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APIXABAN

Clinical Study Report for Study CV185023

A Phase 2, Placebo-Controlled, Randomized, Double-Blind, Parallel-Arm, Dose Ranging Study to Evaluate Safety and Efficacy of Apixaban in Patients with a Recent Acute Coronary Syndrome

Indication:	Thromboprophylaxis
Phase:	2B
Study Initiation Date:	31-May-2006
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THIS STUDY WAS CONDUCTED IN ACCORDANCE WITH GOOD CLINICAL PRACTICE

Sponsor's Responsible Medical Officer:
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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: Apixaban		

SYNOPSIS

Final Clinical Study Report for Study CV185023

TITLE OF STUDY: A Phase 2, Placebo-controlled, Randomized, Double-blind, Parallel-arm, Dose-ranging Study to Evaluate Safety and Efficacy of Apixaban in Patients With a Recent Acute Coronary Syndrome

INVESTIGATORS/STUDY CENTERS: 173 sites in 14 countries (156 sites randomized at least 1 subject)

PUBLICATIONS: The APPRAISE Steering Committee and Investigators. Apixaban, an Oral, Direct, Selective Factor Xa Inhibitor in Combination with Antiplatelet Therapy After Acute Coronary Syndrome: Results of the Apixaban for Prevention of Acute Ischemic and Safety Events (APRAISE) Trial. Circulation. In Press.

STUDY PERIOD: Study Initiation Date: 31-May-2006 **CLINICAL PHASE:** 2B
Study Completion Date: 27-May-2008

OBJECTIVES: The primary objective was to evaluate 4 doses of apixaban as compared to placebo over a 26-week treatment period in selected subjects with recent (≤ 7 days) acute coronary syndrome (ACS) for safety, and to determine the optimal dose and regimen of apixaban for use in Phase 3 ACS treatment.

Secondary safety objectives were:

- To evaluate the incidence of cardiovascular (CV) and all-cause death, non-fatal myocardial infarction (MI), severe recurrent ischemia, and non-hemorrhagic stroke during the 30-day follow-up observation period after discontinuation of therapy
- To assess the incidence of adverse events (AEs) and abnormal clinical laboratory test results

There was no primary efficacy objective for this study. The secondary efficacy objectives were:

- To evaluate the incidence of the composite of CV death, non-fatal MI, severe recurrent ischemia and non-hemorrhagic stroke through Week 26
- To evaluate the incidence of the composite of all-cause death, non-fatal MI, severe recurrent ischemia and non-hemorrhagic stroke through Week 26

METHODOLOGY: CV185023 was a Phase 2B, randomized, double-blind, parallel-group, placebo-controlled study assessing the safety and efficacy of 4 doses of apixaban in subjects with recent (≤ 7days) ACS.

The study was conducted in 2 phases (A and B). In Phase A, subjects were randomized in a 1:1:1 ratio to placebo, apixaban 2.5 mg twice daily (BID) or apixaban 10 mg once daily (QD). In Phase B, subjects were randomized, originally in a 3:1:1:2:2 ratio, to placebo or apixaban 2.5 mg BID, 10 mg QD, 10 mg BID, or 20 mg QD. In both phases, all subjects were to receive ≤ 165 mg of aspirin daily. Randomization was stratified by clopidogrel status.

Approximately 6 months after the start of Phase B, the Data Safety Monitoring Board recommended that the apixaban 20 mg QD group, and subsequently the 10 mg BID group, be terminated due to excess bleeding for subjects receiving aspirin and clopidogrel concomitantly with the 2 high doses of apixaban. The sponsor, in consultation with the Steering Committee, made the decision to terminate the apixaban 20 mg QD and the 10 mg BID groups, halting continued treatment and any new randomization into these 2 groups, while continuing randomization and treatment in the lower dose apixaban groups. Subjects in Phase B were, from that point forward, randomized in a 3:1:1 ratio to placebo, apixaban 2.5 mg BID, and 10 mg QD.

Because of the premature termination of the 2 apixaban high-dose groups (10 mg BID and 20 mg QD) in Phase B, the median length of exposure in the apixaban 2.5 mg BID and 10 mg QD groups was approximately twice that of the 10 mg BID and 20 mg QD groups. Therefore, the primary analyses reported in this clinical study report are based on data for the placebo and 2 apixaban low-dose groups (2.5 mg BID and 10 mg QD) combined across Phase A and Phase B. The analyses of Phase B data across all doses of apixaban are secondary because of the premature termination of the apixaban high-dose groups and the lower duration of exposure.

