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

Clinical Study Report CV185010

TITLE OF STUDY: A Phase 2 Randomized, Double-Blind (BMS-562247 and enoxaparin), Active-Controlled (enoxaparin and warfarin), Parallel-Arm, Dose-Response Study of the Oral Factor Xa Inhibitor BMS-562247 in Subjects Undergoing Elective Total Knee Replacement Surgery

STUDY CENTERS: 100 centers in 8 countries enrolled subjects. 97 centers randomized ≥ 1 subject.

PUBLICATIONS: None

STUDY PERIOD: Date first subject enrolled: 14-Oct-2004

Date last subject completed: 25-Nov-2005

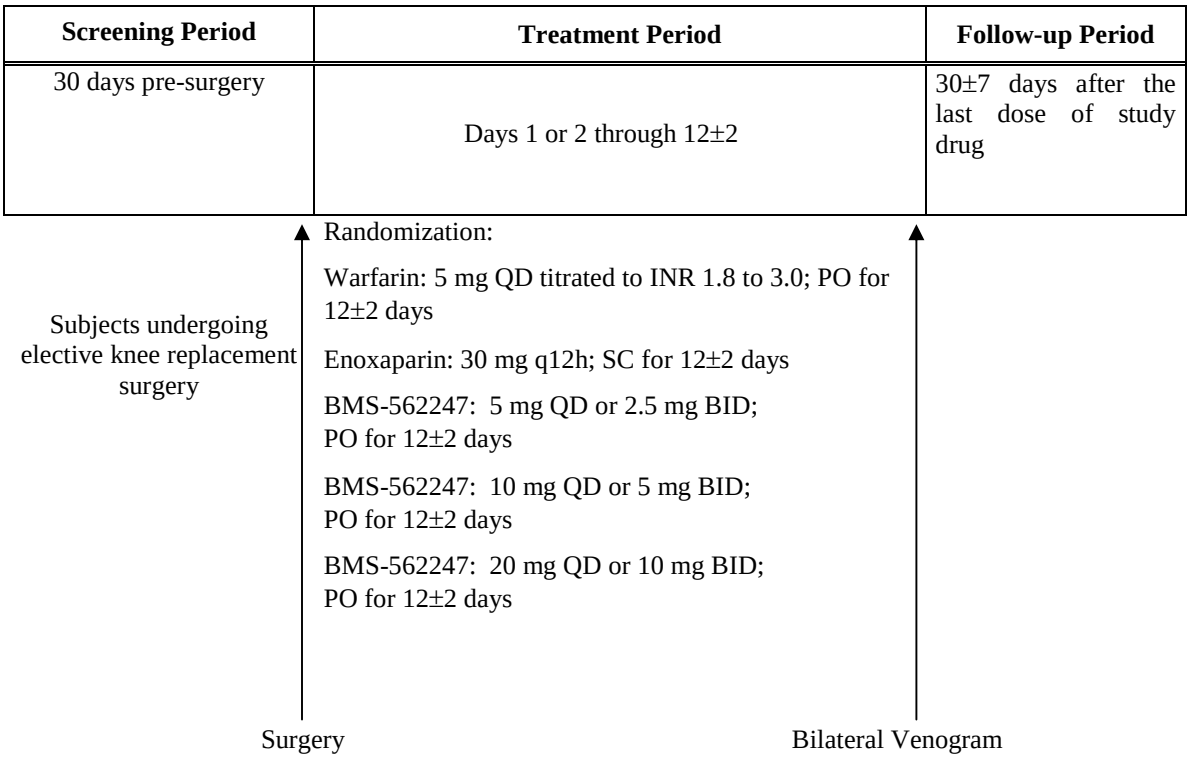
CLINICAL PHASE: 2

PRIMARY OBJECTIVES: To determine the dose-response relationship among the 3 once-daily (QD) and 3 twice-daily (BID) doses of oral BMS-562247 (apixaban) on the composite endpoint of adjudicated venous thromboembolic events ([VTE]: asymptomatic and symptomatic deep vein thrombosis [DVT] and non-fatal pulmonary embolism [PE]) and all-cause deaths in subjects treated for 12 ± 2 days following elective unilateral total knee replacement surgery.

