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 for Study CV185047

TITLE OF STUDY: A Phase 3, Randomized, Double-blind, Active-controlled (Enoxaparin 40 mg QD), Parallel Group, Multi-center Study to Evaluate the Safety and Efficacy of Apixaban in Subjects Undergoing Elective Total Knee Replacement Surgery

INVESTIGATORS/STUDY CENTERS: 125 study sites in 27 countries (outside the US and Canada)

PUBLICATIONS: None

STUDY PERIOD: Study Initiation Date: 29-Jun-2007 **CLINICAL PHASE:** 3
Study Completion Date: 30-Jan-2009

OBJECTIVES:

Primary Efficacy Objective: To compare the effect of apixaban 2.5 mg twice daily (BID) orally (PO) vs. enoxaparin 40 mg once daily (QD) subcutaneously (SC) on the composite endpoint of adjudicated asymptomatic and symptomatic deep vein thrombosis (DVT), non-fatal pulmonary embolism (PE), and all cause death at the end of the double-blind Intended Treatment Period in subjects undergoing elective unilateral or same day bilateral total knee replacement (TKR) surgery.

Key Secondary Efficacy Objective: To demonstrate that apixaban 2.5 mg BID PO was non-inferior (NI) to enoxaparin 40 mg QD SC for the composite endpoint of adjudicated proximal DVT, non-fatal PE, and venous thromboembolic event (VTE)-related death at the end of the double-blind Intended Treatment Period.

Safety Objectives: To assess the effect of apixaban 2.5 mg BID PO vs. enoxaparin 40 mg QD SC on:

- Adjudicated major bleeding
- Composite of adjudicated major and clinically relevant non-major (CRNM) bleeding events
- Adjudicated clinically relevant non-major bleeding

at the end of the double-blind Treatment Period.

Other safety objectives were to assess the overall safety and tolerability of apixaban and enoxaparin during the double-blind Treatment Period.

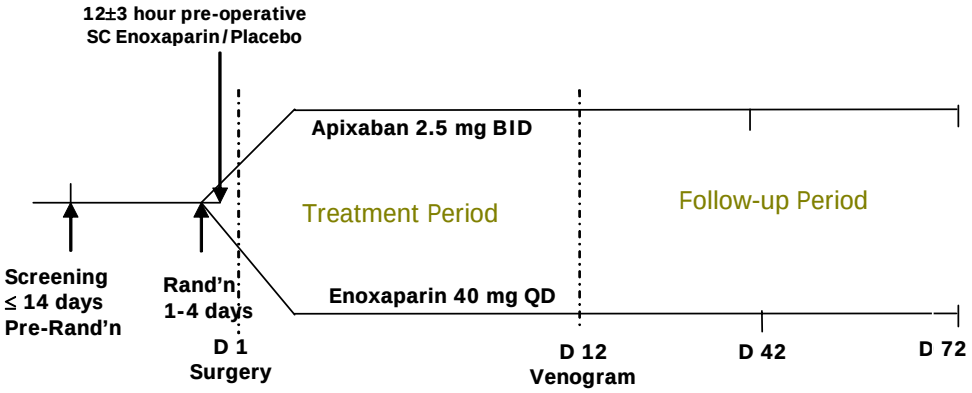
Pharmacokinetic Objectives: Amendment 3 to the study protocol added the following objectives:

- To characterize the population pharmacokinetics (PK) of apixaban and variability in PK parameters in subjects undergoing TKR surgery
- To characterize the relationship between plasma anti-factor Xa (FXa) activity and apixaban concentration
- To quantify the effect of selected covariates on variability in apixaban PK parameters in subjects undergoing TKR surgery
- To characterize the exposure-response relationships for primary efficacy endpoints, as well as selected clinically relevant secondary efficacy and safety endpoints
- To assess the impact of selected covariates on the exposure-response relationships.

METHODOLOGY: This was a Phase 3, multicenter, randomized, parallel-group study to evaluate the efficacy and safety of apixaban 2.5 mg BID PO compared to enoxaparin 40 mg QD SC, a drug approved and widely used for VTE prophylaxis following TKR and total hip replacement surgeries.

Subjects were randomized to double-blind treatment with (1) apixaban 2.5 mg BID or (2) enoxaparin 40 mg QD.

