Name of Sponsor/Company: Bristol-Myers Squibb	Individual Study Table Referring to the Dossier	*(For National Authority Use Only)*
Name of Finished Product:		
Name of Active Ingredient: Apixaban		

SYNOPSIS

Final Clinical Study Report for Study CV185036

TITLE OF STUDY: A Phase 3 Randomized, Double-blind, Parallel-group, Multi-center Study of the Safety and Efficacy of Apixaban for Prophylaxis of Venous Thromboembolism (VTE) in Acutely Ill Medical Subjects During and Following Hospitalization

INVESTIGATORS/STUDY CENTERS: 302 study sites in 35 countries.

PUBLICATIONS: None

STUDY PERIOD: First Subject First Visit: 20-Jun-2007 **CLINICAL PHASE:** 3
Last Subject Last Visit: 18-May-2011

OBJECTIVES:

Primary Objective: To demonstrate that oral administration of apixaban 2.5 mg twice daily (BID) for 30 days reduces the rate of total VTE and VTE-related death compared to standard, subcutaneous (SC) administration of enoxaparin 40 mg once daily (QD) for a minimum period of 6 days, in subjects with acute medical illness.

Secondary Objectives:

The secondary efficacy objectives were:

- To demonstrate that oral administration of apixaban 2.5 mg BID is not inferior to SC administration of enoxaparin 40 mg QD for the prevention of total VTE and VTE-related death occurring up to the time of hospital discharge.
- To demonstrate that oral administration of apixaban 2.5 mg BID for 30 days reduces the rate of total VTE and all cause death compared to SC administration of enoxaparin 40 mg QD.
- To assess the effect of orally-administered apixaban 2.5 mg BID on the incidence and time to occurrence of symptomatic pulmonary embolism (PE) and symptomatic deep vein thrombosis (DVT).
- To assess the effect of orally-administered apixaban 2.5 mg BID on the rate of all-cause mortality at 30 and 90 days after randomization.

The secondary safety objectives were:

- To assess the effect of orally administered apixaban 2.5 mg BID for 30 days on the rate of major bleeding.

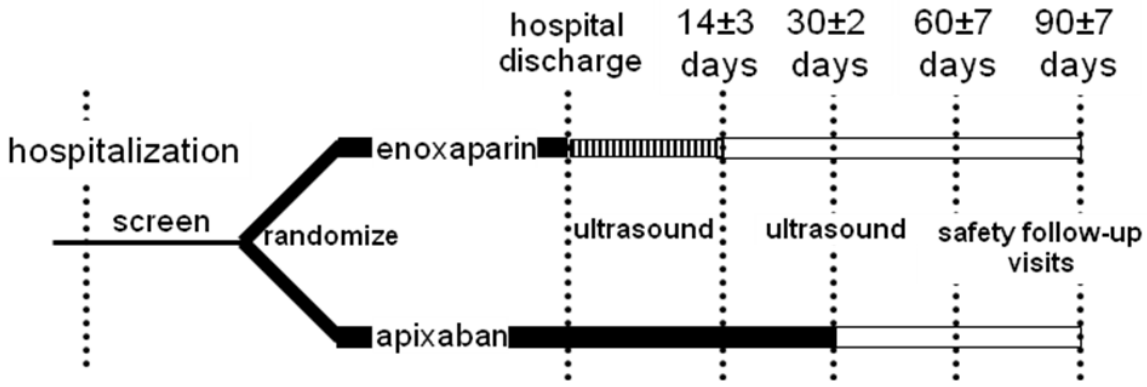
- To assess the effect of orally administered apixaban 2.5 mg BID for 30 days on the rate of clinically relevant non-major (CRNM) bleeding and on the composite of major bleeding and CRNM bleeding.
- To demonstrate that orally administered apixaban 2.5 mg BID for 30 days is generally safe and well tolerated in this patient population.

