# CLINICAL STUDY REPORT SYNOPSIS

**Sponsor**: Bristol-Myers Squibb

**Investigational Product**: Apixaban

**Clinical Study Report Synopsis**: Protocol CV185057 (B0661002)

**Protocol Title**: A Safety and Efficacy Trial Evaluating the Use of Apixaban for the Extended Treatment of Deep Vein Thrombosis and Pulmonary Embolism

**Investigators**: [redacted]

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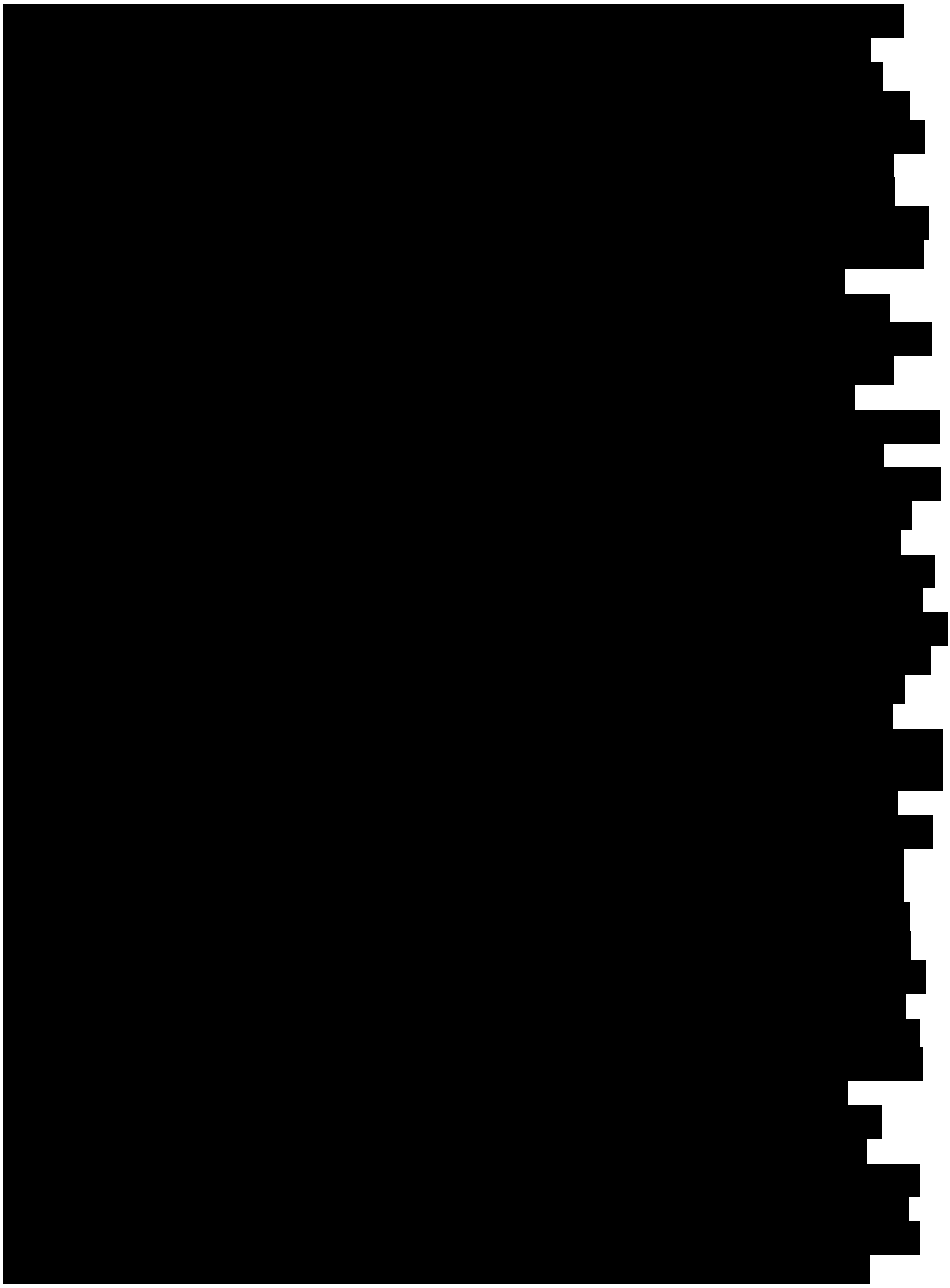

