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 CV185034

TITLE OF STUDY: A Phase 3 Randomized, Double-Blind, Active-Controlled (Enoxaparin), Parallel-Group, Multi-Center Study to Evaluate the Safety and Efficacy of Oral Apixaban in Subjects Undergoing Elective Total Knee Replacement Surgery

INVESTIGATORS/STUDY CENTERS: 129 study sites in 14 countries

PUBLICATIONS: None

STUDY PERIOD: Study Initiation Date: 7-Nov-2006 **CLINICAL PHASE:** 3

Study Completion Date: 28-May-2008

OBJECTIVES:

Primary Efficacy Objective: To compare the effect of oral apixaban 2.5 mg twice daily (BID) versus subcutaneous (SC) enoxaparin 30 mg every 12 hours (q12h) on the composite endpoint of adjudicated asymptomatic and symptomatic deep vein thrombosis (DVT), non-fatal pulmonary embolism (PE), and all-cause death after 12 ± 2 days of double-blind treatment in subjects undergoing elective total knee replacement (TKR) surgery.

Secondary Efficacy Objectives:

To compare the effect of oral apixaban 2.5 mg BID versus SC enoxaparin 30 mg q12h on the composite of adjudicated proximal DVT, non-fatal PE, and all-cause death after 12 ± 2 days of double-blind treatment in subjects undergoing elective total knee replacement surgery.

To assess the effect of oral apixaban 2.5 mg BID versus subcutaneous enoxaparin 30 mg q12h on:

- Composite of adjudicated symptomatic DVT, non-fatal and fatal PE during 12 ± 2 days of double-blind treatment
- Single adjudicated endpoints of distal DVT, proximal DVT, non-fatal PE, venous thromboembolism (VTE)-related deaths, and all-cause death during 12 ±2 days of double-blind treatment
- Composite of adjudicated symptomatic VTE and all-cause death during the Follow-up period (60 days after discontinuation of study drug)
- Single adjudicated endpoints of symptomatic VTE and symptomatic DVT during 12 ± 2 days of double-blind treatment

- Single adjudicated endpoints of symptomatic VTE and all-cause death during the Follow-up period (60 days after discontinuation of study drug)
- Single adjudicated endpoints of symptomatic VTE and all-cause death during 12 ± 2 days of double-blind treatment plus the Follow-up period (60 days after discontinuation of study drug)

Safety Objectives:

To assess the effect of oral apixaban 2.5 mg BID versus SC enoxaparin 30 mg q12h on:

- Adjudicated major bleeding events during 12 ± 2 days of double-blind treatment
- Composite of adjudicated major and clinically relevant non-major bleeding events during 12 ± 2 days of double-blind treatment
- Composite of adjudicated acute myocardial infarction (MI), acute ischemic stroke and other systemic thromboembolic events occurring during the 12 ± 2 days of double-blind treatment plus the Follow-up period (60 days after discontinuation of study drug)
- Adjudicated clinically relevant non-major bleeding during 12 ± 2 days of double-blind treatment
- Platelet count, hemoglobin concentration, liver function tests (LFT [alanine aminotransferase or ALT, aspartate aminotransferase or AST, and total and direct bilirubin]), and adjudicated thrombocytopenia during 12 ± 2 days of double-blind treatment

To assess overall safety and tolerability of apixaban and enoxaparin during 12 ± 2 days of double-blind treatment.

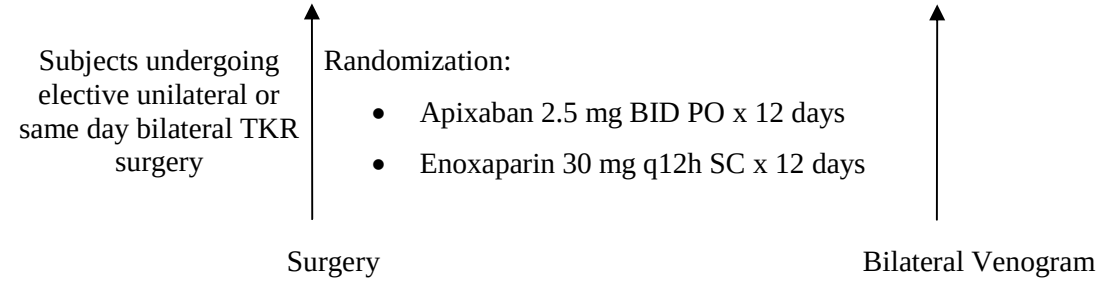
METHODOLOGY:

This was a Phase 3, multicenter, randomized, parallel-group study of the efficacy and safety of apixaban and enoxaparin in subjects undergoing elective TKR surgery.