METHODOLOGY:

This was a Phase 3 randomized, double-blind, parallel-group, multi-center study of the safety and efficacy of apixaban for prophylaxis of VTE in acutely ill medical subjects during and following hospitalization.

Subjects were randomized (1:1) while in hospital to either SC enoxaparin 40 mg QD or oral apixaban 2.5 mg BID for 30 days. Subjects randomized to apixaban received SC injections of enoxaparin placebo QD while in hospital. Subjects randomized to enoxaparin received oral apixaban placebo tablets BID for 30 days.

The study included: (1) A screening period - selected hospitalized subjects not admitted for surgery or trauma, were eligible for inclusion if they had medical conditions and risk factors that are associated with an increased incidence of VTE. Subjects were eligible for randomization if they had been hospitalized for less than 72 hours and were expected to be hospitalized for an additional 3 or more days, were free of symptoms and signs of VTE and had not received standard prophylaxis against VTE for more than 3 days prior to randomization, and had severely or moderately restricted mobility. (2) A double-blind treatment period, starting with Day 1 (Randomization), followed by the Day of hospital discharge, Day 14 after randomization (telephone contact only), and Day 30. (3) A follow-up period with visits on Days 60 (± 7) and 90 (± 7).



While hospitalized, subjects were evaluated for symptomatic VTE (DVT and/or PE) and bleeding events. Following hospital discharge, subjects were to report all adverse events (AEs) including symptoms suggestive of DVT and/or PE and bleeding to the investigator. Suspected DVT and/or PE were evaluated using appropriate diagnostic assessment. A mandatory bilateral compression ultrasound (CUS) was performed on all subjects on the Day of Hospital Discharge and on Day 30 for detection of asymptomatic proximal DVT. Blood samples were obtained for routine clinical chemistry and hematology.

NUMBER OF SUBJECTS (Planned and Analyzed): The study was planned to randomize 6524 subjects (approximately 3262 subjects per treatment). The number of subjects enrolled was 6758, and the final number randomized was 6528 (apixaban 3255; enoxaparin 3273). A total of 6401 subjects (apixaban 3184; enoxaparin 3217) were treated with blinded study drug and 4495 subjects (apixaban: 2211; enoxaparin: 2284) were included in the primary efficacy data set.

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION: Males and females, including women of childbearing potential, over the age of 40 who had been hospitalized with congestive heart failure or acute respiratory failure, infection (without septic shock), acute rheumatic disorder, or inflammatory bowel disease, and had an expected hospitalization of an additional 3 or more days after randomization.

Other than subjects with congestive heart failure or respiratory failure, subjects must have had at least one additional risk factor for VTE including age ≥ 75, previous VTE, cancer, body mass index (BMI) ≥ 30, hormone therapy, chronic heart or respiratory failure. Subjects were not eligible if they had received more than 3 days of prophylaxis for VTE. Subjects with surgery in the past 30 days, conditions that required chronic anticoagulation, active bleeding or at high risk of bleeding were excluded.

TEST PRODUCT, DOSE AND MODE OF ADMINISTRATION, DURATION OF TREATMENT, BATCH NUMBERS: Apixaban, 2.5 mg oral tablets or matching placebo, administered BID for 30 days. Apixaban batch numbers were 6E17717, 7A28991, 7B29116, 7H25317, and 8B41849. Matching apixaban-placebo batch numbers were 6E18428, 7A28986, 7A29111, and 7C28811.

REFERENCE THERAPY, DOSE AND MODE OF ADMINISTRATION, DURATION OF TREATMENT, BATCH NUMBERS: Enoxaparin 40 mg SC or matching enoxaparin-placebo injections QD for duration of hospitalization (for a minimum of 6 days). Enoxaparin batch numbers were 19417, 19427, 6F21444, 6J19616, 6M08763, 7D21822, 7H25787, 7L29290, and 8F33265. Matching enoxaparin-placebo batch numbers were 6G20198, 6G20204, 6G20210, 6G20216, 6G20219, 6H13900, 7D24030, 7D24033, 7D24036, 7D24046, 7D24047, 7E31035, 7E31036, 7F30130, 7F30141, and 7H22703.