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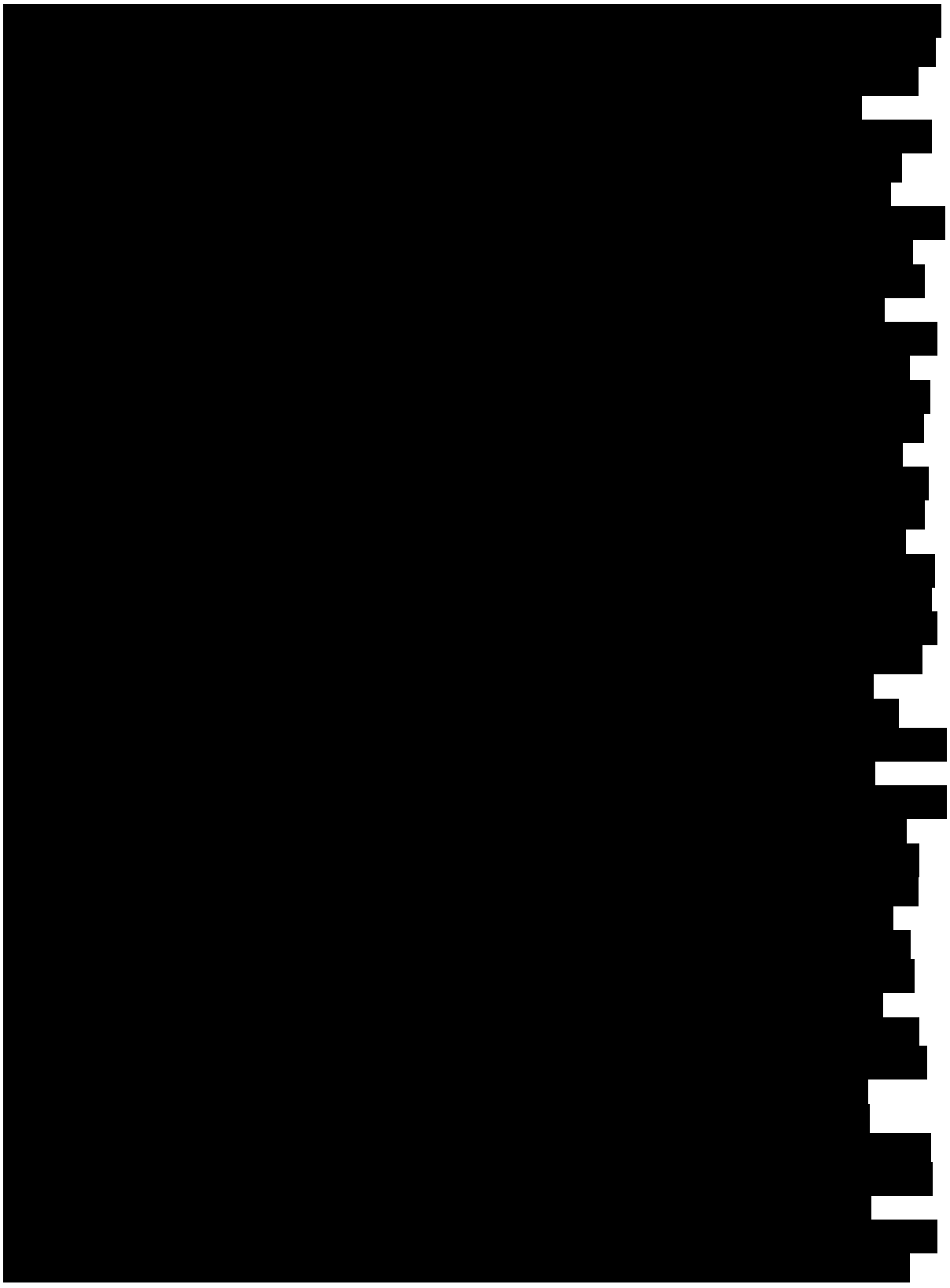

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[redacted]

* No Subjects Randomized

‡ Site never received drug but was filed to FDA

**Study Centers**: The study was conducted at 328 centers in Argentina, Australia, Austria, Brazil, Canada, Chile, Czech Republic, Denmark, France, Germany, Hong Kong, India, Israel, Italy, Mexico, Norway, Philippines, Poland, Portugal, Romania, Russia, Singapore, South Africa, Korea, Spain, United Kingdom, Ukraine, and United States.

