BRISTOL-MYERS SQUIBB COMPANY

APIXABAN

Clinical Study Report for Study CV185017

A PHASE 2 RANDOMIZED, PARALLEL-ARM STUDY OF ORAL DIRECT FACTOR Xa-INHIBITOR APIXABAN AND LOW MOLECULAR WEIGHT HEPARIN, OR FONDAPARINUX WITH A VITAMIN K ANTAGONIST IN SUBJECTS WITH ACUTE SYMPTOMATIC DEEP VEIN THROMBOSIS

Indication:	Deep Vein Thrombosis
Phase:	2
Study Initiation Date:	First Subject First Visit: 01-Dec-2005
Study Completion Date:	Last Subject Last Visit: 26-Feb-2007
Report Date:	3-Dec-2007
Document Control Number:	930024518
Previous Version(s) of this Report:	None

THIS STUDY WAS CONDUCTED IN ACCORDANCE WITH GOOD CLINICAL PRACTICE

Sponsor's Responsible Medical Officer:

[redacted]

Study Director:

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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:		

SYNOPSIS

Clinical Study Report for Study CV185017

TITLE OF STUDY: A Phase 2 Randomized, Parallel-Arm Study of Oral Direct Factor Xa-Inhibitor Apixaban and Low Molecular Weight Heparin, or Fondaparinux With a Vitamin K Antagonist in Subjects With Acute Symptomatic Deep Vein Thrombosis

INVESTIGATORS/STUDY CENTERS: 64

PUBLICATIONS: None

STUDY PERIOD: Study Initiation Date: 01-Dec-2005 **CLINICAL PHASE:** 2

Study Completion Date: 26-Feb-2007

OBJECTIVES: To assess the efficacy and safety of 3 doses of apixaban (5 mg twice daily [BID], 10 mg BID, and 20 mg once daily [QD]) versus conventional treatment with low molecular weight heparin (LMWH) or fondaparinux and vitamin K antagonist (VKA) in the treatment of subjects with acute deep vein thrombosis (DVT) and to determine the optimal dose and regimen of apixaban for use in Phase 3.

METHODOLOGY: This was a Phase 2, multicenter, randomized, parallel-group study of the efficacy and safety of apixaban and conventional therapy with LMWH or fondaparinux and VKA in subjects with confirmed acute proximal or extensive calf-vein thrombosis that involved the upper third part of the calf veins (trifurcation area), without concomitant symptomatic pulmonary embolism (PE). Subjects were randomized to 1) double-blind treatment with oral apixaban 5 mg BID, 2) double-blind treatment with oral apixaban 10 mg BID, 3) double-blind treatment with oral apixaban 20 mg QD, or 4) open-label subcutaneous treatment with LMWH (only enoxaparin or tinzaparin) or fondaparinux with VKA (only warfarin, phenprocoumon, or acenocoumarol), given per label requirements as per standard of care (LMWH/fondaparinux/VKA group). No subjects received fondaparinux during the study; therefore, the comparator will be designated LMWH/VKA.

The study included 1) a Screening Period of up to 24 hours before randomization, 2) a 12-week Treatment Period with double-blind apixaban or open-label LMWH/VKA, and 3) a 30-day Follow-up Period, as shown below:

<table>
<tr><th>Screening Period</th><th colspan="2">Treatment Period</th><th>Follow-up Period</th></tr>
<tr><td>≤ 24 Hours Before Randomization</td><td colspan="2">12 Weeks (Day 1 Through Day 84 - 91)</td><td>30 Days</td></tr>
<tr><td rowspan="3"></td><td>Baseline ultrasound and perfusion lung scan obtained ≤ 36 hours after randomization</td><td>Repeat ultrasound and perfusion lung scan at Week 12 (Days 84 - 91)</td><td rowspan="3"></td></tr>
<tr><td colspan="2">Randomization to 1 of 4 groups:</td></tr>
<tr><td colspan="2">• Double-blind oral apixaban 5 mg BID
• Double-blind oral apixaban 10 mg BID
• Double-blind oral apixaban 20 mg QD
• Open-label LMWH and VKA</td></tr>
</table>

Pre-randomization treatment with therapeutic doses of unfractionated heparin (UFH), LMWH, or fondaparinux was allowed for up to a maximum of 24 hours. In addition, a single, pre-randomization starting dose of VKA was also allowed.