The study included: (1) a screening period that began no more than 14 days prior to randomization, (2) a randomization period 1 to 4 days prior to surgery, (3) a treatment period, starting with the first dose of SC study drug 12 (± 3) hours prior to surgery and extending through 11 days (± 2 days) after the surgery day, and (4) a 60 (± 5) day follow-up period starting the day after the last dose of study drug.



All apixaban-treated subjects received a matching enoxaparin-placebo injection. All enoxaparin-treated subjects received matching apixaban-placebo tablets.

A mandatory bilateral ascending contrast venogram was to be obtained 11 (± 2) days after the surgery day. 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). The number of subjects enrolled was 3221, and the final

number randomized was 3057 (apixaban 1528; enoxaparin 1529). A total of 3009 subjects (apixaban 1501; enoxaparin 1508) were treated with blinded study drug and 1973 subjects (apixaban 976; enoxaparin 997) were included in the primary efficacy data set.

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION: Males and females, including women of childbearing potential, ≥ 18 years of age, scheduled to undergo elective unilateral or same day bilateral TKR surgery (including revisions) who met the inclusion/exclusion criteria.

TEST PRODUCT, DOSE AND MODE OF ADMINISTRATION, DURATION OF TREATMENT, BATCH NUMBERS: Apixaban 2.5 mg or matching apixaban-placebo tablets. First PO dose 12 to 24 hours after completing skin wound closure; BID dosing through 11 days after the surgery day. Apixaban batch numbers were 7B27015, 7C229606, and 7H25317. Matching apixaban-placebo batch numbers were 7A29111, 6E18428, 7A28986, 7F30132, and 7C28811.

REFERENCE THERAPY, DOSE AND MODE OF ADMINISTRATION, DURATION OF TREATMENT, BATCH NUMBERS: Enoxaparin 40 mg SC or matching enoxaparin-placebo injections. Initial dose injected 12 ± 3 hours prior to surgery. The next dose was injected after skin wound closure as per investigator standard of care; QD dosing through 11 days after the surgery day. Enoxaparin batch numbers were 7B30375 and 6J19616. Matching enoxaparin-placebo batch numbers were 6M10413, 6M10414, 7E31029, 7F30132, and 7F30141.

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 myocardial infarction (MI), suspected acute stroke, and cause of death.

Efficacy: The primary efficacy endpoint was the composite of all adjudicated VTE (PE, symptomatic DVT, asymptomatic DVT) and all-cause death during the Intended Treatment Period. The key secondary efficacy endpoint was the composite of adjudicated asymptomatic and symptomatic proximal DVT, non-fatal PE, and VTE-related death during the Intended Treatment Period.

Safety: Bleeding was the primary safety endpoint, and included the following, if occurring during the Treatment Period (1) confirmed adjudicated major bleeding events, (2) composite of confirmed adjudicated major bleeding and confirmed adjudicated clinically relevant non-major (CRNM) bleeding events, and (3) adjudicated CRNM bleeding events.

Secondary Safety Endpoints: Assessment of adverse events (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).

Pharmacokinetics: The peak plasma concentration (Cmax), minimum plasma concentration (Cmin), and the time to reach the peak concentration (Tmax) were obtained from experimental observations. The area under the concentration-time curve in 1 dosing interval, AUC(TAU), was determined by summing the areas under the curve in 1 dosing interval, calculated by using conventional trapezoidal and log-trapezoidal methods.

Pharmacodynamics: The peak anti-factor Xa activity (peak anti-FXa), trough anti-FXa and the time to reach the observed peak anti-FXa activity (Tmax) were obtained from experimental observations for both treatment groups.

STATISTICAL CONSIDERATIONS: The primary and key secondary efficacy analyses were performed on randomized subjects who either had an event being part of the primary or key secondary efficacy outcomes in the Intended Treatment Period, or had adjudicated evaluable bilateral venograms (proximal venograms for key-secondary) in the Intended Treatment Period.

In order to control the overall type-I error rate, a sequential test procedure was performed to compare the effect of apixaban vs. enoxaparin on the primary and key secondary efficacy endpoints.

NI of apixaban vs. enoxaparin for the primary efficacy endpoint was tested first at a 1-sided $\alpha = 0.025$ level.