**Publications Based on the Study**: Agnelli G, Buller HR, Cohen A, et al. Apixaban for extended treatment of venous thromboembolism. N Engl J Med 2013;368(8):699-708. .

**Study Initiation and Completion Dates**: 16 May 2008 to 24 August 2012

**Date of Report**: 16 September 2013

**Phase of Development**: Phase 3

**Study Objectives**:

The primary objective was to determine if at least 1 of the apixaban dose regimens was superior to placebo in the combined endpoint of symptomatic, recurrent venous thromboembolism (VTE) (nonfatal deep-vein thrombosis [DVT] or nonfatal pulmonary embolism [PE]) or all-cause death in subjects who had an objectively documented index event of symptomatic proximal DVT or symptomatic PE, had completed approximately 6 to 12 months of anticoagulant therapy for the treatment of the index event, and had no objectively documented symptomatic recurrence of VTE after the index event.

Secondary Objectives were:

- To characterize treatment effects of the 2 apixaban doses relative to placebo for the adjudicated composite of recurrent symptomatic VTE or VTE-related death, adjudicated composite of recurrent symptomatic VTE or cardiovascular (CV)-related death, adjudicated symptomatic nonfatal DVT, adjudicated symptomatic nonfatal PE, adjudicated VTE-related death, adjudicated CV-related death, all-cause death, adjudicated major bleeding, the adjudicated composite of major bleeding and clinically relevant non-major bleeding.

- 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.

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### METHODS

**Study Design**: This was a randomized, parallel-group, double-blind, placebo-controlled study in subjects with symptomatic proximal DVT or symptomatic PE. Randomization was stratified by the type of disease treated (symptomatic proximal DVT only or symptomatic PE with or without DVT) and by the type of previous treatment (enoxaparin/warfarin in Study CV185056 [Apixaban after the initial Management of PuLmonary embolIsm and deep vein thrombosis with First-line therapY {AMPLIFY}], apixaban in Study CV185056 [AMPLIFY], or standard anti-coagulant therapy outside of Study CV185056 [AMPLIFY]). If a subject had both symptomatic DVT and symptomatic PE, the subject was stratified to the symptomatic PE group. After completing approximately 6 to 12 months of anticoagulant therapy for the treatment of the index event, eligible subjects were randomized at a 1:1:1 ratio to receive 1 of 3 oral treatments twice daily (BID): apixaban 2.5 mg, apixaban 5 mg, or placebo. Total participation in the study for each subject was approximately 13 months (12 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 Week 2 and at Months 3, 6, 9, and 12. Other visits at Months 1, 2, 4, 5, 7, 8, 10, and 11 were conducted either in person or by telephone contact.

**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 objectively documented index event of symptomatic proximal DVT (defined as symptomatic DVT with evidence of proximal thrombosis that involved at least the popliteal vein or a more proximal vein, demonstrated by imaging with compression ultrasound [CUS], including grey-scale or color-coded Doppler, or ascending contrast venography) or symptomatic PE (symptomatic PE with evidence of thrombosis demonstrated by imaging as: an intraluminal filling defect in segmental or more proximal branches on spiral computed tomography scan; or an intraluminal filling defect or a sudden cutoff of vessels more than 2.5 mm in diameter on the pulmonary angiogram; or a perfusion defect of at least 75% of a segment with a local normal ventilation result [high-probability] on ventilation/perfusion lung scan);
- completed approximately 6 to 12 months of standard anticoagulant therapy, or completed assigned CV185056 (AMPLIFY) study treatment, for the treatment of the index event;
- no objectively documented symptomatic recurrence of VTE after the index event.

Subjects were to be randomized within approximately 7 days of the last dose of their initial 6- to 12-month treatment. If a Vitamin K antagonist (VKA) was used as standard anticoagulant therapy, then an international normalized ratio (INR) must have been

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documented as ≤2 before randomization. If the subject received CV185056 (AMPLIFY) study treatment, then a blinded INR must have been documented as ≤2 before randomization.