METHODOLOGY: Randomized, 8-arm, double-blind (apixaban and enoxaparin), active-controlled (enoxaparin and warfarin), multi-center study. There were 3 study periods extending to a maximum of 81 days in duration: (1) a screening period of up to 30 days; (2) a 12 ± 2 day Treatment period; and (3) a 30 ± 7 day Follow-up period. Subjects were randomized on the day of surgery (Day 1) following the post-operative Screening period.

While hospitalized, subjects were evaluated daily for symptomatic VTE (DVT and/or PE) and bleeding events. A mandatory bilateral ascending contrast venogram was obtained on Day 12 ± 2 but no later than 2 calendar days after the last dose of study medication. The result of this venogram was a component of the primary endpoint of the protocol. Subjects shown to have an asymptomatic DVT upon venography were to be treated for DVT as per the Investigator's standard of care.

Following hospital discharge, subjects were to report all AEs including symptoms suggestive of DVT and/or PE and bleeding to the Investigator. Suspected DVT and/or PE were evaluated using an appropriate diagnostic assessment.



NUMBER OF SUBJECTS/PATIENTS: Approximately 150 subjects/treatment group were randomized to 1 of 8 treatments: 1 warfarin treatment group titrated to an INR of 1.8-3.0, 1 enoxaparin treatment group (30 mg q12 h), or 1 of 6 apixaban treatment groups (5, 10 or 20 mg QD; 2.5, 5 or 10 mg BID).

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION: Males and females who were not of childbearing potential, of any race, 18 to 90 years of age and scheduled to undergo elective unilateral total knee replacement were eligible. Subjects were to have no known or suspected hereditary or acquired bleeding or coagulation disorder or increased risk for thromboembolic events.

TEST PRODUCT, DOSE AND MODE OF ADMINISTRATION, BATCH NUMBERS:

Apixaban 2.5 or 10 mg tablets or matching placebo for each; first oral dose 12 to 24 hours after completing skin wound closure. Apixaban 2.5 mg batch numbers 4E83425 and 4K90273, apixaban 10 mg batch numbers 4E86214 and 4K92189, enoxaparin 30 mg batch numbers 3K77129, 803951AA, 900063, and 4K93246 and warfarin 1.0 and 2.5 mg batch numbers 4F86031, 4F86032, and ERK552A, ERK566A.

DURATION OF TREATMENT: QD or BID dose schedule for 12±2 days.

REFERENCE THERAPY, DOSE AND MODE OF ADMINISTRATION, BATCH NUMBERS:

Enoxaparin: 30 mg or matching placebo; first subcutaneous dose 12 to 24 hours after completing skin wound closure; q12h dose schedule for 12±2 days. **Warfarin:** Scored 1.0 and 2.5 mg tablets**;** initial dose 5 mg the evening following surgery; titrated number of tablets to achieve an INR of 1.8-3.0; QD evening dose schedule for 12±2 days.

CRITERIA FOR EVALUATION

Efficacy:

Primary efficacy outcome measure:

- Composite endpoint of adjudicated VTE events (asymptomatic and symptomatic DVT, non-fatal PE) and all-cause death during the Evaluation period. Any asymptomatic DVT during and after the Evaluation period was also counted.

Secondary efficacy outcome measures:

- Composite endpoint of adjudicated proximal DVT, non-fatal PE, and all-cause death during the Evaluation period.
- Incidence of adjudicated and confirmed major bleeding events during the Evaluation period.

The "Evaluation period" refers to the period between randomization and 2 days after the last administration of study drug. The Evaluation period was the basis for all analyses of efficacy and for primary summaries of safety.

The "Treatment period" refers to the period between the first administration of study drug and 2 days after the last administration of study drug. This period was the basis for the secondary summaries of safety.

The primary efficacy data set consisted of all randomized subjects who:

- had an adjudicated and evaluable end-of-treatment bilateral venogram performed at any time during or after the Evaluation period, or
- had an event for the parameter of interest (symptomatic PE, symptomatic DVT, or asymptomatic DVT) that was confirmed by adjudication during the Evaluation period, or
- died due to any cause during the Evaluation period.