NUMBER OF SUBJECTS (Planned and Analyzed): The study was originally sized so that a total of 1800 subjects would be randomized: 450 subjects in a 1:1:1 ratio to placebo, apixaban 2.5 mg BID or apixaban 10 mg QD in Phase A, and 1350 subjects in a 3:1:1:2:2 ratio to placebo, apixaban 2.5 mg BID, apixaban 10 mg QD, apixaban 10 mg BID and apixaban 20 mg QD in Phase B. Because of the termination of the 2 apixaban high-dose groups in Phase B, the actual number of subjects randomized was 1715: 547 in Phase A (184 to placebo, 179 to apixaban 2.5 mg BID, and 184 to apixaban 10 mg QD) and 1168 in Phase B (427 to placebo, 138 to apixaban 2.5 mg BID, 134 to apixaban 10 mg QD, 248 to apixaban 10 mg BID, and 221 to apixaban 20 mg QD).

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION: Eligible subjects were males and females between 18 and 90 years of age with a recent (≤ 7 days) ACS, characterized by symptoms of myocardial ischemia and either elevation in cardiac markers or dynamic ST segment deviation, and with either unknown coronary anatomy or angiographic evidence of atherosclerotic plaque in any major coronary artery, significant branch, or coronary bypass graft, plus 1 additional cardiovascular risk characteristic. Subjects were to be clinically stable and receiving standard care for ACS, including antiplatelet therapy (aspirin ≤ 165 mg/day, with or without clopidogrel 75 mg/day based on the choice of the treating physician).

TEST PRODUCT, DOSE AND MODE OF ADMINISTRATION, DURATION OF TREATMENT, BATCH NUMBERS: Apixaban 2.5 mg or 10 mg tablets and matching placebo were supplied in blister packs. Subjects took 3 tablets BID orally; the 3 tablets were a combination of active and placebo tablets such that a dose of 2.5 mg BID, 10 mg QD, 10 mg BID, and 20 mg QD of apixaban was taken daily for 26 weeks. The apixaban tablets were taken from the following batch numbers: 5E05267, 5M01128, 6D20372, 5M02622, 6D16028, 6D16098, and 6E17172.

REFERENCE THERAPY, DOSE AND MODE OF ADMINISTRATION, DURATION OF TREATMENT, BATCH NUMBERS: Placebo tablets identical in appearance to the apixaban 2.5 mg and 10 mg tablets were supplied in blister packs. Subjects took 3 tablets BID orally for 26 weeks. The placebo tablets were taken from the following batch numbers: 4L75638, 5K9998, 5K9999, 6D16574, 5K06306, 5K06307, 5K06310, 5K08727, 6D16577, and 6F20082.

CRITERIA FOR EVALUATION: All suspected efficacy events and all non-trivial bleeding events were adjudicated by the Clinical Events Committee.

Efficacy: The primary objective of this study was related to safety. Therefore, there was no primary efficacy endpoint. Secondary efficacy endpoints were the time from randomization to the first occurrence of:

- the composite of confirmed CV death, non-fatal MI, severe recurrent ischemia, and non-hemorrhagic stroke through Week 26
- the composite of confirmed all-cause death, non-fatal MI, severe recurrent ischemia, and non-hemorrhagic stroke through Week 26.

An additional secondary efficacy endpoint was added after unblinding of treatment assignments: the time from randomization to the first occurrence of confirmed composite of CV death, non-fatal MI, and non-hemorrhagic stroke occurring through Week 26.

Safety: The primary safety endpoint was the composite of major bleeding, adjudicated according to the International Society on Thrombosis and Hemostasis (ISTH), and clinically relevant non-major bleeding (CRNM) occurring between first dose of study drug and 2 days after study drug discontinuation. Additional bleeding-related safety measures were the individual components of major and CRNM bleeding, bleeding-related AEs, and all bleeding outcomes identified by the investigators. Safety was also assessed through review of all reported AEs, AEs of special interest, including liver function test elevations reported as AEs, neurologic AEs, and clinical laboratory test results occurring between the first dose of study drug and 2 days after study drug discontinuation.

Pharmacokinetics: Plasma concentrations in peak and trough sampling windows were assessed.

Pharmacodynamics: Individual exploratory pharmacodynamic biomarkers of coagulation, thrombogenesis, and inflammation were assessed.

STATISTICAL CONSIDERATIONS:

The safety data set included all treated subjects. The proportion of subjects with confirmed major bleeding or CRNM bleeding events during the Treatment Period (defined as the period from the first dose through 2 days after the last dose of study drug) was summarized by treatment group. Point estimates and 95% confidence intervals (CIs) for event rates were presented by treatment group, together with point estimates and 95% CIs for the difference in event rates between each apixaban group and placebo.