Subjects were randomized to 1) double-blind treatment with oral apixaban 2.5 mg BID or 2) double-blind treatment with SC enoxaparin 30 mg q12h.

The study included 1) a screening period that began no more than 30 days prior to surgery through 24 hours after surgery; 2) a 12 (±2) day treatment period, starting on the day of the first dose of study drug; and 3) a 60 (±3) day follow-up period, starting the day after the last dose of study drug:

screening period	treatment period	follow-up period
30 days prior to surgery through 24 hours after-surgery	12 days of treatment starting on the day of surgery or the next day	60 days after the last dose of study drug



The initial dose of oral (PO) apixaban was administered 12 to 24 hours after completing skin wound closure, followed by BID dosing for 12 days. Subjects randomized to apixaban also received enoxaparin-matching placebo injections starting 12 to 24 hours after completing skin wound closure, followed by dosing (q12h) for 12 days.

The initial dose of SC enoxaparin was injected 12 to 24 hours after completing skin wound closure followed by q12h dosing for 12 ± 2 days. Subjects randomized to enoxaparin also received apixaban-matching placebo tablets starting 12 to 24 hours after completing skin wound closure, followed by BID dosing for 12 ± 2 days. The dose regimen and initiation of enoxaparin were in accordance with approved labels for this regimen.

A mandatory bilateral ascending contrast venogram was obtained after 12 ± 2 days of study drug. The result of this venogram contributed to the primary endpoint of the protocol. Subjects who were shown to have asymptomatic DVT upon venography were to be treated for DVT according to the Investigator's standard of care.

NUMBER OF SUBJECTS (Planned and Analyzed): The study was planned to randomize 3058 subjects (approximately 1529 subjects per treatment). All subjects that had been enrolled at the time that the target of 3058 subjects had been randomized were allowed, if eligible, to continue on to randomization. When the target of 3058 subjects had been randomized, no other subjects were then allowed to be enrolled in the study. The final number randomized was 3195 (apixaban 1599 subjects; enoxaparin 1596 subjects). A total of 3184 subjects (apixaban 1595 subjects; enoxaparin 1589 subjects) were treated with blinded study drug and 2287 subjects (apixaban 1157 subjects; enoxaparin 1130 subjects) were included in the Primary Efficacy data set.

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION:

Males and females, including women of child bearing potential, 18 years of age or older, scheduled to undergo elective unilateral or same day bilateral TKR surgery (including revisions) who meet the inclusion/exclusion criteria were eligible.

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

Apixaban 2.5 mg or matching placebo; first oral dose 12 to 24 hours after completing skin wound closure; BID dose schedule for 12 days.

The apixaban tablets were taken from the following batch numbers: 6E17717 and 7B27015. Matching placebo tablets were taken from the following batch numbers: 6E18428 and 7A29111.

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

Enoxaparin: 30 mg or matching placebo; first SC dose 12 to 24 hours after completing skin wound closure; q12h dose schedule for 12 days.

BMS batch numbers for enoxaparin: 6C16955 and 7D25679. Matching placebo batch numbers: 6E15447, 6E15448, 6F17124, 6F17416, 6M10448, 6M10449 and 7D30578.

CRITERIA FOR EVALUATION:

Within the analysis and reporting period, an Independent Central Adjudication Committee (ICAC) adjudicated all venograms, suspected symptomatic DVT and PE, acute clinically overt bleeding events, suspected thrombocytopenia, suspected acute MI, suspected acute stroke, and cause of death.

Efficacy:

Primary:

The primary objective was to compare the effect of oral apixaban 2.5 mg BID versus SC enoxaparin 30 mg q12h on the composite endpoint of adjudicated asymptomatic and symptomatic DVT, non-fatal PE, and all-cause death following 12 ± 2 days of double-blind treatment in subjects undergoing elective TKR surgery.

Secondary:

The key secondary efficacy outcome was the composite of adjudicated proximal DVT, non-fatal PE and all-cause death during the Intended Treatment Period.

Safety:

Bleeding was the primary safety endpoint and included the following if occurring during the Treatment Period:

- confirmed adjudicated major bleeding events per International Society on Thrombosis and Hemostasis (ISTH) guidelines modified for surgical patients
- composite of confirmed adjudicated major bleeding (per ISTH guidelines) and confirmed adjudicated clinically relevant non-major bleeding events
- all bleeding endpoints (adjudicated or reported by the investigator)

Secondary Safety Endpoints:

Safety was also assessed via the review of all reported adverse events (AE), vital signs, laboratory test results, and Events of Special Interest (AEs related to LFT increases, neurologic AEs, thrombocytopenia, MI, and stroke). All AEs were listed and summarized by preferred term and system organ class, using the Medical Dictionary for Regulatory Activities.