**Study Treatment**: Subjects were randomized to receive 2.5 mg apixaban and apixaban 5 mg matching placebo, apixaban 5 mg and apixaban 2.5 mg matching placebo or apixaban 2.5 matching placebo and apixaban 5 mg matching placebo. Study subjects took 2 tablets in the morning and 2 tablets in the evening (approximately every 12 hours).

**Efficacy Evaluations**: The primary efficacy endpoint was the incidence of an adjudicated composite of symptomatic, recurrent VTE (nonfatal DVT or nonfatal PE) or all-cause 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 intended treatment period was defined as the longer of the dosing period plus 2 days or 355 days. If there was missing endpoint information, such as subjects who withdrew consent or were lost to follow-up, they were scored (imputed) as having had a primary efficacy outcome event. Subjects were considered to have a missing endpoint if 1) they did not have an event during the intended treatment period and 2) it could not be determined prior to Day 331 whether or not the endpoint occurred (data from the Study Outcomes and Events of Special Interests Visit Assessment Case Report Form [CRF] was not available). Day 331 was used to define subjects entering the $12^{th}$ month of the study.

The secondary efficacy endpoints were incidence of adjudicated composite of recurrent symptomatic VTE or VTE-related death; incidence of adjudicated composite of recurrent symptomatic VTE or CV-related death; incidence of adjudicated symptomatic nonfatal DVT; incidence of adjudicated symptomatic nonfatal PE; incidence of adjudicated VTE-related death; incidence of adjudicated CV-related death and incidence of all-cause death. These secondary endpoints 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).

**Pharmacokinetic, Pharmacodynamic, and Outcome Research Evaluations**:

Pharmacokinetic Evaluations: For those sites that participated in the sparse or intense pharmacokinetic (PK) sample collection, blood samples from all subjects who consented to participate were collected at the Week 2 and Month 3 visits (sparse) or at any time from the Week 2 to the Month 3 visits (intense) to maintain the study blind at that site; however, specimens from subjects randomized to placebo 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 (LC-API/MS/MS) method.

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Pharmacodynamic (PD) Evaluations: Anti-coagulation factor Xa activity was measured using an aliquot from the sparse 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 were assessed as a part of health care utilization analysis. 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.

**Safety Evaluations**:

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

Secondary Safety Endpoints: Adjudicated composite of major and clinically relevant non-major bleeding during the treatment period; adjudicated minor bleeding during the treatment period; and total adjudicated bleeding defined as adjudicated major, clinically relevant non-major 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, targeted physical examinations, and laboratory evaluations were performed at appropriate intervals. In addition to bleeding, thrombocytopenia, elevated liver function tests (LFTs), neuropathy, 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 consisted of all randomized subjects. Subjects were categorized to the group to which they were assigned by the interactive voice response system (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).

Generally, continuous variables were summarized using mean and standard deviation and categorical variables were summarized using proportion of subjects with an event. Descriptive statistics for binary endpoints included the proportion of subjects with an event in each group with a 95% confidence interval (CI). The estimated relative risk and the 95% CI about the relative risk were provided using a stratified analysis. Hypotheses were tested using the Cochran-Mantel-Haenszel (CMH) test stratified by type of index event (DVT or PE with/without DVT). 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.

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For primary efficacy analyses, the CMH statistic was used to test the hypothesis. Superiority over placebo was to be claimed for a dose if the Hochberg adjusted p-value was ≤0.05 and the relative risk was <1. The analyses were supported by Kaplan-Meier curves. Sensitivity analyses were performed to assess robustness of the results of the primary efficacy analysis to missing data. The sensitivity analyses repeated the primary analysis by varying a hypothetical event rate in the missing data.

Point and interval estimates of the incidence rates of the secondary efficacy endpoints were calculated and reported. Relative risks of apixaban versus placebo (ratio of proportions) were reported for adjudicated composite of recurrent symptomatic VTE or VTE-related death and adjudicated composite of recurrent symptomatic VTE or CV-related death during the intended treatment period. Estimation was performed using analyses for binary endpoints.

Point estimates and 2-sided 95% CI for the proportion of subjects in each treatment group with an adjudicated major bleed as well as for the risk difference of each apixaban dose versus placebo (difference of proportions) were presented. The incidence of adjudicated clinically relevant non-major bleeding, the adjudicated composite of major and clinically relevant non-major bleeding, adjudicated minor bleeding, and adjudicated total bleeding were analyzed using the same method.