Two sets of safety analyses were performed for all safety endpoints:

- Analyses that included data from all subjects randomized to placebo and the 2 low doses of apixaban (2.5 mg BID and 10 mg QD); study phase was an additional stratum in the calculation of the CIs
- Analyses that included data from all subjects randomized to the 5 treatment groups in Phase B using data from subjects with comparable exposures

The efficacy data set included all randomized subjects. Point estimates and 95% CIs for the hazard ratio between each apixaban group and placebo were calculated for each efficacy endpoint using a Cox proportional hazard model, with randomization group and use of clopidogrel at randomization as stratification factors. Kaplan-Meier curves were plotted for each of the efficacy endpoints by treatment group.

Two sets of analyses were performed for the efficacy endpoints:

- Analyses that included data from all subjects randomized to placebo and the 2 low doses of apixaban (2.5 mg BID and 10 mg QD)
- Analyses that included data from all subjects randomized to the 5 treatment groups in Phase B using data from subjects with comparable exposures

SUMMARY OF RESULTS:

Disposition and Baseline/Demographic Characteristics: Among all randomized subjects, most subjects (approximately 76% to 77%) in each of the apixaban low-dose groups and the placebo group completed the 26-week treatment period, while only 6% of subjects in each of the apixaban high-dose groups completed the 26-week treatment period (Table 1).

Table 1: Subject Disposition: All Randomized Subjects

	Number of Subjects (%)				
		Apixaban			
	Placebo N = 611	2.5 mg BID N = 317	10 mg QD N = 318	10 mg BID N = 248	20 mg QD N = 221
Completed the period	463 (76)	245 (77)	243 (76)	15 (6)	13 (6)
Did not complete the period	148 (24)	72 (23)	75 (24)	233 (94)	208 (94)
Most common reason for not completing					
Adverse event	53 (9)	23 (7)	29 (9)	23 (9)	19 (9)
Withdrew consent	55 (9)	26 (8)	32 (10)	15 (6)	19 (9)
Administrative reason	3 (<1)	1 (<1)	0	193 (78)	164 (74)

Baseline demographic characteristics, qualifying events, and ACS treatments for index events were similar between treatment groups. Most subjects were white (99%) and male (76%). The mean age was 61 years; 38% of subjects were ≥ 65 years. Approximately 63% of subjects were randomized following ST segment elevation MI; approximately half of the subjects had at least mild renal impairment (Table 2).

Table 2: Baseline Disease and Other Characteristics: All Randomized Subjects

	Number of Subjects (%)				
		Apixaban			
	Placebo N = 611	2.5 mg BID N = 317	10 mg QD N = 318	10 mg BID N = 248	20 mg QD N = 221
Characteristic of index event					
STE-MI	374 (61)	197 (62)	213 (67)	150 (61)	140 (63)
Non STE-MI	194 (32)	89 (28)	84 (26)	73 (29)	64 (29)
Unstable angina	43 (7)	31 (10)	21 (7)	25 (10)	17 (8)
Most common risk factors					
Elevation in cardiac markers & dynamic ST deviation ≥ 1mm	463 (76)	238 (75)	257 (81)	189 (76)	173 (78)
Age ≥65 years	237 (39)	130 (41)	121 (38)	83 (34)	89 (40)
Mild or moderate renal insufficiency	196 (32)	106 (33)	91 (29)	71 (29)	58 (26)

The most common ACS treatments for the index event reported at baseline were aspirin (99%), clopidogrel (76%), unfractionated heparin (76%), and percutaneous coronary intervention (65%).

Exposure:

The per protocol treatment period was 26 weeks. Because of the early termination of the apixaban high-dose groups in Phase B, the median exposures in the 10 mg BID and 20 mg QD groups were approximately half the exposures for the placebo and apixaban 2.5 mg BID and 10 mg QD groups (Table 3).

Table 3: Length of Exposure - All Treated Subjects

		Apixaban			
Weeks	Placebo N = 599	2.5 mg BID N = 315	10 mg QD N = 315	10 mg BID N = 244	20 mg QD N = 218
Mean (SD)	22 (9.1)	22 (8.6)	22 (9.1)	13 (8.3)	11 (8.2)
Median	26	26	26	13	9
Min, max	0.1, 31	0.1, 30	0.1 29	0.1, 27	0.1, 29

Concomitant medications: Consistent with the protocol, 99% of treated subjects received concomitant aspirin; 79% received concomitant clopidogrel. Concomitant standard ACS medications such as beta-blockers (92%), angiotensin converting enzyme inhibitors and angiotensin receptor blockers (86%), and statins (89%) were also common.