Pharmacokinetics: Not applicable for this study.

Pharmacodynamics: Not applicable for this study.

STATISTICAL CONSIDERATIONS:

In the efficacy analyses subjects were categorized to the group to which they were assigned by the IVRS regardless of the treatment actually received.

The data sets used to perform the analyses of each efficacy endpoints were all randomized subjects when asymptomatic events were not part of the endpoint, or a subset of the randomized subjects who had either an adjudicated event that was part of the endpoint or an adjudicated evaluable bilateral venogram to detect presence or absence of the asymptomatic event of interest (proximal DVT, distal DVT or both depending on the endpoint).

Point estimates and 95% CIs for the risk ratio and risk difference between apixaban and enoxaparin were calculated for primary and key secondary efficacy outcomes using knee replacement surgery type (unilateral or bilateral) as stratification factor.

Non-inferiority for apixaban on the primary efficacy endpoint would be demonstrated if both conditions below were met:

- upper bound of the two-sided 95% CI for relative risk (RR) < 1.25, and
- upper-bound of the two-sided 95% CI for risk difference < 5.6%.

The safety analysis included all treated subjects. The proportion of subjects with confirmed major or clinically relevant non-major bleeding events during the treatment period was summarized by treatment and by treatment and knee replacement surgery type. Point estimates and 95% CIs for event rates were presented by treatment group, together with point estimates and 95% CIs for the difference of event rates between apixaban and enoxaparin groups.

SUMMARY OF RESULTS:

Disposition, Demographics, and Other Pertinent Baseline Characteristics:

A total of 3195 subjects were randomized to active study drug (Table 1). For randomized subjects, discontinuation rates from the Treatment Period of the study were similar for apixaban and enoxaparin treatment (5.6% vs 6.7%, respectively). Study discontinuation rates due to AEs were also similar for apixaban and enoxaparin treatment (3.8% vs 3.6%, respectively).

Baseline demographic characteristics were balanced between treatment groups. Most subjects were white (94.8%) and female (62.1%). The mean age was 65.8 years; 56.6% of subjects were ≥ 65 years of age.

There were no differences in the incidence or type of risk factors at baseline between subjects randomized to apixaban or enoxaparin that were deemed to be clinically relevant to the efficacy or safety analyses (Table 2). The majority of subjects in both groups (67.1% apixaban; 69.9% enoxaparin) had no risk factors at baseline. Of those subjects that did have risk factors at baseline, most had only 1 risk factor.

Table 1: Subject Disposition - Randomized Subjects

	APIX 2.5MG BID N = 1599	ENOX 30MG Q12H N = 1596
SUBJECTS	1599	1596
SUBJECTS COMPLETING THE PERIOD (%)	1509 (94.4)	1489 (93.3)
SUBJECTS NOT COMPLETING THE PERIOD (%)	90 (5.6)	107 (6.7)
REASON FOR NOT COMPLETING THE PERIOD (%)		
DEATH	1 (<0.1)	1 (<0.1)
ADVERSE EVENT	60 (3.8)	58 (3.6)
STROKE	0	2 (0.1)
THROMBOCYTOPENIA	3 (0.2)	2 (0.1)
MI	0	4 (0.3)
BLEEDING	9 (0.6)	14 (0.9)
DVT	3 (0.2)	7 (0.4)
PE	16 (1.0)	5 (0.3)
OTHER	29 (1.8)	24 (1.5)
SUBJECT WITHDREW CONSENT	18 (1.1)	37 (2.3)
LOST TO FOLLOW-UP	0	1 (<0.1)
POOR/NON-COMPLIANCE	0	0
PREGNANCY	0	0
SUBJECT NO LONGER MEETS STUDY CRITERIA	1 (<0.1)	2 (0.1)
ADMINISTRATIVE REASON BY SPONSOR	1 (<0.1)	0
OTHER	9 (0.6)	8 (0.5)
SUBJECTS CONTINUING THE STUDY (%)	1553 (97.1)	1533 (96.1)
SUBJECTS NOT CONTINUING THE STUDY (%)	46 (2.9)	63 (3.9)

The denominator to calculate each percentage is the total number of randomized subjects in the treatment group(s)