The Independent Central Adjudication Committee (ICAC) adjudicated all venograms, suspected symptomatic DVT and PE, major and minor bleeding events, potentially significant non-overt bleeding, thrombocytopenia, and deaths.

Safety:

The primary safety outcome was bleeding. Bleeding events were adjudicated and classified by the ICAC as major bleeding, minor bleeding, potentially significant non-overt bleeding (PSB) or a non-event, i.e., did not meet pre-specified criteria to be classified as 1 of the 3 other bleeding events. Events in this last category of events were captured as bleeding adverse events (AE). The sites did not classify bleeding by category. Safety was also assessed via the review of all reported AEs and laboratory test results.

All AEs were listed and summarized by preferred term and system organ class, using the Medical Dictionary for Regulatory Activities (MedDRA). Non-serious AEs were listed and summarized through 2 days post treatment with study medication. Serious adverse events (SAEs) were summarized through the last day of follow-up. The primary analyses of safety included AEs between randomization and the start of treatment.

STATISTICAL METHODS: The dose-response relationship for the primary endpoint was tested sequentially using the Cochran-Armitage Test (one-sided $\alpha = 0.025$) among the 3 apixaban BID dose groups (2.5 mg, 5 mg and 10 mg) and the 3 apixaban QD dose groups (5 mg, 10 mg and 20 mg). With 150 subjects randomized to each group, there was 82% power to detect a dose-response among the BID dose

groups if the true rates for the 3 dose groups were 16%, 8% and 4%, respectively. These calculations assumed a venogram nonevaluability rate of 30%.

STUDY POPULATION: Baseline demographics were comparable between the apixaban, enoxaparin and warfarin randomized treatment groups.

Subject Disposition and Demographics

	BMS* QD 5 mg (N= 157)	BMS QD 10 mg (N=156)	BMS QD 20 mg (N= 156)	BMS BID 2.5mg (N=153)	BMS BID 5mg (N=157)	BMS BID 10mg (N=154)	Enoxaparin (N=152)	Warfarin (N=153)
Number of Subjects treated	151 (96.2)	155 (99.4)	151 (96.8)	154 (100.7)	153 (97.5)	153 (99.4)	149 (98.0)	151 (98.7)
Number of Subjects completing the double-blind period (%)	140 (89.2)	142 (91.0)	141 (90.4)	139 (90.8)	142 (90.4)	139 (90.3)	141 (92.8)	146 (95.4)
Number of Subjects Discontinued (%)	17 (10.8)	14 (9.0)	15 (9.6)	14 (9.2)	15 (9.6)	15 (9.7)	11 (7.2)	7 (4.6)
Reason for Discontinuation, (%)								
Adverse Event	5 (3.2)	7 (4.5)	8 (5.1)	9 (5.9)	6 (3.8)	8 (5.2)	4 (2.6)	4 (2.6)
Subject withdrew Consent	3 (1.9)	7 (4.5)	3 (1.9)	2 (1.3)	4 (2.5)	3 (1.9)	5 (3.3)	1 (0.7)
Death	0	0	0	1 (0.7)	0	0	0	0
Subject no longer meets study criteria	6 (3.8)	0	4 (2.6)	1 (0.7)	3 (1.9)	2 (1.3)	2 (1.3)	1 (0.7)
Poor/Non-Compliance	1 (0.6)	0	0	0	1 (0.6)	1 (0.6)	0	0
Other	2 (1.3)	0	0	1 (0.7)	1 (0.6)	1 (0.6)	0	1 (0.7)
Age: mean (min, max)	66.9 (31, 87)	67.2 (28, 86)	65.8 (35, 90)	67.6 (46, 88)	66.4 (46, 84)	66.4 (37, 87)	66.5 (36, 88)	66.8 (43, 85)
Gender: male	55 (35.0)	64 (41.0)	55 (35.3)	49 (32.0)	54 (34.4)	59 (38.3)	58 (38.2)	60 (39.2)
Race: White	145 (92.4)	147 (94.2)	145 (92.9)	143 (93.5)	147 (93.6)	144 (93.5)	142 (93.4)	138 (90.2)
Black	8 (5.1)	7 (4.5)	7 (4.5)	5 (3.3)	5 (3.2)	4 (2.6)	7 (4.6)	4 (2.6)
Asian	0	0	1 (0.6)	1 (0.7)	1 (0.6)	0	1 (0.7)	0
Other	4 (2.5)	2 (1.3)	3 (1.9)	4 (2.6)	4 (2.5)	6 (3.9)	2 (1.3)	11 (7.2)