A bilateral venous compression ultrasound (CUS) of the legs and a perfusion lung scan (PLS) were obtained within 36 hours after randomization and at Week 12. During the 12-week Treatment Period, visits were scheduled on Day 1, Day 7 ± 1 (Week 1; phone), Day 14 ± 1 (Week 2; phone), Day 21 ± 3 (Week 3; visit), Day 35 ± 3 (Week 5; phone), Day 49 ± 4 (Week 7; visit), Day 63 ± 4 (Week 9; phone), and Day 84 to 91 (Week 12; visit). A follow-up phone interview was conducted with each subject at Week 16 (end of 30-day Follow-up Period). Subjects who were not treated or who prematurely discontinued from the study were to be seen at the end of the 12-week Treatment Period or at the investigator's discretion. The Treatment Period was followed by a 30-day Follow-up Period regardless of the duration of study drug administration.

NUMBER OF SUBJECTS (Planned and Analyzed): The study was planned to include approximately 520 subjects (approximately 130 subjects per treatment group). A total of 520 subjects were randomized: 130 to the apixaban 5 mg BID group, 134 to the apixaban 10 mg BID group, 128 to the apixaban 20 mg QD group, and 128 to the LMWH/VKA group. A total of 511 subjects were treated with study drug and 476 subjects were included in the primary efficacy analysis.

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION: Males and females of any race, aged 18 (or legal age of consent) to 90 years, who had a confirmed acute proximal or extensive calf-vein thrombosis that involved at least the upper third part of the calf veins (trifurcation area), without concomitant symptomatic PE were eligible. Subjects were to have no active bleeding and were not to be at high risk for bleeding or to have any other history that would have contraindicated treatment with LMWH or VKA.

TEST PRODUCT, DOSE AND MODE OF ADMINISTRATION, DURATION OF TREATMENT, BATCH NUMBERS: Apixaban 2.5 or 10 mg tablets and matching placebo for each were supplied in blister packs. Subjects took 4 tablets orally in the morning and 4 tablets orally in the evening; the 4 tablets were a combination of active and placebo tablets such that a dose of 5 mg BID, 10 mg BID, or 20 mg QD of apixaban was taken daily for 12 weeks. The apixaban tablets were taken from the following batch numbers: 4K90273 and 4K92189. Matching placebo batch numbers: 4L75632 and 4L75638.

REFERENCE THERAPY, DOSE AND MODE OF ADMINISTRATION, DURATION OF TREATMENT, BATCH NUMBERS: The choice of LMWH (tinzaparin or enoxaparin) or fondaparinux and the choice of the VKA (warfarin, acenocoumarol, or phenprocoumon) were at the investigator's discretion. However, no subject received fondaparinux. Dosages were as follows: tinzaparin, 175 IU/kg QD subcutaneously or enoxaparin, 1.5 mg/kg QD or 1.0 mg/kg BID subcutaneously. The minimum duration of treatment with LMWH was 5 calendar days. The VKA dosages were to be adjusted to maintain the international normalized ratio (INR) within the therapeutic range (target, 2.5; range, 2.0 - 3.0). Treatment with VKA was continued for 12 weeks. The LMWH and VKA were obtained commercially by the sites with the exception of sites in Poland, where comparator drug was provided by BMS. BMS batch numbers for the open-label LMWH/VKA treatment: 6B18493 and 6B14872.

CRITERIA FOR EVALUATION:

Efficacy:

Primary efficacy measure:

Composite of symptomatic recurrent venous thromboembolism (VTE) (ie, recurrent DVT or fatal or non-fatal PE) and deterioration (increase) of thrombotic burden as assessed by repeat bilateral CUS and PLS.

Secondary efficacy measures:

- Symptomatic DVT and
- Symptomatic PE (fatal or non-fatal) and
- Deterioration, improvement, and no relevant change on proximal thrombus based on CUS and
- Deterioration, improvement, and no relevant change on composite lung thrombus score based on PLS

The Central Independent Adjudication Committee (CIAC) adjudicated all suspected thromboembolic complications, deaths, baseline and repeat CUS and PLS, and episodes of suspected bleeding.