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

## RESULTS

**Subject Disposition and Demography**: A total of 2482 subjects were randomized to treatment and 2477 (99.8%) subjects received at least 1 dose of study medication (this is excluding data from Site [redacted] which was excluded due to audit findings). The demographic characteristics were balanced across the treatment groups. A total of 1663 subjects were aged <65 years, 490 subjects were aged 65 years to 75 years and 329 subjects were aged ≥75 years. The overall mean age was 56.7 years and 57.4% of the overall subjects were male. Most subjects were white (85.3%, overall). A total of 204 (8.2%) subjects were diagnosed with provoked VTE and 2275 (91.7%) subjects were diagnosed with unprovoked VTE.

Of the 2477 subjects treated, 840 received apixaban 2.5 mg, 811 received apixaban 5 mg, and 826 received placebo. A higher proportion of subjects in the apixaban 2.5 mg and 5 mg treatment groups (86.4% and 84.1%, respectively) completed 12 months of treatment compared to the placebo group (77.3%). A total of 431 (17.4%) subjects discontinued study treatment during the intended treatment period (these subjects were encouraged to remain in the study); 114 (13.6%) subjects were in the apixaban 2.5 mg treatment group, 129 (15.9%) subjects were in the apixaban 5 mg treatment group, and 188 (22.7%) subjects were in the placebo group. The most frequent reason for discontinuation was AEs (249 [10.0%] subjects). The proportion of subjects who discontinued due to AEs was similar in the apixaban 2.5 mg and 5 mg treatment groups (7.7% and 7.1%, respectively) and was

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higher in the placebo group (15.2%). This difference was primarily driven by recurrent VTE (0.6%, 1.0%, and 6.9% subjects discontinued due to AE of DVT; and 0.5%, 0.2%, and 2.2% subjects discontinued due to AE of PE in the apixaban 2.5 mg treatment group, apixaban 5 mg treatment group, and placebo group, respectively). All 2482 randomized subjects were included in the efficacy analysis and 2477 treated subjects were included in the safety analysis.

**Efficacy Results**:

Primary: The results of the primary efficacy analysis are presented in Table S1. There was a statistically significant reduction in adjudicated composite of symptomatic, recurrent VTE (nonfatal DVT or nonfatal PE) or all-cause death for both apixaban doses compared to placebo ($p<0.0001$). The proportion of subjects with an adjudicated composite of symptomatic, recurrent VTE (nonfatal DVT or nonfatal PE) or all-cause death rate was low in both the apixaban treatment groups compared to the placebo group (0.0381 and 0.0418 for the apixaban 2.5 mg treatment group and the apixaban 5 mg treatment group, respectively versus 0.1158 for the placebo group). Results of the 3 sensitivity analyses were consistent with the primary efficacy analysis. Results of the sensitivity analysis based on the assumption that 0% subjects with missing VTE/all-cause death would achieve the endpoint (analysis with imputation) are summarized in Table S1. Relative risk reductions for the 2.5 mg and 5 mg apixaban doses were 67% and 64%, respectively for imputed endpoints and were 76% and 81% for non-imputed endpoints.

The results of analyses of primary efficacy endpoints without imputation (only adjudicated events considered) were consistent with results with imputation. The incidence of a nonfatal DVT, nonfatal PE, VTE-related death, CV-related death and all-cause death was low in both the apixaban treatment groups compared to the placebo group. The adjudicated composite of symptomatic, recurrent VTE (nonfatal DVT or nonfatal PE) or all-cause death were also assessed by subgroups (index event type, gender, age, renal impairment, body mass index [BMI], weight, race, ethnicity and geographic region). The estimated relative risk was <1 for all subgroup analyzed.