* Apixaban is listed as BMS in all table headings

EFFICACY RESULTS:

Primary Objective:

Dose Response for VTE in Evaluable Subjects: Across the once- and twice-daily apixaban arms, a dose-response was observed for the primary endpoint of adjudicated VTE events (asymptomatic and symptomatic DVT, non-fatal PE) and all-cause death, although this did not reach statistical significance ($p = 0.188$ for QD administration; $p = 0.132$ for BID administration).

Secondary Objectives:

Incidence of VTE/death in Primary Subjects: VTE/all cause death for apixaban ranged from a high of 12.4% (95% CI = 6.8-20.2) for the apixaban 10 mg QD treatment arm to a low of 4.8% (95% CI = 1.6-10.8) for the apixaban 5 mg BID treatment arm. All doses of apixaban, had at least a 21% reduction in VTE/all cause death compared with enoxaparin (15.6% [95% CI = 9.4-23.8]) and at least a 53% reduction in VTE/all cause death compared with warfarin (26.6% [95% CI = 18.6-35.9]). The predominant VTE event for all treatment arms was distal DVT.

When the composite endpoint of proximal DVT/PE/all cause death was assessed as the outcome variable, all doses of apixaban had rates that were lower (0-2.7%) than the rate in the enoxaparin arm (4.6%). The rate in the warfarin arm was 1.8%.

Comparison of Incidences of VTE/All-cause Death during the Evaluation Period

	BMS QD 5mg (N= 97)	BMS QD 10mg (N= 105)	BMS QD 20mg (N= 110)	BMS BID 2.5mg (N= 111)	BMS BID 5mg (N= 105)	BMS BID 10mg (N= 110)	Enoxaparin (N = 109)	Warfarin (N = 109)
VTE / All-cause Death, n	11	13	9	11	5	6	17	29
Event rate (%)	11.3	12.4	8.2	9.9	4.8	5.5	15.6	26.6
95% CI	(5.8, 19.4)	(6.8, 20.2)	(3.8, 15.0)	(5.1, 17.0)	(1.6, 10.8)	(2.0, 11.5)	(9.4, 23.8)	(18.6, 35.9)
Individual Components								
DVT, n	11	13	8	10	5	5	15	29
Symptomatic PE, n	0	0	1	0	0	1	2	0
Death, n	0	0	0	1	0	0	0	0
Comparisons to BMS Low Dose								
Diff (%) (High - Low)	N/A	1.0	-3.2	N/A	-5.1	-4.5	N/A	N/A
95% CI		(-8.3, 10.4)	(-12.0, 5.3)		(-12.8, 2.0)	(-12.2, 2.9)		
Comparisons to Enoxaparin								
Ratio (%) (BMS/Enox)	0.73	0.79	0.52	0.64	0.31	0.35	N/A	N/A
95% CI	(0.33, 1.49)	(0.38, 1.56)	(0.23, 1.11)	(0.29, 1.31)	(0.09, 0.77)	(0.11, 0.82)		
Diff (%) (BMS-Enox)	-4.3	-3.2	-7.4	-5.7	-10.8	-10.1		
95% CI	(-14.0, 5.4)	(-13.0, 6.4)	(-16.5, 1.3)	(-14.9, 3.3)	(-19.5, -2.7)	(-18.9, -1.9)		
Comparisons to Warfarin								
Ratio (%) (BMS/Warf)	0.43	0.47	0.31	0.37	0.18	0.21	N/A	N/A
95% CI	(0.21, 0.79)	(0.24, 0.84)	(0.14, 0.60)	(0.19, 0.69)	(0.06, 0.42)	(0.07, 0.45)		
Diff (%) (BMS-Warf)	-15.3	-14.2	-18.4	-16.7	-21.8	-21.2		
95% CI	(-25.9, -4.2)	(-24.9, -2.9)	(-28.6, -7.8)	(-27.0, -5.1)	(-31.7, -12.3)	(-31.0, -11.6)		
p-value*		0.188			0.132			