CRITERIA FOR EVALUATION: Within the analysis and reporting period, an Independent Central Adjudication Committee (ICAC) adjudicated all CUS, suspected symptomatic DVT and PE, major bleeding events, CRNM bleeding events, thrombocytopenia, acute myocardial infarction (MI), acute stroke and cause of death.

Efficacy Endpoints: The primary efficacy endpoint was the composite of adjudicated total VTE and VTE-related death during the Intended Treatment Period. This endpoint includes VTE-related death (fatal PE or a sudden death for which VTE cannot be excluded as a cause), nonfatal PE, symptomatic DVT, or asymptomatic proximal DVT detected by bilateral CUS.

The key secondary efficacy endpoint is the composite of adjudicated total VTE and VTE-related death during the Parenteral Treatment Period (the period that started on the first dose of parenteral study drug and ended the day after the last dose of parenteral study drug). Other efficacy endpoints were the following (if confirmed by adjudication): total VTE/all-cause death, proximal DVT/non-fatal PE/ all-cause death, proximal DVT/non-fatal PE/ VTE-related death, all-cause death, VTE related death, symptomatic VTE/all-cause death, symptomatic VTE/VTE related death, PE (fatal or non-fatal), non-fatal PE, symptomatic DVT, proximal DVT, symptomatic proximal DVT, asymptomatic proximal DVT, and symptomatic distal DVT.

Safety Endpoints: Bleeding was the primary safety endpoint, and included the following, if occurring during the Double-blind Treatment Period (1) adjudicated major bleeding events, (2) Composite of adjudicated major and CRNM bleeding events.

Secondary Safety Endpoints: AEs, vital signs, abnormal standard clinical laboratory test results, and events of special interest (adjudicated thrombocytopenia, adjudicated MI, adjudicated stroke, AEs related to liver function test [LFT] increases, and neurologic AEs).

STATISTICAL CONSIDERATIONS:

Sample size determination: With a total of 6524 randomized subjects allocated in a 1:1 ratio to apixaban or enoxaparin group, there was 90% power to demonstrate superiority for the primary efficacy endpoint at a one-sided 0.02498 level, if the true event rates were 2.5% and 4% in the apixaban and enoxaparin groups,

respectively. With a total of 6524 randomized subjects allocated in a 1:1 ratio to apixaban or enoxaparin group, there was 85% power to demonstrate non-inferiority for the key secondary efficacy endpoint at a one-sided 0.02498 level, if the true event rates were 1.6% and 2% in the apixaban and enoxaparin groups, respectively. The planned sample size of 6,524 subjects was based on an assumption that only 10% of subjects would not be evaluable for the primary endpoint.

Statistical testing strategy: In order to preserve type I error, the following statistical tests were run in sequence. First, superiority of apixaban versus enoxaparin on the primary efficacy endpoint was tested. To conclude superiority, the upper bound of the two-sided 95.004% confidence interval (CI) for the relative risk (RR) (p_a/ p_e) must be less than 1. This condition corresponds to a test of hypothesis H_0: $p_a=p_e$ against the alternative H_a: $p_a<p_e$ using the Mantel-Haenszel test stratified by status of previous VTE (yes, no) and active or previous cancer (yes, no) performed at the one-sided $\alpha=0.02498$ level. Here p_a and p_e represent the proportions of subjects with primary efficacy endpoints in the apixaban and enoxaparin groups, respectively.