Safety: The primary safety measure was the composite of major and clinically relevant non-major (CRNM) bleeding as adjudicated by CIAC. Additional bleeding-related safety measures were the individual components of major and CRNM bleeding, in addition to bleeding-related adverse events. Safety was also assessed via the review of all reported adverse events (AE) and laboratory test results.

All adverse events (AEs) were listed and summarized by preferred term and system organ class, using the Medical Dictionary for Regulatory Activities (MedDRA). The primary analysis of safety included AEs during the "Treatment Period" which refers to the period from first administration of study drug to 2 days (or 30 days for SAEs only) after the last administration of the study drug.

Pharmacokinetics: Plasma concentration results collected on Weeks 3 and 12 were pooled for peak and trough summary statistics and concentration versus time plots. The time after last dose for each plasma concentration result was derived as the difference in time and date between the last active dose and each individual sample collection. For the 20 mg QD dose group the time since last active apixaban dose could not be unambiguously distinguished from time since last placebo dose. Therefore, the data from the 20 mg QD dose group was excluded from any plots and summaries involving time since last active dose.

Pharmacodynamics: Data from all four treatment groups were included in the pharmacodynamic (PD) analyses. Summary statistics were tabulated for modified prothrombin time (mPT), anti-Xa activity, D-dimer, prothrombin fragment F1.2 (F1.2), and thrombin-antithrombin III (TAT) complex. Box plots of D-dimer, F1.2 and TAT were generated by treatment group and week. Individual anti-Xa and mPT values were plotted versus apixaban plasma concentration.

STATISTICAL CONSIDERATIONS: No statistical testing was planned or performed. The 95% confidence intervals (CI) for the difference in the event rate of the primary efficacy measures between each apixaban regimen and the LMWH/VKA regimen were calculated.

For secondary efficacy measures, point estimates of these event rates with 95% CIs were presented for each treatment group.

SUMMARY OF RESULTS:

Disposition, Demographics, and Other Pertinent Baseline Characteristics:

Baseline demographics for all randomized subjects were similar among the apixaban and LMWH/VKA groups (Table 1). The discontinuation rates overall were higher in the apixaban 5 mg BID and 20 mg QD groups (13.1% and 16.4%, respectively) compared to either the apixaban 10 mg BID or comparator treatment group (9% and 7.8%, respectively). Discontinuation rates due to AEs were also higher in the apixaban 5 mg BID and 20 mg QD treatment groups. These findings were expected as the standard of care is VKA, and the comparator arm was open label, resulting in fewer discontinuations in that treatment arm.

Differences in baseline disease characteristics between apixaban treatment groups and the LMWH/VKA group were not considered to have an impact on the overall outcome of the study. On entry, 25% of all apixaban subjects and ~24% of comparator subjects had previous VTE. Twenty-six (6.6%) apixaban subjects and 11 (8.6%) comparator subjects had been diagnosed with cancer prior to randomization.

Table 1: Subject Disposition and Demographics

	Apixaban BID 5 mg (N= 130)	**Apixaban BID 10 mg (N=134)**	**Apixaban QD 20 mg (N= 128)**	**LMWH/Fond and VKA (N=128)**
Subjects treated: n, (%)	128 (98.5)	133 (99.3)	124 (96.9)	126 (98.4)
Subjects completing the double-blind period: n, (%)	113 (86.9)	122 (91.0)	107 (83.6)	118 (92.2)
Subjects Discontinued n, (%)	17 (13.1)	12 (9.0)	21 (16.4)	10 (7.8)
Reason for Discontinuation n, (%)				
Adverse Event	9 (6.9)	5 (3.7)	11 (8.6)	4 (3.1)
Subject withdrew Consent	4 (3.1)	1 (0.7)	3 (2.3)	1 (0.8)
Death	1 (0.8)	0	0	0
Subject no longer meets study criteria	0	2 (1.5)	2 (1.6)	1 (0.8)
Lost to follow-up	0	1 (0.7)	0	0
Poor/Non-Compliance	0	0	1 (0.8)	0
Lack of Efficacy	1 (0.8)	2 (1.5)	1 (0.8)	1 (0.8)
Other	2 (1.5)	1 (0.7)	3 (2.3)	3 (2.3)
Age: mean (min, max)	56.4 (18, 89)	58.5 (21, 86)	60.3 (24, 88)	59 (20, 89)
Gender: n, (%) male	83 (63.8)	76 (56.7)	83 (64.8)	81 (63.3)
Race: n, (%) White	125 (96.2)	131 (97.8)	120 (93.8)	125 (97.7)
Black	5 (3.8)	1 (0.7)	5 (3.9)	3 (2.3)
Asian	0	0	2 (1.6)	0
Other	0	2 (1.5)	1 (0.8)	0