N = Number of subjects included in the analysis for each treatment arm
*p-value for dose-response across the 3 QD or acros the 3 BID treatment arms.

PHARMACOKINETIC RESULTS:

Apixaban exposure, as measured by peak and trough concentrations, exhibited a dose-related increase within the once- and twice-daily regimens. It appeared that steady state was achieved within 3 days after administration of the first oral dose regardless of dosing regimen.

PHARMACODYNAMIC RESULTS:

Dose-dependent increases in peak and trough INR and modified prothrombin time (mPT) were apparent for both the once- and twice-daily regimens. The pattern of increases appeared to reflect the corresponding plasma apixaban concentrations. Relative increases in mPT were more pronounced than those in INR.

SAFETY RESULTS:

AEs:

Post randomization and up to 2 days post double-blind therapy: The number of subjects with AEs and drug-related AEs was comparable between the apixaban and comparator treatment arms. There were no obvious dose-dependent increases in event rates. The number of AEs leading to discontinuation of study therapy was low and comparable between all treatment arms. No individual AE caused discontinuation for more than 1 patient in any treatment arm.

Follow-up period:

The overall safety profile of subjects during the 30-day Follow-up period was comparable for the apixaban and comparator treatment groups. The number (percent) of subjects experiencing AEs during the 30-day Follow-up period ranged from 17.1% - 25.0% for apixaban-treated subjects versus 19.3% and 22.4%, respectively, for enoxaparin- and warfarin-treated subjects.

Death: There were 3 deaths reported from this Phase 2 study for the prevention of DVT, all in the apixaban-treated groups. Deaths included those events that occurred during the Evaluation period + 30 days. The causes of death were: (1) pulmonary embolism and cardiac arrest on Day 8 (apixaban 2.5 mg BID for 8 days); 2) myocardial infarction on Day 4 (apixaban 2.5 mg BID for 4 days) and death on day 25; 3) cachexia (dehydration, malnutrition, and progressive CHF) on Day 47 (apixaban 20 mg QD for 4 days). The investigator considered the PE death possibly related to study medication whereas the MI and cachexia were considered unrelated. One subject signed informed consent but died of a PE prior to randomization.

SAEs: There were 120 SAEs reported in the Evaluation period for this study. Ninety-six (96) were reported in 80 of 917 (8.7%) subjects in the apixaban group, 12 SAEs were reported in 10 of 149 (6.7%) subjects in the enoxaparin treatment group, and 12 SAEs were reported in 9 of 151 (6.0%) subjects in the warfarin group during the Evaluation period. In addition, 5 subjects had an SAE in the pre-surgery period, 1 subject had an SAE post-surgery but before treatment, 1 subject (apixaban 5 mg BID) had an SAE > 30 days post-surgery. In the Follow-up period, 40 SAEs were reported in 26 of 872 (3%) subjects in the apixaban group, 7 SAEs were reported in 5 of 140 (3.6%) subjects in the enoxaparin group, and 4 SAEs were reported in 2 of 147 (1.4%) subjects in the warfarin group. Although infrequent, the most common SAE in all treatment arms was DVT. There appeared to be no obvious dose-dependent increases in SAEs event rates.

Myocardial infarction (MI) was reported as an SAE in 3 subjects receiving apixaban and 1 subject on warfarin. Cerebrovascular accidents (CVA) were reported in 5 subjects randomized to apixaban; none were reported in subjects randomized to enoxaparin or warfarin. None of the MI or CVA events were considered by the investigator to be related to study drug. Clinical findings and results from diagnostic testing were consistent with an SAE of amyotropic lateral sclerosis (ALS) in 1 apixaban subject and an SAE of Guillain-Barre Syndrome in another apixaban subject. Upon review by neurologic specialists, both events were considered to be unlikely related to study drug and evidence indicated that the ALS was a pre-existing condition.