If superiority of apixaban versus enoxaparin on the primary efficacy endpoint was demonstrated, then non-inferiority of apixaban versus enoxaparin on the key secondary efficacy outcome would be tested. To conclude non-inferiority, it is necessary to demonstrate that the apixaban event rate was not materially higher than the enoxaparin event rate, as measured by the RR (p_{as} / p_{es}), where p_{as} and p_{es} represent the proportions of subjects with key secondary efficacy endpoints in the apixaban and enoxaparin groups, respectively. The upper bound of the two-sided 95.004% CI for the RR (p_{as}/ p_{es}) must not exceed 1.43. The non-inferiority margin of 1.43 is intended to represent a difference that is clinically acceptable.

SUMMARY OF RESULTS:

Disposition, and Baseline Demographic and Disease Characteristics:

A total of 6758 subjects were randomized to active study drug. For randomized subjects, discontinuation rates from the Treatment Period were similar in both groups. Study discontinuation rates due to AEs were also similar for the apixaban and enoxaparin groups.

Baseline demographic characteristics were balanced between treatment groups (Table 1).

There were no clinically meaningful differences in the incidence or type of risk factors at baseline between the groups (Table 2). For the risk factors described in Table 2, and additional risk factors of acute respiratory failure, infection without septic shock, acute rheumatic disorder, and inflammatory bowel disease, the majority of the subjects overall (76.3%) had only 1 risk factor.

Exposure: The extent of exposure to double-bind study drug was similar for subjects in both treatment groups.

Table 1: Demographic Characteristics Summary at Baseline - Randomized Subjects

	Apix 2.5mg BID N = 3255	Enox 40mg QD N = 3273	Total N = 6528
AGE			
N	3255	3273	6528
MEAN	66.8	66.7	66.7
MEDIAN	68.0	67.0	67.0
MIN , MAX	40 , 101	40 , 98	40 , 101
Q1 , Q3	58.0 , 76.0	57.0 , 76.0	58.0 , 76.0
STANDARD DEVIATION	11.98	12.04	12.01
AGE CATEGORIZATION (%)			
<65	1401 (43.0)	1411 (43.1)	2812 (43.1)
>=65 AND <75	890 (27.3)	884 (27.0)	1774 (27.2)
>=75	964 (29.6)	978 (29.9)	1942 (29.7)
NOT REPORTED	0	0	0
GENDER (%)			
MALE	1626 (50.0)	1577 (48.2)	3203 (49.1)
FEMALE	1629 (50.0)	1696 (51.8)	3325 (50.9)
NOT REPORTED	0	0	0

The denominator to calculate each percentage is the total number of randomized subjects in the treatment group(s), overall or within each stratum

Table 2: Summary of Risk Factors at Baseline - Randomized Subjects

	Apix 2.5mg BID N = 3255	Enox 40mg QD N = 3273	Total N =6528
SUBJECTS WITH RISK FACTORS	1855 (57.0)	1846 (56.4)	3701 (56.7)
TYPE OF RISK FACTOR (%)			
PREVIOUS VTE	141 (4.3)	124 (3.8)	265 (4.1)
ESTROGENIC HORMONE THERAPY	49 (1.5)	27 (0.8)	76 (1.2)
HISTORY OF MALIGNANCY	312 (9.6)	320 (9.8)	632 (9.7)
ACTIVE OR TREATED CANCER	113 (3.5)	98 (3.0)	211 (3.2)
REMOTE CANCER	199 (6.1)	222 (6.8)	421 (6.4)
CHRONIC HEART FAILURE	1531 (47.0)	1537 (47.0)	3068 (47.0)
NYHA CLASS			
I	60 (1.8)	47 (1.4)	107 (1.6)
II	228 (7.0)	240 (7.3)	468 (7.2)
III	854 (26.2)	833 (25.5)	1687 (25.8)
IV	380 (11.7)	411 (12.6)	791 (12.1)
NOT REPORTED	9 (0.3)	6 (0.2)	15 (0.2)

The denominator to calculate each percentage is the total number of randomized subjects in the treatment group(s), overall or within each stratum

Efficacy Results: The superiority of apixaban for the primary efficacy endpoint (prevention of the composite endpoint of Total VTE and VTE-related Death during the Intended Treatment Period) was not demonstrated (two-sided p-value=0.44; Table 3).