Efficacy Results:

Primary Efficacy Objectives

Primary Endpoint:

Composite of Adjudicated Symptomatic VTE/Deterioration: Events were infrequent across all treatment groups (Table 2). The differences in rates between the apixaban and the LMWH/VKA treatment groups were not statistically significant (95% CIs for the difference included zero). The apixaban 20 mg QD arm had a lower incidence of symptomatic recurrent VTE/deterioration than the remaining treatment groups (apixaban and comparator).

Secondary Endpoint:

Individual Components of Symptomatic Recurrent VTE/Deterioration: The number of symptomatic recurrent DVT or PE was low and the rates were similar across apixaban treatment arms and comparator. Similar results for all dose groups were also observed for deterioration of the thrombotic burden as assessed by repeat bilateral CUS and/or PLS. Improvement (assessed by CUS) was observed in >70% of subjects in each apixaban treatment arm compared with ~65% of subjects in the LMWH/VKA group. Improvement (assessed by PLS) was observed in ~37-40% of subjects in each apixaban treatment arm compared with ~44% of subjects in the LMWH/VKA group.

Secondary Efficacy Objectives

No secondary objectives were defined for this study.

Table 2: Summary of Symptomatic Recurrent VTE/Deterioration during the Treatment Period -- Primary Subjects

	APIX BID 5mg (N=117)	APIX BID 10mg (N=125)	APIX QD 20mg (N=116)	Any APIX (N=358)	LMWH/Fond and VKA (N=118)
Symptomatic Recurrent VTE / Deterioration, n	7	7	3	17	5
Event rate (%)	6.0	5.6	2.6	4.7	4.2
95% CI	(2.4, 11.9)	(2.3, 11.2)	(0.5, 7.4)	(2.8, 7.5)	(1.4, 9.6)
Individual Components *					
Fatal PE, n	0	0	1	1	0
Non-Fatal PE, n	0	0	0	0	1
Symptomatic Recurrent DVT, n	3	4	1	8	2
Deterioration, n	4	3	1	8	2
Comparisons to Control Group					
Difference (%) (APIX - LMWH)	1.7	1.4	-1.7		
95% CI	(-4.4, 8.2)	(-4.6, 7.5)	(-7.3, 3.6)		
No Change, n **	21	16	22	59	18
Event rate (%)	17.9	12.8	19.0	16.5	15.3
95% CI	(11.5, 26.1)	(7.5, 20.0)	(12.3, 27.3)	(12.8, 20.7)	(9.3, 23.0)
Improvement, n ***	89	102	91	282	95
Event rate (%)	76.1	81.6	78.4	78.8	80.5
95% CI	(67.3, 83.5)	(73.7, 88.0)	(69.9, 85.5)	(74.2, 82.9)	(72.2, 87.2)

*. Intent-to-treat analysis. If a subject has multiple events, only the most severe one will be counted. Individual components are presented in decreasing order of severity.
**. If a subject does not have a recurrent VTE, and the results from his/her ultrasound tests are normal, and perfusion lung scan results are normal or no relevant change, then the subject is categorized as 'no change' on the primary endpoint
***. If a subject does not have a recurrent VTE, and the results from his/her perfusion lung scan and ultrasound tests have at least one improvement and no deterioration, then the subject is categorized as 'Improvement' on the primary endpoint.

Safety Results:

Adjudicated Bleeding Events:

For the composite of major bleeding and clinically relevant non-major (CRNM) bleeding the event rates during both the treatment period and the intended treatment period were comparable across all treatment groups with the apixaban 10 mg BID treatment group having the lowest observed rate (Table 3).

Major bleeding events occurred infrequently with only one event occurring in each of the apixaban 5mg BID and 20 mg QD treatment groups during the treatment period. No major bleeding events were observed in the LMWH/VKA arm.

Bleeding rates (based on all adjudicated bleeds) during the treatment period were lower in each of the apixaban treatment groups than in the comparator group.

Adjudicated bleeding was also summarized by reported cancer status at baseline. The results for treated subjects without reported active cancer at baseline were qualitatively similar to those for the overall population.