Clinical Laboratory Evaluation: Hemoglobin reductions, thrombocytopenia, and hepatic transaminase elevations were infrequent and comparable for all treatment arms. Overall, no clinically significant laboratory test results, vital signs or physical examination findings were noted for the apixaban or comparator treatment groups. The number of subjects with High ALT identified as a Marked Laboratory Abnormality was low; however, the incidence for all apixaban treatment arms was approximately half that observed for the enoxaparin group.

The incidence of hepatic transaminase elevations in subjects treated for ≥ 10 days was infrequent and comparable for all treatment arms. A slightly greater number of enoxaparin subjects with ALT and/or AST ≥ 3 x ULN was observed.

Overall, no clinically significant vital sign, physical examination or electrocardiogram (ECG) findings related to apixaban treatment were noted.

Number (Percent) of Adverse Events during the Evaluation Period

	BMS QD 5mg (N= 151)	BMS QD 10mg (N= 155)	BMS QD 20mg (N= 151)	BMS BID 2.5mg (N= 154)	BMS BID 5mg (N= 153)	BMS BID 10mg (N= 153)	Enoxaparin (N = 149)	Warfarin (N = 151)
AE, Total subjects, n (%)	129 (85.4)	137 (88.4)	133 (88.1)	134 (87.0)	132 (86.3)	132 (86.3)	129 (86.6)	134 (88.7)
SAE, n (%)	20 (13.2)	14 (9.0)	13 (8.6)	12 (7.8)	9 (5.9)	12 (7.8)	10 (6.7)	9 (6.0)
Bleeding AE, n (%)	16 (10.6)	30 (19.4)	32 (21.2)	22 (14.3)	25 (16.3)	27 (17.6)	21 (14.1)	22 (14.6)
Related AE, n (%)	32 (21.2)	47 (30.3)	35 (23.2)	39 (25.3)	35 (22.9)	41 (26.8)	37 (24.8)	40 (26.5)
Death, n (%)	0	0	1 (0.7)	2 (1.3)	0	0	0	0
Discontinuation due to AE, n (%)	5 (3.3)	7 (4.5)	8 (5.3)	9 (5.8)	6 (3.9)	8 (5.2)	4 (2.7)	4 (2.6)

Adjudicated Bleeding Events:

There were no major bleeding events in the enoxaparin or warfarin arms; in similar published studies, the rate has generally been 1-2% for enoxaparin and <1% for warfarin. The rate of major bleeding with apixaban ranged from 0-3.3%. The frequencies of major bleeding and clinically relevant bleeding (major plus minor bleeding) were comparable for twice-daily and once-daily apixaban arms. At daily doses of 20 mg apixaban, the rate of clinically relevant bleeding was approximately 2-fold higher than enoxaparin and warfarin arms. At lower doses of apixaban, rates of clinically relevant bleeding were comparable to enoxaparin and warfarin arms.

Dose-dependent bleeding was evident for both the once- and twice-daily regimens when the composite endpoint of major/minor/potentially significant bleeding events was assessed. Event rates ranged from 3.3% at the low dose to 9.9% at the high dose. Event rates for enoxaparin and warfarin were 5.4% and 5.3%, respectively.

Dose-dependent bleeding-related adverse events were evident primarily for the once-daily regimen. There were no hemorrhagic cerebral vascular accidents (CVA).