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

	APIX 2.5MG BID N = 1599	ENOX 30MG Q12H N = 1596	Total N = 3195
ANY RISK FACTOR? (%)			
YES	526 (32.9)	480 (30.1)	1006 (31.5)
NO	1073 (67.1)	1115 (69.9)	2188 (68.5)
NOT REPORTED	0	1 (<0.1)	1 (<0.1)
TYPE OF RISK FACTOR (%)			
KNEE REPLACEMENT	374 (23.4)	347 (21.7)	721 (22.6)
HIP REPLACEMENT	91 (5.7)	73 (4.6)	164 (5.1)
HIP OR KNEE FRACTURE SURGERY	65 (4.1)	62 (3.9)	127 (4.0)
DVT	57 (3.6)	47 (2.9)	104 (3.3)
PE	10 (0.6)	6 (0.4)	16 (0.5)

The denominator to calculate each percentage is the total number of randomized subjects in the treatment group(s)

Exposure

The mean number of days from first to last dose of double-blind study drug was 11.7 (range 1 to 16) for apixaban and 11.6 (range 1 to 15) for enoxaparin (Table 3).

Greater than 99% of subjects in each treatment group received at least 1 dose of study drug.

Table 3: Extent of Exposure from First Through Last Day of Dosing, Not Taking Into Account Interruptions - Treated Subjects

Length of Exposure Days (%)	APIX 2.5MG BID N = 1596	ENOX 30MG Q12H N = 1588
=<3	48 (3.0)	45 (2.8)
4 - =<6	25 (1.6)	34 (2.1)
7 - =<9	74 (4.6)	102 (6.4)
10 - =<14	1418 (88.8)	1392 (87.7)
>14	31 (1.9)	15 (0.9)
MEAN(SD)	11.7 (2.49)	11.6 (2.51)
MEDIAN	12.0	12.0
MIN,MAX	1.0, 16.0	1.0, 15.0
TOTAL PATIENT-MONTHS	612.07	605.04

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

Efficacy Results:

The incidence of the primary efficacy endpoint was 8.99% for apixaban and 8.85% for enoxaparin (Table 4). The observed RR of apixaban versus enoxaparin for the primary efficacy endpoint was 1.02 and the adjusted risk difference was 0.11%. Although the upper bound of the 95% CI for risk difference (2.44%) was below 5.6% (the non-inferiority [NI] margin for the risk difference), the upper bound of the 95% CI for RR (1.32) was above 1.25 (the NI margin) and therefore the non-inferiority criteria for the primary efficacy endpoint was not met.

The observed event rates for the key secondary efficacy endpoint (composite of adjudicated proximal DVT, non-fatal PE, and all-cause death) were 2.05% for apixaban and 1.64% for enoxaparin. The observed RR for the key secondary endpoint was 1.25 with 95% CI of (0.70, 2.23).

Table 4: Primary Efficacy Endpoint - Summary of Adjudicated VTE Events and All-Cause Death with Onset during the Intended Treatment Period - Primary Subjects

	Apixaban N = 1157	Enoxaparin N = 1130
All VTE/All-Cause Death, N	104	100
Event Rate (%)	8.99	8.85
95% CI For Event Rate	(7.47, 10.79)	(7.33, 10.66)
Relative Risk (Apix/Enox)	1.02	
95% CI For Relative Risk	(0.78, 1.32)	
One-Sided p-Value For Non-Inferiority Test on RR	0.0635	
Risk Difference (%) (Apix-Enox)	0.11	
95% CI For Risk Difference	(-2.22, 2.44)	
One-Sided p-Value For Non-Inferiority Test on Difference	<0.0001	

Safety Results:

The Treatment Period refers to the period from first dose through 2 days (or through 30 days for SAE and deaths as an outcome of SAE tabulations only) after discontinuation of study drug. This period was the basis for the summaries of safety. The incidence of AEs, SAEs, and AEs leading to discontinuation during the Treatment Period was similar between apixaban and enoxaparin groups (Table 5). The incidence of bleeding-related AEs was lower in the apixaban group versus the enoxaparin group.

Eight deaths occurred during the Treatment Period. Of the 8 deaths, 3 (0.2%) occurred in apixaban-treated subjects and 5 (0.3%) occurred in enoxaparin-treated subjects. One death occurred during the Follow-up Period in an enoxaparin-treated subject.