For the composite of major bleeding and clinically relevant non-major (CRNM) bleeding in the follow-up period, the event rates were lower in the 5 mg BID and 10 mg BID apixaban treatment groups than in either the apixaban 20 mg QD or comparator dose groups. Major bleeding events occurred infrequently in follow-up with only one event occurring in each of the apixaban 20 mg QD and comparator treatment groups. No apixaban dose-dependent bleeding (all adjudicated bleeding) was evident in the follow-up period.

AEs:

The incidence of bleeding-related adverse events during the treatment period was lower in all apixaban treatment groups as compared to the LMWH/VKA treatment group (Table 4). Haematuria and haematoma were the only bleeding-related AEs that were experienced by > 3% of subjects in any treatment group during the treatment period.

The incidences of AEs were similar across all treatment groups with lower rates observed in the apixaban 10 mg BID group and higher rates observed in the apixaban 20 mg QD group. With the exception of rates for all apixaban-treated subjects for nervous system and psychiatric system disorders (14.0% and 3.1%, respectively), which were higher compared to comparator (6.3% and 0.8%, respectively), the incidences of AEs by system organ class were comparable for all treatment groups. There were no obvious dose-dependent increases in event rates.

Death: One death (suicide) occurred while the subject was actively taking study drug, and 2 deaths occurred within 30 days after cessation of drug treatment; therefore, there were 3 deaths included in the counting of on-treatment events. An additional 5 deaths occurred between 31-87 days following discontinuation of apixaban, for a total of 8 deaths reported in study CV185017. All occurred in apixaban-treated patients, and none of the deaths were considered by the investigator to be related to study drug.

SAEs: During the treatment period (from first dose of study drug up to 30 days after the last dose of study drug) SAEs were reported in 47 of 385 (12.2%) treated subjects in the apixaban group, and 16 of 126 (12.7%) treated subjects in the LMWH/VKA treatment group.

Rates for SAEs in the nervous system and psychiatric system disorders for the apixaban 5 mg BID and 20 mg QD treated subjects were higher than observed for either apixaban 10 mg BID or comparator treatment groups. The incidence of SAEs for other system organ class events was comparable for all treatment groups. There were no obvious dose-dependent increases in event rates. With the exception of dizziness (1.6%) in the 20 mg QD apixaban group, no SAE preferred term was observed in >1% of subjects.

Seven (1.8%) and 3 (2.3%) subjects in the all-apixaban and comparator groups, respectively, were diagnosed with cancer reported as an SAE during the course of the study.

There were 2 reported SAEs related to liver function test (LFT) elevation (>2xULN alkaline phosphatase and >5xULN ALT/AST), both in subjects treated with 20 mg QD apixaban. These were SAEs of mild to moderate intensity and required no treatment. The elevated ALP was considered by the investigator to be unrelated to study drug and resolved. The elevated ALT/AST, although considered by the investigator to be possibly related to study drug, upon hospital discharge, was considered to be due to an allergy associated with antibiotic treatment, and the event resolved.

There was 1 incident of cerebral hemorrhage and 1 of ischemic stroke, both in the apixaban 20 mg QD group, and both considered unrelated to study drug.

SAEs considered drug related occurred with greater frequency in the 20 mg QD apixaban group (6.5%) compared with either the 5 mg BID group (1.6%) or 10 mg BID group (0.8%), and with comparable frequency compared to the LMWH/VKA group (4.8%).

Adverse Events Leading to Discontinuation of Study Therapy:

Relative to the LMWH/VKA group, the frequency of discontinuations due to AEs was higher in the 5 mg BID and 20 mg QD apixaban treatment groups. Nine (9) of 128 (7.0%), 6 of 133 (4.5%), 11 of 124 (8.9%), and 5 of 126 (4.0%) in the 3 apixaban and LMWH/VKA treatment groups, respectively, discontinued study drug during the treatment period due to AEs. Only dizziness (2/124, apixaban 20 mg QD) caused discontinuation from study drug for more than 1 subject in any treatment arm.

Given the open label design of this Phase 2 trial and the lack of suitable alternatives for VKA, the low discontinuation rate in the LMWH/VKA treatment group was not unexpected.

