjects experienced elevated CK (>10 × ULN) during the treatment period (2 subjects in the apixaban treatment group and 8 subjects in the enoxaparin/warfarin treatment group).

Vital Signs:

No clinically relevant changes from baseline were observed in vital signs. Results were consistent across the treatment groups.

Conclusions:

- The primary objective of this study was achieved by demonstrating non-inferiority of apixaban to standard enoxaparin/warfarin therapy with respect to the combined endpoint of adjudicated recurrent symptomatic VTE (nonfatal DVT or nonfatal PE) or VTE-related death.

- The study demonstrated superiority for major bleeding and statistically significant reductions in all bleeding related endpoints for apixaban compared to standard enoxaparin/warfarin therapy.

- The results of analyses of other secondary endpoints were consistent with the results of the primary endpoint analysis.

- Based on demonstrated efficacy with a superior bleeding profile, apixaban has a favorable benefit/risk profile compared with standard enoxaparin/warfarin therapy.