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### Table S1. Analysis of Adjudicated VTE/All-Cause Death During the Intended Treatment Period (Randomized Subjects)

| Symptomatic VTE (Nonfatal DVT or nonfatal PE) / All-Cause Death | Apixaban 2.5 mg (N=840) | Apixaban 5 mg (N=813) | Placebo (N=829) |
|---|---|---|---|
| **Analysis (Adjudicated Events With Imputation for Missing Data[a])** | | | |
| n | 32 | 34 | 96 |
| Number of imputed events[b] | 13 | 20 | 19 |
| Event rate (95% CI)* | 0.0381 (0.0252, 0.0510) | 0.0418 (0.0281, 0.0556) | 0.1158 (0.0940, 0.1376) |
| Relative risk (95% CI)† | 0.3283 (0.2225, 0.4844) | 0.3615 (0.2475, 0.5281) | |
| p-value for superiority† | <0.0001 | <0.0001 | |
| Hochberg adjusted p-value for superiority‡ | <0.0001 | <0.0001 | |
| Risk difference (95% CI)§ | -0.0779 (-0.1032, -0.0526) | -0.0740 (-0.0997, -0.0482) | |
| p-value for superiority§ | <0.0001 | <0.0001 | |
| **Sensitivity Analysis[c] (Adjudicated Events Without Imputation)** | | | |
| n | 19 | 14 | 77 |
| Event rate (95% CI)* | 0.0226 (0.0126, 0.0327) | 0.0172 (0.0083, 0.0262) | 0.0929 (0.0731, 0.1126) |
| Relative risk (95% CI)† | 0.2422 (0.1476, 0.3975) | 0.1861 (0.1062, 0.3261) | |
| p-value for superiority† | <0.0001 | <0.0001 | |
| Hochberg adjusted p-value for superiority‡ | <0.0001 | <0.0001 | |
| Risk difference (95% CI)§ | -0.0707 (-0.0928, -0.0486) | -0.0751 (-0.0968, -0.0535) | |

* Event rate was calculated as n/N. CI for single event rate was calculated based on the Wald asymptotic confidence limits.

† Relative risk, risk difference, and associated CIs were based on stratified analyses with initial diagnosis as the stratification factor. Differences between treatment arms were assessed using the CMH test.

‡ Hochberg adjusted p-value for superiority was based on 2 hypotheses tests for apixaban 2.5 mg group comparing with placebo group and for apixaban 5 mg group comparing with placebo group.

§ Risk difference, CI, and p-value for superiority comparing each apixaban dose group with placebo group 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; N=Total number of subjects in respective group; PE=Pulmonary embolism; VTE=Venous thromboembolism.

a. Subjects with missing endpoint information were classified as having an event during the intended treatment period.

b. Number of imputed events was calculated by subtracting number of adjudicated events with imputation from the number of adjudicated events without imputation.

c. Sensitivity analysis was based on the assumption that 0% of subjects with missing VTE/all-cause death during the intended treatment period on apixaban and 0% of subjects on placebo would achieve the endpoint.

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Secondary: The incidence of a symptomatic, recurrent VTE (nonfatal DVT or nonfatal PE)/VTE-related death rate was lower in both the apixaban treatment groups compared to the placebo group (0.0321 and 0.0418 for the apixaban 2.5 mg treatment group and the apixaban 5 mg treatment group, respectively versus 0.1110 for the placebo group). Similarly, the incidence of a symptomatic, recurrent VTE (nonfatal DVT or nonfatal PE)/CV-related death rate was lower in both the apixaban treatment groups compared to the placebo group (0.0321 and 0.0418 for the apixaban 2.5 mg treatment group and the apixaban 5 mg treatment group, respectively versus 0.1146 for the placebo group).

Other adjudicated efficacy endpoints included nonfatal DVT, nonfatal PE, VTE-related death, CV-related death, and all-cause death; reductions in number of all events were observed for both apixaban doses compared to placebo. The results of analyses of other adjudicated endpoints without imputation were consistent with results with imputation.

**Pharmacokinetic, Pharmacodynamic, and Outcome Research Results**:

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

Outcome Research Results: There were more numbers of hospitalizations in the placebo group compared to the apixaban groups. The reason for the majority of hospitalizations in the placebo group was VTE.

**Safety Results**:

Primary and Secondary Safety Endpoint Results: Results of the primary safety endpoint (adjudicated major bleeding during the treatment periods) are presented in Table S2. There were no fatal bleeding events in any treatment arm. Overall, the number of major bleeding events was low; 2 events (both intra-ocular) in the apixaban 2.5 mg treatment group, 1 event (gastrointestinal) in the apixaban 5 mg treatment group, and 4 events (intra-ocular, intracranial, urogenital, and gastrointestinal) in the placebo group.