Clinical Laboratory Evaluation: With the exception of higher frequencies in the 20 mg QD apixaban and comparator groups for low hemoglobin (4.3% and 4.8%, respectively) and higher alkaline phosphatase (4.2%) levels in the 20 mg QD apixaban group, the incidences of laboratory values that met the criteria for MA were comparable among the apixaban and LMWH/VKA groups.

Mean hemoglobin levels for all treatment groups were relatively unchanged throughout the course of the study. The percentage of apixaban-treated subjects with a decrease to abnormally low hemoglobin was very low (~1-3%) and was comparable across the dose groups. A higher percentage of comparator subjects (~6-8%) displayed a decrease to abnormally low hemoglobin at some point throughout the study. There was no apparent increase in the frequency of change to abnormally low hemoglobin with increasing time of exposure for any treatment group.

Throughout the study the number of subjects with low platelet count was low. There were 2 apixaban-treated subjects and no comparator subjects with a post-dose platelet count decreased from baseline to $<100{,}000/mm^3$. There were no SAEs of thrombocytopenia.

Overall, no other clinically significant laboratory test results or vital sign findings were noted for the apixaban or comparator treatment groups.

No subject in any treatment group having a concomitant elevation of total bilirubin>2xULN and ALT>3xULN. The incidence of elevations >3x ULN in liver transaminases (ALT or AST) at any time after the start of study drug was low and comparable among the apixaban and LMWH/VKA groups.

The frequency of patients with High ALT identified as a Marked Laboratory Abnormality (>3xULN) was low and comparable to or lower than that observed for the comparator. No discontinuations due to ALT or AST elevation(s) were reported.

There were 6 AEs of elevated CK in the apixaban groups: 5 mg BID (2); 20 mg QD (4). There was 1 AE of elevated CK in the open-label LMWH/VKA group. The 2 incidences in the 5 mg BID group were considered MA (CK>5x ULN) and 2/4 incidences in the 20 mg QD group were considered a MA. The 1 AE of elevated CK in the LMWH/VKA group was not a MA. In all patients with elevated CK, CK-MB

isoenzymes were normal. No SAEs were reported in association with these CK elevations. There were no reports of rhabdomyolysis or other significant renal abnormalities.

Table 3: Summary of Bleeding Events Confirmed by Adjudication during the Treatment Period -- All Treated Subjects

	APIX BID 5mg (N= 128)	APIX BID 10mg (N= 133)	APIX QD 20mg (N= 124)	Any APIX (N= 385)	LMWH/Fond and VKA (N= 126)
Major Bleeding or Clinically Relevant Non-major Bleeding, n	11	6	9	26	10
Event Rate (%)	8.6	4.5	7.3	6.8	7.9
95% CI	(4.4, 14.9)	(1.7, 9.6)	(3.4, 13.3)	(4.5, 9.7)	(3.9, 14.1)
Major Bleeding*, n	1	0	1	2	0
Event Rate (%)	0.8	0.0	0.8	0.5	0.0
95% CI	(0.0, 4.3)	(0.0, 2.7)	(0.0, 4.4)	(0.1, 1.9)	(0.0, 2.9)
Clinically Relevant Non-major Bleeding*, n	10	6	8	24	10
Trivial Bleeding*, n	3	11	4	18	10
All Bleeding**, n	14	17	13	44	20
Event Rate (%)	10.9	12.8	10.5	11.4	15.9
95% CI	(6.1, 17.7)	(7.6, 19.7)	(5.7, 17.3)	(8.4, 15.0)	(10.0, 23.4)

*. If a subject has multiple events, only the most severe one will be counted.
**. All bleeding is a composite of major bleeding, clinically relevant non-major bleeding, and trivial bleeding.

Table 4: Adverse Events Summary during the Treatment Period -- All Treated Subjects

	APIX BID 5mg N = 128	APIX BID 10mg N = 133	APIX QD 20mg N = 124	Any APIX N = 385	LMWH/Fond and VKA N = 126
AE, Total subjects, n(%)	77 (60.2)	72 (54.1)	82 (66.1)	231 (60.0)	72 (57.1)
SAE, n(%)	16 (12.5)	11 (8.3)	20 (16.1)	47 (12.2)	16 (12.7)
Bleeding AE, n(%)	15 (11.7)	17 (12.8)	13 (10.5)	45 (11.7)	24 (19.0)
Related AE, n(%)	28 (21.9)	29 (21.8)	32 (25.8)	89 (23.1)	33 (26.2)
Death, n(%)	2 (1.6)	0	1 (0.8)	3 (0.8)	0
Discontinuation due to AE, n(%)	9 (7.0)	6 (4.5)	11 (8.9)	26 (6.8)	5 (4.0)