For the key secondary efficacy endpoint (Total VTE and VTE-Related Death during the Parenteral Treatment Period), the event rates were 1.7% for apixaban and 1.6% for enoxaparin (Table 4). The RR was 1.06 with 95% CI of 0.69, 1.63. Formal testing of non-inferiority for the key secondary efficacy endpoint was not performed since the superiority of the primary efficacy endpoint was not demonstrated. There was a trend for fewer symptomatic DVTs in subjects randomized to apixaban, along with fewer overall efficacy events after the parenteral treatment period.

Table 3: Summary of Adjudicated Total VTE and VTE-related Death with Onset during the Intended Treatment Period - Primary Subjects

	Apix 2.5 mg BID N=2211	Enox 40 mg QD N=2284
TOTAL VTE/VTE-RELATED DEATH, n	60	70
EVENT RATE (%)	2.71	3.06
95% CI	(2.11, 3.49)	(2.43, 3.86)
RELATIVE RISK (APIX/ENOX)	0.87	
95.004% CI	(0.62, 1.23)	
95% CI	(0.62, 1.23)	
ADJ. RISK DIFFERENCE (%) (APIX-ENOX)	-0.39	
95% CI	(-1.37, 0.59)	
TWO-SIDED P-VALUE FOR SUPERIORITY TEST	0.4364	

* denotes that the result is statistically significant at the two-sided 0.04996 level.

Table 4: Summary of Adjudicated Total VTE and VTE-Related Death during the Parenteral Treatment Period - Key Secondary Subjects

	Apix 2.5 mg BID N=2485	Enox 40 mg QD N=2488
TOTAL VTE/VTE-RELATED DEATH, n	43	40
EVENT RATE (%)	1.73	1.61
95% CI	(1.28, 2.33)	(1.18, 2.19)
RELATIVE RISK (APIX/ENOX)	1.06	
95.004% CI	(0.69, 1.63)	
95% CI	(0.69, 1.63)	
ADJ. RISK DIFFERENCE (%) (APIX-ENOX)	0.10	
95% CI	(-0.61, 0.81)	

Safety Results:

Overall Safety Summary: The event rates for deaths, AEs, bleeding-related AEs, serious AEs, and discontinuations due to AEs were similar for both groups during the double-blind Treatment Period (Table 5).

Table 5: Summary of Safety During the Treatment Period - Treated Subjects

	Apix 2.5mg BID N = 3184	Enox 40mg QD N = 3217
AE (%)	1871 (58.8)	1910 (59.4)
SAE (%)	611 (19.2)	601 (18.7)
BLEEDING AE (%)	244 (7.7)	221 (6.9)
DISCONTINUATIONS DUE TO AE (%)	290 (9.1)	262 (8.1)
DEATHS (%)	131 (4.1)	133 (4.1)

The denominator to calculate each percentage is the total number of treated subjects within each treatment group

Bleeding Assessment: There were no fatal bleeding events in apixaban-treated subjects during the treatment period of this study; there were 2 cases of fatal bleeding in the enoxaparin group during the treatment period. The observed event rate for major bleeding was 0.47% in the apixaban group and 0.19% in the enoxaparin group with an adjusted difference of 0.29% (p=0.0437; Table 6). In addition, 2 subjects in the enoxaparin group had non-fatal intracranial bleeding during the treatment period.