Summary of Incidence of Adjudicated Bleeding Events during Evaluation Period, by Treatment Group - Treated Subjects

	BMS QD 5mg (N= 151)	BMS QD 10mg (N= 155)	BMS QD 20mg (N= 151)	BMS BID 2.5mg (N= 154)	BMS BID 5mg (N= 153)	BMS BID 10mg (N= 153)	Enoxaparin (N = 149)	Warfarin (N = 151)
Major Bleeding, n	4	1	5	0	4	4	0	0
Event rate (%)	2.6	0.6	3.3	0.0	2.6	2.6	0.0	0.0
95% CI	(0.7, 6.6)	(0.0, 3.5)	(1.1, 7.6)	(0.0, 2.4)	(0.7, 6.6)	(0.7, 6.6)	(0.0, 2.4)	(0.0, 2.4)
Minor Bleeding, n	1	9	10	6	6	11	6	8
Event rate (%)	0.7	5.8	6.6	3.9	3.9	7.2	4.0	5.3
95% CI	(0.0, 3.6)	(2.7, 10.7)	(3.2, 11.8)	(1.4, 8.3)	(1.5, 8.3)	(3.6, 12.5)	(1.5, 8.6)	(2.3, 10.2)
Potentially Significant Bleed (PSB), n	0	1	0	0	0	0	2	0
Event rate (%)	0	0.6	0	0	0	0	1.3	0
95% CI	(0.0, 2.4)	(0.0, 3.5)	(0.0, 2.4)	(0.0, 2.4)	(0.0, 2.4)	(0.0, 2.4)	(0.2, 4.8)	(0.0, 2.4)
Thrombocytopenia	0	1	0	0	0	0	0	0
Event rate (%)	0.0	0.6	0.0	0.0	0.0	0.0	0.0	0.0
95% CI	(0.0, 2.4)	(0.0, 3.5)	(0.0, 2.4)	(0.0, 2.4)	(0.0, 2.4)	(0.0, 2.4)	(0.0, 2.4)	(0.0, 2.4)
Major Bleeding / PSB	4	2	5	0	4	4	2	0
Event rate (%)	2.6	1.3	3.3	0.0	2.6	2.6	1.3	0.0
95% CI	(0.7, 6.6)	(0.2, 4.6)	(1.1, 7.6)	(0.0, 2.4)	(0.7, 6.6)	(0.7, 6.6)	(0.2, 4.8)	(0.0, 2.4)
Major Bleeding / PSB / Minor Bleed	5	11	15	6	10	15	8	8
Event rate (%)	3.3	7.1	9.9	3.9	6.5	9.8	5.4	5.3
95% CI	(1.1, 7.6)	(3.6, 12.3)	(5.7, 15.9)	(1.4, 8.3)	(3.2, 11.7)	(5.6, 15.7)	(2.3, 10.3)	(2.3, 10.2)

CONCLUSIONS:

- Across the once- and twice-daily apixaban arms, a dose-response was observed for the primary endpoint of adjudicated VTE events (asymptomatic and symptomatic DVT, non-fatal PE) and all-cause death, although this did not reach statistical significance.
- All doses of apixaban had at least a 21% reduction in VTE/all cause death compared with enoxaparin and at least a 53% reduction in VTE/all cause death compared with warfarin.
- The frequencies of major bleeding events were low (0 - 3.3%) and comparable between all apixaban arms. No major bleeding events were observed in either the enoxaparin or warfarin arms.
- Dose-dependent bleeding was evident for both the once- and twice-daily regimens when the composite endpoint of major/minor/PSB events was assessed. Event rates ranged from 3.3% at the low dose to 9.9% at the high dose. Event rates for enoxaparin and warfarin were 5.4% and 5.3%, respectively.
- Adverse events were frequent but the incidence was comparable for apixaban and comparator regimens. With the exception of DVT, serious adverse events were infrequently reported. Hemoglobin reductions, thrombocytopenia, and hepatic transaminase elevations were infrequent and comparable for all treatment arms. The pattern of adverse events was consistent with the known profile of apixaban and comparator treatment, and was consistent with expected events in this surgical setting.
- Apixaban exposure, as measured by peak and trough concentrations, exhibited a dose-related increase within the once- and twice-daily regimens. It appeared that steady state was achieved within 3 days after administration of the first oral dose regardless of dosing regimen.
- Administration of apixaban was associated with dose-dependent increases in the clotting time parameters INR and mPT.

DATE OF REPORT: 02-Nov-2006