- If NI on the primary efficacy endpoint was demonstrated, superiority for the primary efficacy outcome was then tested at the 1-sided $\alpha = 0.025$ level
- If superiority was demonstrated on the primary efficacy endpoint, NI was then tested on the key secondary efficacy endpoint at a 1-sided $\alpha = 0.025$ level
- If NI of the key secondary efficacy endpoint was demonstrated, superiority for the key secondary efficacy endpoint was then tested at the 1-sided $\alpha = 0.025$ level.

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

- Upper bound of the 2-sided 95% confidence interval (CI) for relative risk (RR) < 1.25, and
- Upper bound of the 2-sided 95% CI for risk difference < 5.6%.

NI for apixaban on the key secondary efficacy endpoint would be demonstrated if the upper bound of the 2-sided 95% CI for RR < 1.5.

Superiority for an efficacy outcome would be demonstrated if the upper bound of the 2-sided 95% CI for relative risk was < 1.

The safety analysis included all treated subjects. For each primary safety endpoint, 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 the apixaban and enoxaparin groups.

SUMMARY OF RESULTS:

Disposition, Demographics, and Other Pertinent Baseline Characteristics:

A total of 3057 subjects were randomized to active study drug (Table 1). For randomized subjects, discontinuation rates from the Treatment Period were the same for 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. Most subjects were White and female. The mean age was 66 years. Approximately 20% of subjects were ≥ 75 years of age.

There were no clinically meaningful differences in the incidence or type of risk factors at baseline between the groups (Table 2). The majority of subjects in both groups had no risk factors at baseline. Of those subjects who did have risk factors at baseline, most had 1 risk factor only.

Table 1: Subject Disposition - Randomized Subjects

	Apix 2.5mg BID N = 1528	Enox 40mg QD N = 1529
SUBJECTS	1528	1529
SUBJECTS COMPLETING THE PERIOD (%)	1392 (91.1)	1393 (91.1)
SUBJECTS NOT COMPLETING THE PERIOD (%)	136 (8.9)	136 (8.9)
REASON FOR NOT COMPLETING THE PERIOD (%)		
LACK OF EFFICACY	0	0
DEATH	1 (<0.1)	0
ADVERSE EVENT	40 (2.6)	44 (2.9)
STROKE	2 (0.1)	0
THROMBOCYTOPENIA	1 (<0.1)	1 (<0.1)
MI	1 (<0.1)	1 (<0.1)
BLEEDING	4 (0.3)	5 (0.3)
DVT	11 (0.7)	8 (0.5)
PE	3 (0.2)	1 (<0.1)
OTHER	18 (1.2)	28 (1.8)
SUBJECT WITHDREW CONSENT	68 (4.5)	57 (3.7)
LOST TO FOLLOW-UP	1 (<0.1)	0
POOR/NON-COMPLIANCE	1 (<0.1)	2 (0.1)
PREGNANCY	0	0
SUBJECT NO LONGER MEETS STUDY CRITERIA	18 (1.2)	22 (1.4)
ADMINISTRATIVE REASON BY SPONSOR	0	0
OTHER	7 (0.5)	11 (0.7)
SUBJECTS CONTINUING THE STUDY (%)	1407 (92.1)	1422 (93.0)
SUBJECTS NOT CONTINUING THE STUDY (%)	121 (7.9)	107 (7.0)

The denominator to calculate each percentage is the number of randomized subjects.

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

	Apix 2.5mg BID N = 1528	Enox 40mg QD N = 1529	Total N = 3057
ANY RISK FACTOR? (%)			
YES	405 (26.5)	415 (27.1)	820 (26.8)
NO	1123 (73.5)	1113 (72.8)	2236 (73.1)
NOT REPORTED	0	1 (<0.1)	1 (<0.1)
TYPE OF RISK FACTOR (%)			
KNEE REPLACEMENT	257 (16.8)	286 (18.7)	543 (17.8)
HIP REPLACEMENT	90 (5.9)	80 (5.2)	170 (5.6)
HIP OR KNEE FRACTURE SURGERY	55 (3.6)	49 (3.2)	104 (3.4)
DVT	36 (2.4)	32 (2.1)	68 (2.2)
PE	10 (0.7)	10 (0.7)	20 (0.7)

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

Exposure: The extent of exposure to double-bind study drug was similar for subjects in both groups (Table 3).