Efficacy Results:

The main efficacy endpoints of interest were time from randomization to first occurrence of:

- the composite of confirmed CV death, non-fatal MI, severe recurrent ischemia, or non-hemorrhagic stroke
- the composite of CV death, non-fatal MI, or non-hemorrhagic stroke

A dose-related reduction was observed (based on estimates of hazard ratios) for both of these endpoints, but the 95% CIs for the hazard ratios associated with each apixaban group versus placebo included 1 (Table 4). Note that this study was designed to assess safety and was not powered to detect a treatment effect (hazard reduction of apixaban versus placebo) for any of the efficacy endpoints.

Risk reductions (hazard ratios < 1) for the quadruple endpoint were observed for both the apixaban low-dose groups within each of the clopidogrel subgroups; the 95% CIs for the hazard ratios included 1 for both apixaban low-dose groups versus placebo.

Table 4: Summary of Selected Efficacy Endpoints During the Intended Treatment Period - Subjects Randomized to Placebo or Apixaban Low Doses

	Placebo N = 611	Apix 2.5 mg BID N = 317	Apix 10 mg QD N = 318
CV death/non-fatal MI/ severe recurrent ischemia/non-hemorrhagic stroke			
n	53	24	19
Hazard ratio (95% CI)		0.7 (0.4, 1.2)	0.6 (0.4, 1.0)
Baseline clopidogrel	(N = 462)	(N = 232)	(N = 243)
n	30	13	12
Hazard ratio (95% CI)		0.8 (0.4, 1.5)	0.7 (0.3, 1.3)
Baseline no clopidogrel	(N = 149)	(N = 85)	(N = 75)
n	23	11	7
Hazard ratio (95% CI)		0.7 (0.3, 1.5)	0.5 (0.2, 1.3)
CV death/non-fatal MI/non-hemorrhagic stroke			
n	32	17	10
Hazard ratio (95% CI)		0.9 (0.5, 1.7)	0.6 (0.3, 1.2)
All-cause death/non-fatal MI/severe recurrent ischemia/non-hemorrhagic stroke			
n	54	24	20
Hazard ratio (95% CI)		0.7 (0.4, 1.2)	0.6 (0.4, 1.1)

Safety Results:

A dose-related increase in the composite of adjudicated major or CRNM bleeding was observed with the addition of apixaban to antiplatelet therapy (Table 5). The 95% CIs for the event rate differences (apixaban versus placebo) included 0 (no difference) for apixaban 2.5 mg BID group and were above 0 for the apixaban 10 mg QD group.

A dose-related increase in this endpoint was most apparent in the subgroup of subjects receiving clopidogrel at baseline.

Table 5: Summary of Selected Bleeding Endpoints During the Treatment Period - Subjects Treated with Placebo or Apixaban Low Doses

	Placebo	Apix 2.5 mg BID	Apix 10 mg QD
Major or CRNM bleeding (Primary endpoint)	N = 599	N = 315	N = 315
n	18	18	25
Event rate, % (95% CI)	3.0 (1.8, 4.7)	5.7 (3.4, 8.9)	7.9 (5.2, 11.5)
Adjusted rate difference (95% CI)		2.2 (-1.0, 5.4)	3.8 (0.4, 7.3)
Baseline clopidogrel	N = 453	N = 230	N = 241
n	14	16	22
Event rate, % (95% CI)	3.1 (1.7, 5.1)	7.0 (4.0, 11.1)	9.1 (5.8, 13.5)
Adjusted rate difference (95% CI)		3.2 (-0.5, 7.0)	5.5 (1.3, 9.8)
Baseline no clopidogrel	N = 146	N = 85	N = 74
n	4	2	3
Event rate, % (95% CI)	2.7 (0.8, 6.9)	2.4 (0.3, 8.2)	4.1 (0.8, 11.4)
Adjusted rate difference (95% CI)		-0.7 (-6.3, 4.9)	0.8 (-4.9, 6.5)
Major bleeding	N = 599	N = 315	N = 315
n	5	5	6
Event rate, % (95% CI)	0.8 (0.3, 1.9)	1.6 (0.5, 3.7)	1.9 (0.7, 4.1)
Adjusted rate difference (95% CI)		0.3 (-1.3, 2.0)	0.8 (-1.1, 2.7)
All bleeding	N = 599	N = 315	N = 315
n	63	65	71
Event rate, % (95% CI)	10.5 (8.2, 13.3)	20.6 (16.3, 25.5)	22.5 (18.0, 27.6)
Adjusted rate difference (95% CI)		6.6 (1.8, 11.3)	10.0 (4.8, 15.2)