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

| | Apixaban 2.5 mg (N=840) | Apixaban 5 mg (N=811) | Placebo (N=826) |
|---|---|---|---|
| Major bleeding, n | 2 | 1 | 4 |
| Event rate (95% CI)* | 0.0024 (0.0000, 0.0057) | 0.0012 (0.0000, 0.0036) | 0.0048 (0.0001, 0.0096) |
| Relative risk (95% CI)† | 0.4850 (0.0891, 2.6391) | 0.2457 (0.0269, 2.2437) | |
| Hochberg adjusted p-value‡ | 0.3925 | 0.3551 | |

* Event rate was calculated as n/N. CI for event rate was calculated based on the Wald asymptotic confidence limits.
† Relative risk, risk difference, and associated CIs were based on stratified analyses with initial diagnosis as the stratification factor. Differences between treatment arms were assessed using the CMH test.
‡ Hochberg adjusted p-value for superiority was based on 2-hypotheses tests for apixaban 2.5 mg group comparing with placebo group and for apixaban 5 mg group comparing with placebo group.
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/ clinically relevant non-major bleeding, clinically relevant non-major bleeding, minor bleeding, and total bleeding. Adjudicated composite of major/ clinically relevant non-major bleeding was similar in the apixaban 2.5 mg and placebo groups but were numerically higher in the apixaban 5 mg group. Clinically relevant non-major bleeding, minor bleeding and total bleeding were similar in the apixaban 2.5 mg and placebo groups but higher in the apixaban 5 mg group. Results by index event strata were generally consistent with overall results.

Adverse Events and Serious Adverse Events:

The proportion of subjects with any AE with onset during the treatment period was similar across the treatment groups (71.0% in the apixaban 2.5 mg treatment group, 66.8% in the apixaban 5 mg treatment group, and 73.4% in the placebo group). Results were generally consistent in each index event strata (DVT and PE) with the overall findings.

The most frequently reported AEs (>5% in any treatment group) with onset during the treatment period were pain in extremity (5.2%, 6.4% and 6.5%, respectively, in the apixaban 2.5 mg treatment group, apixaban 5 mg treatment group and placebo group), back pain (3.2%, 5.5% and 2.9%, respectively, in the apixaban 2.5 mg treatment group, apixaban 5 mg treatment group and placebo group), headache (5.2%, 5.2% and 5.1%, respectively, in the apixaban 2.5 mg treatment group, apixaban 5 mg treatment group and placebo group), and DVT (1.8%, 2.1% and 7.5%, respectively, in the apixaban 2.5 mg treatment group, apixaban 5 mg treatment group and placebo group).

The majority of AEs in each treatment group was mild or moderate in severity. Severity was comparable across the treatment groups. Overall, 8.0% subjects in the apixaban 2.5 mg

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treatment group, 7.6% in the apixaban 5 mg treatment group and 9.1% in the placebo group experienced severe AEs. Overall, 1.4% subjects in the apixaban 2.5 mg treatment group, 1.5% in the apixaban 5 mg treatment group and 2.2% in the placebo group experienced very severe AEs. The most frequently reported (>1 subject in any treatment group) very severe AEs were pneumonia and metastatic neoplasm in the apixaban 2.5 mg treatment group, sudden death, death, myocardial infarction, and PE in the placebo group.

The number of treated subjects who discontinued due to AEs was lower in the apixaban groups (8.0% and 7.5% in the apixaban 2.5 mg and apixaban 5 mg treatment groups, respectively) compared to the placebo group (16.2%). The higher rate of discontinuation in the placebo group was primarily driven by recurrent DVT and PE.

There was a higher rate of SAEs in the placebo group (19.1%) compared to either active treatment group (13.3% and 13.2% in the apixaban 2.5 mg and apixaban 5 mg treatment groups, respectively). This difference was evident in both index event strata (DVT and PE). 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 low in all treatment groups (0.7% in the apixaban 2.5 mg treatment group, 1.4% in the apixaban 5 mg treatment group and 1.2% in the placebo group).