All non-serious AEs occurring from the first dose of study drug through 2 days after the last dose of study drug and all SAEs and death occurring from first dose of study drug through 30 days after the last dose of study drug will be included in the tabulation

Pharmacokinetic Results: There was a dose-related increase in apixaban plasma concentrations for the apixaban 5 mg and 10 mg BID treatment groups. Peak and trough apixaban concentrations appeared generally comparable to those obtained in normal healthy volunteers.

Pharmacodynamic Results: Administration of apixaban was associated with dose- and concentration-dependent increases in plasma anti-Xa activity and in the clotting time parameter mPT, consistent with the expected effects of a direct FXa inhibitor. The relative increases in anti-Xa activity and mPT associated with the range of plasma apixaban concentrations in this study appeared similar to those that have been observed in healthy volunteers. Apixaban plasma concentration was estimated with greater accuracy and precision by anti-Xa activity than by mPT.

Baseline levels of D-dimer were markedly elevated, as expected in patients with acute DVT. All 4 treatments were associated with a decrease in median D-dimer values by Week 3, and median values were within normal limits at Week 12. The time course and magnitude of decreases in D-dimer were similar for the 3 apixaban treatments and for the comparator group. In all 4 treatments, some individuals had D-dimer values greater than normal at 12 weeks.

Baseline levels of the circulating markers of thrombogenesis F1.2 and TAT were around the upper limit of normal. Administration of apixaban and comparator was associated with a decrease in F1.2 and TAT.

CONCLUSIONS:

1) Apixaban was effective in the treatment of symptomatic DVT, preventing the recurrence of symptomatic DVT or new onset symptomatic PE while reducing the size of the index thrombus during a 12-week treatment period. The bleeding and overall safety profile for apixaban was assessed as acceptable and was comparable to the LMWH/VKA regimen.

2) All 3 of the apixaban doses (10 and 20 mg/day) were effective in preventing recurrent VTE, and data were consistent with an acceptable safety profile for Phase 3 development. No unexpected safety issues were encountered.

- For the primary efficacy endpoint of symptomatic recurrent VTE or deterioration of the thrombotic burden, events were infrequent across all treatment groups. The 95% CI for the differences in rates between the apixaban and the LMWH/VKA treatment groups included zero.
- The number of symptomatic recurrent DVT or PE was low and the rates were similar across apixaban treatment arms and comparator. Similar results for all dose groups were also observed for deterioration of the thrombotic burden as assessed by repeat bilateral compression ultrasound and/or perfusion lung scans.
- Improvement (assessed by CUS) was observed in >70% of subjects in each apixaban treatment arm compared with ~65% of subjects in the LMWH/VKA group. Improvement (assessed by PLS) was observed in ~37-40% of subjects in each apixaban treatment arm compared with ~44% of subjects in the LMWH/VKA group.
- For the composite of major bleeding and clinically relevant non-major (CRNM) bleeding the event rates were comparable across all treatment groups with the apixaban 10 mg BID treatment group having the lowest observed rate.
- Bleeding rates (adjudicated or as reported by the investigator) were lower in each apixaban treatment group than in the comparator group.

- The incidences of AEs were similar across all treatment groups with lower rates observed in the apixaban 10 mg BID group and higher rates observed in the apixaban 20 mg QD group
- 12-week exposure to apixaban was not associated with any appreciable liver function test abnormalities or other significant laboratory abnormalities.
- There was a dose-related increase in apixaban plasma concentrations for the apixaban 5 mg and 10 mg BID treatment groups.
- Administration of apixaban was associated with dose and concentration-dependent increases in anti-Xa activity and the clotting time parameter mPT. Anti-Xa activity provides a more accurate and precise estimate of apixaban plasma concentration than mPT.
- Over the 12-week treatment period, decreases in circulating markers of thrombogenesis, D-dimer, F1.2 and TAT, associated with apixaban treatment were similar to those associated with LMWH/VKA comparator.

DATE OF REPORT: 3-Dec-2007