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

	APIX 2.5MG BID (N = 1596)	ENOX 30MG Q12H (N = 1588)
AE (%)	1149(72.0)	1172(73.8)
SAE (%)	123(7.7)	123(7.7)
Bleeding AE (%)	110(6.9)	144(9.1)
Discontinuations due to AE (%)	60(3.8)	58(3.7)
Deaths (%)	3(0.2)	5(0.3)

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

Fatal bleeding occurred in 1 subject (enoxaparin) during the Treatment Period.

Major bleeding events during the Treatment Period were infrequent and lower for apixaban-treated subjects than for enoxaparin-treated subjects (0.69% and 1.39%, respectively) (Table 6). The two-sided 95% CI for the apixaban to enoxaparin difference of adjudicated major bleeding event rates was below zero providing evidence that the major bleeding rate was lower for apixaban than for enoxaparin.

Event rates during the Treatment Period for clinically relevant non-major (CRNM) bleeding and Any Bleeding (adjudicated or as reported by the investigator) were similar or lower for apixaban-treated subjects compared to enoxaparin. The event rate for the composite of the adjudicated major or CRNM bleeding endpoint during the Treatment Period was lower for apixaban-treated subjects than for enoxaparin-treated subjects (2.88% and 4.28%, respectively). The two-sided 95% CI for the apixaban to enoxaparin difference of adjudicated major or CRNM bleeding event rates was below zero providing evidence that the adjudicated major or CRNM rate was lower for apixaban than for enoxaparin.

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

	Apix 2.5 mg BID N=1596	Enox 30 mg q12h N=1588
MAJOR BLEEDING, N	11	22
EVENT RATE (%)	0.69	1.39
95% CI	(0.37, 1.25)	(0.91, 2.11)
ADJ. DIFF OF EVENT RATES (APIX-ENOX) (%)	-0.81	
95% CI	(-1.49, -0.14)	
p-value	0.0533	
CLINICALLY RELEVANT NON-MAJOR BLEEDING, N	35	47
EVENT RATE (%)	2.19	2.96
95% CI	(1.58, 3.05)	(2.23, 3.93)
ADJ. DIFF OF EVENT RATES (APIX-ENOX) (%)	-0.77	
95% CI	(-1.87, 0.33)	
p-value	0.1709	
MAJOR OR CLINICALLY RELEVANT NON-MAJOR BLEEDING, N	46	68
EVENT RATE (%)	2.88	4.28
95% CI	(2.16, 3.84)	(3.39, 5.41)
ADJ. DIFF OF EVENT RATES (APIX-ENOX) (%)	-1.46	
95% CI	(-2.75, -0.17)	
p-value	0.0338	
ANY BLEEDING, N	85	108
EVENT RATE (%)	5.33	6.80
95% CI	(4.33, 6.55)	(5.66, 8.16)
ADJ. DIFF OF EVENT RATES (APIX-ENOX) (%)	-1.52	
95% CI	(-3.18, 0.13)	
p-value	0.0816	

Adjusted difference of event rates takes into consideration type of surgery as a stratification factor

CONCLUSIONS:

- The pre-specified non-inferiority criterion was not met for the primary efficacy composite endpoint of all VTE (adjudicated symptomatic and asymptomatic DVT and non-fatal PE) and all-cause death. The observed rates for the primary efficacy endpoint were similar for apixaban and enoxaparin but the enoxaparin rate was lower than expected and was lower than seen in previous orthopedic VTE prevention trials.
- The observed rate for the key secondary efficacy composite endpoint of adjudicated proximal DVT, non-fatal PE, and all-cause death was higher for apixaban than enoxaparin.
- The observed rates for endpoints including fatal PE (VTE-related death) or non-fatal PE (individually or as part of a composite) were higher for apixaban than enoxaparin during the treatment period; the opposite trend (lower rates for apixaban than enoxaparin) was observed during the follow-up period, albeit based on a smaller number of events.
- The observed rate of DVT (including symptomatic, asymptomatic, proximal and distal endpoints) was similar for apixaban and enoxaparin.
- The rates of major bleeding and the rates of the composite endpoint of major plus clinically relevant non-major bleeding were lower for apixaban than enoxaparin. The 95% CIs for the difference of event rates between apixaban and enoxaparin for both of these bleeding indices were below zero, indicating that apixaban has a more favorable bleeding profile than enoxaparin.
- The observed rates for AEs, SAEs, all-cause death and discontinuations due to AEs were similar for apixaban and enoxaparin.
- The observed rates for the infrequent events of MI, stroke, and thrombocytopenia were lower for apixaban than enoxaparin.
- LFT elevations were infrequent and the observed rates of LFT elevations were lower for apixaban than enoxaparin.

DATE OF REPORT: 23-Feb-2009