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<br>Preferred Term | Apixaban 2.5 mg (N=840), n (%) | Apixaban 5 mg (N=811), n (%) | Placebo (N=826), n (%) |
|---|---|---|---|
| Total subjects with an event (%) | 3 (0.4) | 4 (0.5) | 10 (1.2) |
| Cardiac disorders | 1 (0.1) | 2 (0.2) | 3 (0.4) |
| Cardio-respiratory arrest 0 | 0 | 1 (0.1) | 0 |
| Myocardial infarction 0 | 0 | 1 (0.1) | 0 |
| Cardiac arrest | 1 (0.1) | 0 | 1 (0.1) |
| Congestive cardiomyopathy | 0 | 0 | 1 (0.1) |
| Myocardial ischaemia | 0 | 0 | 1 (0.1) |
| General disorders and administration site conditions | 1 (0.1) | 2 (0.2) | 5 (0.6) |
| Multi-organ failure | 0 | 1 (0.1) | 0 |
| Sudden death | 0 | 1 (0.1) | 3 (0.4) |
| General physical health deterioration | 1 (0.1) | 0 | 0 |
| Death | 0 | 0 | 2 (0.2) |
| Renal and urinary disorders | 1 (0.1) | 0 | 0 |
| Renal failure acute | 1 (0.1) | 0 | 0 |
| Respiratory, thoracic and mediastinal disorders | 0 | 0 | 2 (0.2) |
| Pulmonary embolism | 0 | 0 | 2 (0.2) |

The denominator to calculate each percentage was the total number of treated subjects within each treatment group.
The AEs are sorted by SOC and PT in descending order of frequency in the apixaban 5 mg, then apixaban 2.5 mg treatment group.
Deaths: included all deaths that occurred from first dose through 30 days after the last dose of blinded study drug.
AE=Adverse event; n=Number of subjects with AE; N=Total number of subjects in respective group; PT=Preferred term; SOC=System Organ Class.

Adverse Events Related to Bleeding:

The percentage of subjects with any bleeding-related AE was 9.4% in the placebo and 11.8% in the apixaban 2.5 mg treatment groups and was lower in these groups than in the apixaban 5 mg treatment group (15.3%). This was evident in subjects with DVT or PE.

Adjudicated Adverse Events of Special Interest:

Adjudicated AEs of special interest included myocardial infarction, acute stroke (hemorrhagic, non-hemorrhagic, infarction with hemorrhagic conversion, and unknown type), and thrombocytopenia. Overall, the occurrence of all adjudicated events of special interest (myocardial infarction, acute stroke, and thrombocytopenia) was low and numerically lower in the apixaban treatment groups compared to the placebo group.

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Clinical Laboratory Evaluation:

Most frequently reported laboratory abnormalities were the presence of blood RBC, WBC and leucocyte esterase in urine, and decreased hemoglobin and absolute lymphocyte count. Laboratory findings were consistent across the treatment groups.

- Liver Function Tests: LFTs included AST, ALT, total bilirubin, and alkaline phosphatase (ALP). Elevations in LFTs during the treatment period were low (<3%) and similar across the treatment groups. There were 4 cases of ALT>3 x upper limit of normal (ULN) and total bilirubin >2 x ULN (1 in the apixaban 2.5 mg treatment group and 3 in the placebo group). The subject in apixaban 2.5 mg treatment group had comorbities that included cholangitis, pancreatitis, and cholelithiasis that required cholecystectomy.

- Platelet Count: Only 1 subject in the placebo group experienced a decreased platelet count ($<50 \times 10^9$ c/L) during treatment. A total of 21 subjects experienced a decreased platelet count ($<100 \times 10^9$ c/L) during treatment (11 subjects in the apixaban 2.5 mg treatment group, 4 subjects in the apixaban 5 mg treatment group, and 6 subjects in the placebo group).

- Creatine Kinase: A total of 24 subjects experienced an elevated creatine kinase (CK, >5 x ULN) during treatment (5 subjects in the apixaban 2.5 mg treatment group, 10 subjects in the apixaban 5 mg treatment group, and 9 subjects in the placebo group). A total of 9 subjects experienced an elevated CK (>10 x ULN) during the treatment period (2 subjects in the apixaban 2.5 mg treatment group, 6 subjects in the apixaban 5 mg treatment group, and 1 subject in the placebo group).

Vital Signs:

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

**Conclusions**:

- The benefit of both doses of apixaban was demonstrated by a statistically significant reduction compared to placebo ($p<0.0001$) in symptomatic, recurrent VTE (nonfatal DVT or nonfatal PE) or all-cause death.

- Both doses of apixaban demonstrated an acceptable bleeding profile with results in major and clinically relevant non-major bleeding not statistically different from placebo.