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 = 1501	Enox 40mg QD N = 1508
=<3	49 (3.3)	40 (2.7)
4 - =<6	27 (1.8)	26 (1.7)
7 - =<9	30 (2.0)	35 (2.3)
10 - =<14	1202 (80.1)	1226 (81.3)
>14	193 (12.9)	181 (12.0)
MEAN(SD)	12.1 (3.14)	12.1 (2.75)
MEDIAN	12.0	12.0
MIN,MAX	1.0, 67.0	1.0, 41.0
TOTAL PATIENT-MONTHS	596.93	599.56

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

Efficacy Results: Superiority of apixaban relative to enoxaparin for the primary efficacy endpoint was demonstrated (1-sided p-value < 0.0001) (Table 4). Superiority of apixaban relative to enoxaparin for the key secondary efficacy endpoint was also demonstrated (1-sided p-value = 0.019) (Table 5).

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

	Apix 2.5 mg BID N=976	Enox 40 mg QD N=997
ALL VTE/ALL-CAUSE DEATH, N	147	243
EVENT RATE (%)	15.06	24.37
95% CI FOR EVENT RATE	(12.95, 17.46)	(21.81, 27.14)
RELATIVE RISK (APIX/ENOX)	0.62	
95% CI FOR RELATIVE RISK	(0.51, 0.74)	
ONE-SIDED P-VALUE FOR NON-INFERIORITY TEST ON RR	<0.0001*	
TWO-SIDED P-VALUE FOR NON-INFERIORITY TEST ON RR	<0.0001**	
RISK DIFFERENCE (%) (APIX-ENOX)	-9.27	
95% CI FOR RISK DIFFERENCE	(-12.74, -5.79)	
ONE-SIDED P-VALUE FOR NON-INFERIORITY TEST ON DIFFERENCE	<0.0001*	
TWO-SIDED P-VALUE FOR NON-INFERIORITY TEST ON DIFFERENCE	<0.0001**	
ONE-SIDED P-VALUE FOR SUPERIORITY TEST ON RR	<0.0001*	
TWO-SIDED P-VALUE FOR SUPERIORITY TEST ON RR	<0.0001**	

* denotes that the result is statistically significant at the one-sided 0.025 level
** denotes that the result is statistically significant at the two-sided 0.05 level

Table 5: Summary of Adjudicated Proximal DVT, Non-fatal PE and VTE-related Death with Onset During the Intended Treatment Period

	Apix 2.5 mg BID N=1195	Enox 40 mg QD N=1199
PROXIMAL DVT/NON-FATAL PE/VTE-RELATED DEATH, n/N	13	26
EVENT RATE (%)	1.09	2.17
95% CI FOR EVENT RATE	(0.62, 1.88)	(1.47, 3.18)
RELATIVE RISK (APIX/ENOX)	0.50	
95% CI FOR RELATIVE RISK	(0.26, 0.97)	
ONE-SIDED P-VALUE FOR NON-INFERIORITY TEST ON RR	0.0003*	
TWO-SIDED P-VALUE FOR NON-INFERIORITY TEST ON RR	0.0006**	
RISK DIFFERENCE (%) (APIX-ENOX)	-1.04	
95% CI FOR RISK DIFFERENCE	(-2.03, -0.05)	
ONE-SIDED P-VALUE FOR SUPERIORITY TEST ON RR	0.0186*	
TWO-SIDED P-VALUE FOR SUPERIORITY TEST ON RR	0.0373**	

Data set = Randomized subjects with either an adjudicated and evaluable bilateral proximal venogram or an adjudicated event associated with the endpoint, during the Intended Treatment Period
* denotes that the result is statistically significant at the one-sided 0.025 level
** denotes that the result is statistically significant at the two-sided 0.05 level

Safety Results: The event rates for AEs, bleeding-related AEs, SAEs, and discontinuations due to AEs were similar for the both groups during the Treatment Period (starting with the active enoxaparin or matching-placebo pre-surgery dose of study drug) (Table 6). Two (0.1%) deaths occurred in the apixaban group and none in the enoxaparin group from first dose through 30 days after last dose of study drug. Two deaths occurred during the Follow-up Period (1 in each group).