Footnote: Adjusted difference of event rates takes into consideration stratification factor(s)

A dose-related increase in the composite of adjudicated major or CRNM bleeding was observed with the addition of apixaban to antiplatelet therapy during the Phase B Adjusted Treatment Period. Event rates were 0.8% for placebo, 5.0% for apixaban 2.5 mg BID, 5.6% for apixaban 10 mg QD, 7.8% for apixaban 10 mg BID, and 7.3% for apixaban 20 mg QD. All 95% CIs for the event rate differences (for each apixaban dose group versus placebo) were above 0.

The event rates for AEs, SAEs, and AEs leading to discontinuation during the Treatment Period were similar between apixaban 2.5 mg BID and 10 mg QD groups and placebo (Table 6). The event rates for bleeding-related AEs were higher in the apixaban 2.5 mg BID and 10 mg QD dose groups compared with placebo.

Most SAEs with the outcome of death during the Treatment Period were cardiac disorders. SAEs with the outcome of death were reported for 11 (3.5%) subjects in the apixaban 2.5 mg BID group; 5 (1.6%) subjects in the apixaban 10 mg QD group; and 12 (2.0%) subjects in the placebo group (Table 6). The overall incidence of AEs with onset during the Treatment Period was similar for the apixaban low-dose groups and placebo. Adverse events reported for at least 5% of subjects in either apixaban group were chest pain, headache, contusion, epistaxis, angina pectoris, dizziness, hematoma, dyspnea, and hypertension.

Table 6: Summary of Safety During the Treatment Period - Subjects Treated with Placebo or Apixaban Low Doses

	Number of Subjects (%)		
	Placebo N = 599	Apix 2.5 mg BID N = 315	Apix 10 mg QD N = 315
Adverse event	444 (74.1)	230 (73.0)	243 (77.1)
Serious adverse event	125 (20.9)	73 (23.2)	72 (23.0)
Bleeding adverse event	64 (10.7)	65 (20.6)	75 (23.8)
Discontinuation due to adverse event	50 (8.3)	26 (8.3)	29 (9.2)
Deaths	12 (2.0)	11 (3.5)	5 (1.6)

During follow-up, bleeding AEs were reported for ≤ 1.0% of subjects in the 2 apixaban low-dose groups and for 1.6% of subjects in the placebo group.

Low hemoglobin and hematocrit were more frequent for the apixaban 2.5 mg BID and/or the 10 mg QD group compared with placebo, consistent with the expected anticoagulant effect of apixaban versus placebo. There were no treatment differences in the incidence of other marked clinical laboratory abnormalities, such as elevated ALT and total bilirubin, and potassium.

Pharmacokinetic Results: A dose-related increase in both the peak and trough apixaban plasma concentrations was reported for the apixaban 2.5 mg BID and 10 mg BID groups.

Pharmacodynamic Results: Anti-Xa values are expressed in apixaban units (apixaban) and low molecular weight heparin (LMWH) units. There was an apparent linear relationship between anti-Xa (apixaban) and apixaban concentration. A similar linear relationship was observed for anti-Xa (LMWH) and apixaban concentration.

After 3 weeks of treatment, D-dimer and F1.2 values decreased compared to baseline, with larger decreases observed in apixaban groups compared to placebo.

CONCLUSIONS:

- A dose-related increase in bleeding events across all bleeding categories (composite of ISTH major and CRNM bleeding, ISTH major bleeding alone, and all bleeding events reported by the investigator) was observed with the addition of apixaban to contemporary antiplatelet therapy.
- A dose-related trend toward reductions in clinically important ischemic events was observed with the addition of apixaban to contemporary antiplatelet therapy in ACS subjects who received a high standard of ACS care.
- The observed increase in bleeding was more pronounced and the observed reduction in ischemic events was smaller in subjects receiving contemporary dual antiplatelet therapy.
- The observed rates for AEs, SAEs and discontinuations due to AEs were similar for all apixaban groups and placebo.
- Liver function test elevations were infrequent and the observed rates were similar for all apixaban groups and placebo.
- The results of study CV185023 suggest incremental benefit of chronic anticoagulation with apixaban on a background of optimal medical management (including dual anti-platelet therapy) and support further study in a Phase 3 trial of apixaban in subjects at high risk of ischemic events.

DATE OF REPORT: 16-Apr-2009