Table 6: Summary of Bleeding Endpoints During the Treatment Period - Treated Subjects

	Apix 2.5mg BID N = 3184	Enox 40mg QD N = 3217
MAJOR BLEEDING, N	15	6
EVENT RATE (%)	0.47	0.19
95% CI	(0.28, 0.79)	(0.08, 0.42)
ADJ. DIFF OF EVENT RATES (APIX-ENOX) (%)	0.29	
95% CI	(0.01, 0.57)	
TWO-SIDED P-VALUE	0.0437	
CLINICALLY RELEVANT NON-MAJOR BLEEDING, N	72	61
EVENT RATE (%)	2.26	1.90
95% CI	(1.80, 2.84)	(1.48, 2.43)
ADJ. DIFF OF EVENT RATES (APIX-ENOX) (%)	0.36	
95% CI	(-0.33, 1.06)	
TWO-SIDED P-VALUE	0.3096	
MAJOR OR CLINICALLY RELEVANT NON-MAJOR BLEEDING, N	85	67
EVENT RATE (%)	2.67	2.08
95% CI	(2.16, 3.29)	(1.64, 2.64)
ADJ. DIFF OF EVENT RATES (APIX-ENOX) (%)	0.59	
95% CI	(-0.16, 1.33)	
TWO-SIDED P-VALUE	0.1227	
ALL BLEEDING, N	246	219
EVENT RATE (%)	7.73	6.81
95% CI	(6.85, 8.71)	(5.99, 7.73)
ADJ. DIFF OF EVENT RATES (APIX-ENOX) (%)	0.87	
95% CI	(-0.40, 2.14)	
TWO-SIDED P-VALUE	0.1780	

Adjusted difference of event rates takes the stratification factor into consideration: previous VTE (yes, no) and active or previous cancer (yes, no)

Adjudicated MI, stroke, and thrombocytopenia: Among treated subjects, the frequency of subjects with adjudicated MI or stroke was similar in the apixaban group (0.38%) and the enoxaparin group (0.37%) The frequency of subjects with adjudicated thrombocytopenia was in 0.19% the apixaban group and 0.09% in the enoxaparin group.

Hepatic Safety: The hepatic safety of apixaban was assessed by evaluating LFTs, including concurrent elevations of ALT >3x upper limit of normal (ULN) and total bilirubin >2xULN on the same date, and AEs. The cases of concurrent elevations of ALT >3xULN and total bilirubin >2xULN on the same date and/or hepatic SAEs of jaundice, hepatitis, or hepatic failure were assessed by an independent, blinded, panel of 3 hepatologists.

The hepatic safety findings are summarized below and in Table 7.

- Laboratory Values: The frequency of subjects with LFT elevations, including concurrent elevations of ALT >3xULN and total bilirubin >2xULN on the same date, was low, and similar in the apixaban and enoxaparin groups. The frequency of subjects with LFT elevations, including

concurrent elevations of ALT >3xULN, total bilirubin >2xULN, and ALP<2xULN on the same date was balanced between the 2 groups. Almost all cases had other potentially contributing factors, including concomitant medications. None of these cases with the specified LFT elevations on the same date were assessed as having possible or probable relationship to the study drug by the independent, blinded, panel of hepatologists.

- Liver-related AEs, SAEs (including deaths), and Discontinuations: The frequency of these events was low, and similar in the apixaban and enoxaparin groups.
- Other Events: A small number of the reviewed cases did not meet the criterion of concurrent elevations of ALT >3xULN and total bilirubin >2xULN on the same date. These cases were assessed by the independent, blinded, panel of hepatologists as these subjects had SAEs of hepatitis, jaundice, or hepatic failure; the relationship to the study drug was assessed as having a possible relationship to the study drug for 0 subjects in the apixaban group and 2 subjects in the enoxaparin group.