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

	APIX 2.5MG BID (N = 1501)	ENOX 40MG QD (N = 1508)
AE (%)	786 (52.4)	836 (55.4)
SAE (%)	72 (4.8)	88 (5.8)
Bleeding AE (%)	90 (6.0)	112 (7.4)
Discontinuations due to AE (%)	40 (2.7)	44 (2.9)
Deaths (%)	2 (0.1)	0

The denominator to calculate each percentage is the total number of treated subjects within each treatment group
AEs - included events up to 2 days (non-serious) or 30 days (serious) after the last dose of double-blind study drug
SAEs - included events up to 30 days after the last dose of double-blind study drug
Bleeding AEs - included events up to 2 days after the last dose of double-blind study drug
Deaths - included deaths occurring up to 30 days after the last dose of study drug

During the Treatment Period, there were no fatal bleeding events. Major bleeding events were infrequent, and event rates were lower in the apixaban group than in the enoxaparin group (Table 7). Observed event rates for CRNM bleeding, the composite of major or CRNM bleeding endpoint, and any bleeding (adjudicated or reported by the investigator), were also lower in the apixaban group compared to the enoxaparin group.

Table 7: Summary of Bleeding Endpoints During the Treatment Period - Treated Subjects

	Apix 2.5 mg BID N=1501	Enox 40 mg QD N=1508
MAJOR BLEEDING, N	9	14
EVENT RATE (%)	0.60	0.93
95% CI	(0.30, 1.16)	(0.54, 1.57)
ADJ. DIFF OF EVENT RATES (APIX-ENOX) (%)	-0.33	
95% CI	(-0.95, 0.29)	
TWO-SIDED P-VALUE	0.3014	
CLINICALLY RELEVANT NON-MAJOR BLEEDING, N	44	58
EVENT RATE (%)	2.93	3.85
95% CI	(2.19, 3.93)	(2.98, 4.95)
ADJ. DIFF OF EVENT RATES (APIX-ENOX) (%)	-0.91	
95% CI	(-2.20, 0.38)	
TWO-SIDED P-VALUE	0.1668	
MAJOR OR CLINICALLY RELEVANT NON-MAJOR BLEEDING, N	53	72
EVENT RATE (%)	3.53	4.77
95% CI	(2.71, 4.60)	(3.81, 5.98)
ADJ. DIFF OF EVENT RATES (APIX-ENOX) (%)	-1.24	
95% CI	(-2.66, 0.18)	
TWO-SIDED P-VALUE	0.0881	
ANY BLEEDING, N	104	126
EVENT RATE (%)	6.93	8.36
95% CI	(5.75, 8.34)	(7.06, 9.87)
ADJ. DIFF OF EVENT RATES (APIX-ENOX) (%)	-1.39	
95% CI	(-3.29, 0.51)	
TWO-SIDED P-VALUE	0.1412	

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

Pharmacokinetic Results: Limited PK data were available from this study; however, these data are consistent with previous findings. Individual apixaban Cmax and Cmin were comparable to the range reported in the Phase 2 VTE prevention trial (CV185010).

Pharmacodynamic Results: The Day 3 geometric mean apixaban anti-FXa activity profile reached the maximal level of 1.25 IU/mL 3 hours after apixaban administration and remained above 0.57 IU/mL 12 hours after apixaban administration prior to the next dose. The Day 3 geometric mean enoxaparin anti-FXa activity profile reached peak activity, approximately 0.31 IU/mL, 2-4 hours after drug admission and was at or below the assay detection limit 9 hours after administration in the majority of patients (5 out of 6).

CONCLUSIONS:

- Apixaban 2.5 mg BID was statistically significantly superior to enoxaparin 40 mg QD for the prevention of the composite endpoint of VTE/all-cause death
- Apixaban 2.5 mg BID was statistically significantly superior to enoxaparin 40 mg QD for the prevention of the composite endpoint of proximal DVT/non-fatal PE/VTE-related death
- The observed event rates for bleeding (major, CRNM or all bleeding) were lower for the apixaban regimen than the enoxaparin regimen
- The overall safety profile (AEs, SAEs, discontinuations due to AEs, LFT increases) was similar for apixaban and enoxaparin
- The observed rates for the infrequent events of MI, stroke, and thrombocytopenia were low and similar for the apixaban and enoxaparin groups
- The event rates for LFT elevations (alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase) were low and similar for apixaban and enoxaparin.

DATE OF REPORT: 17-Sep-2009