Table 7: Summary of Hepatic Safety of Apixaban During the Treatment Period - Treated Subjects with Available Measurements

	Apixaban 2.5 mg BID N=3184 n (%)	**Enoxaparin 40 mg QD N=3217 n (%)**
ALT>3xULN and TBili>2xULN	4 (0.1%)	5 (0.2)
ALT>3xULN and TBili>2xULN on same date	4 (0.1%)	4 (0.1)
Possible relationship per external hepatologists	2	1
Probable relationship per external hepatologists	0	0
ALT>3xULN and TBili>2xULN and ALP<2xULN on same date	0	1/2849 (<0.1)
Possible relationship per external hepatologists	0	0
Probable relationship per external hepatologists	0	0
Liver-related AEs, SAEs (including deaths), and Discontinuations (per liver SMQs)		
Liver-related AEs	127 (4.0)	142 (4.4)
Liver-related SAEs	9 (0.3)	12 (0.4)
SAEs with outcome of death	0	1 (<0.1)
Liver transplant	0	0
AEs leading to discontinuation	14 (0.4)	16 (0.5)
SAEs of hepatitis, jaundice, and liver failure for subjects who did not meet the criteria for ALT>3xULN and TBili>2xULN on same date	5	8
Possible relationship per external hepatologists	0	2
Probable relationship per external hepatologists	0	0

Note: The denominator to calculate percentages for each event is the total number of treated subjects with available laboratory results associated with that event and treatment group
Note: AE = adverse event; ALP = alkaline phosphatase; ALT = alanine aminotransferase; BID = twice daily; SAE = serious adverse event; SMQ = standardized MedDRA query; TBili = total bilirubin; ULN = upper limit of normal.

Neurologic safety: Overall, no evidence of a neurological safety issue was identified in apixaban-treated subjects in this study; 1 GBS case was reported in the apixaban group but a blinded assessment by external neurologists determined this event to be unlikely related to study drug. Neurologic AEs occurred with similar frequency in the 2 treatment groups; 45 (1.4%) in the apixaban group and 42 (1.3%) subjects in the enoxaparin group. Preferred terms associated with neurologic AEs were reported in <1% of subjects in each treatment group. The frequency of neurologic AEs was similar for the overall apixaban and enoxaparin populations and the treatment strata within these treatment groups. Serious neurological events occurred infrequently in both treatment groups (5 subjects in the apixaban group and 1 subject in the enoxaparin group) and were similar for the overall apixaban and enoxaparin treatment groups. Discontinuations related to neurological AEs were infrequent in the apixaban and enoxaparin groups.

CONCLUSIONS:

- This study did not demonstrate superiority of apixaban 2.5 mg BID over enoxaparin 40 mg QD followed by placebo for the prevention of the composite endpoint of Total VTE/VTE-Related death at 30 days. The RR of apixaban versus enoxaparin was 0.87% with 95% CI of 0.62, 1.23.
- For the key secondary efficacy endpoint of composite of adjudicated total VTE and VTE-related death during the Parenteral Treatment that compared the head-to-head treatment with apixaban vs. enoxparin, the event rates were 1.7% and 1.6%, respectively. The RR was 1.06 with 95% CI of 0.69, 1.63. Formal testing of non-inferiority for the key secondary efficacy endpoint was not performed since the superiority of the primary efficacy endpoint was not demonstrated.
- For subjects who did not have an efficacy event in the Parenteral Treatment Period, there were fewer events observed in the post-parenteral period in subjects who were randomized to apixaban. The difference was consistent with results observed for Total VTE/VTE-related death, symptomatic VTE, and asymptomatic proximal DVT.
- Overall, the observed event rates for major bleeding in the 2 treatment groups were low. Observed event rate of major bleeding in apixaban 2.5 mg BID group was higher than that in the enoxaparin 40mg QD group. Observed event rates for the composite of major and CRNM bleeding, all bleeding and bleeding AEs were also numerically higher in apixaban 2.5 mg BID group.
- Among the safety endpoints of AEs, SAEs, deaths, and discontinuations due to AEs, results for subjects treated with apixaban 2.5 mg BID appeared to be similar to those for subjects treated with enoxaparin 40 mg QD. The number of subjects with MI, stroke or thrombocytopenia was low and similar between the 2 treatment groups.
- Among subjects treated with apixaban in this study, a favorable liver safety profile was observed and the results do not suggest a hepatic safety signal.

DATE OF REPORT: 22-Nov-2011