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 CV185068

TITLE OF STUDY: A Phase 3, Randomized, Double-Blind, Evaluation of the Safety and Efficacy of Apixaban in Subjects with a Recent Acute Coronary Syndrome

INVESTIGATORS/STUDY CENTERS: 861 sites in 40 countries (858 sites randomized at least 1 subject)

PUBLICATIONS: None

STUDY PERIOD: First Subject First Visit: 17-Mar-2009 **CLINICAL PHASE:** 3

Last Subject Last Visit: 04-Mar-2011

OBJECTIVES:

Primary Objective: To determine if apixaban is superior to placebo for preventing the composite of cardiovascular (CV) death, myocardial infarction (MI), or ischemic stroke, in subjects with a recent acute coronary syndrome (ACS).

Secondary Objectives: To determine, in subjects with recent ACS, if apixaban was superior to placebo for preventing:

- the composite of CV death, MI, unstable angina (UA), or ischemic stroke
- the composite of CV death, fatal bleeding, MI, or stroke (ischemic or hemorrhagic)
- the composite of all-cause death, MI, or stroke (ischemic or hemorrhagic).

To determine, in subjects with recent ACS, if apixaban was superior to placebo for preventing the composite of CV death, MI, or ischemic stroke within each of the following baseline subpopulations: subjects with diabetes mellitus; subjects receiving single antiplatelet therapy; subjects receiving dual antiplatelet therapy; subjects undergoing percutaneous coronary intervention (PCI); subjects not undergoing PCI.

To compare apixaban 5 mg twice daily (BID) and placebo with respect to major bleeding, as defined by Thrombolysis in Myocardial Infarction (TIMI) bleeding criteria.

METHODOLOGY: APPRAISE-2 (CV185068) was a Phase 3, multicenter, randomized, placebo-controlled, parallel group study to evaluate the efficacy and safety of apixaban compared with placebo in subjects with recent ACS and at least 2 additional risk factors for recurrent ischemic events.

Subjects were randomized 1:1 to either apixaban or matching placebo following cessation of parenteral anticoagulation therapy. Randomization was stratified by type of antiplatelet (single or dual) therapy at

baseline. Subjects with a calculated creatinine clearance (CrCL) <40 mL/min at the time of randomization received apixaban 2.5 mg BID or matching placebo.

The Treatment Period of the study was planned to be completed after at least 938 subjects had a primary efficacy endpoint confirmed by adjudication. After 7392 subjects had been randomized into the study, and following regular reviews of safety and efficacy data, on 14-Nov-2010, an independent Data Monitoring Committee (DMC) made a recommendation that the study be terminated early due to a clinically important increase in bleeding among subjects randomized to apixaban which was not offset by meaningful reductions in ischemic events. This recommendation was accepted by the APPRAISE-2 Steering Committee chairman and the study sponsors. Investigators were notified and final study visits were scheduled. Therefore, the original target number of subjects randomized, and target number of efficacy events was not achieved prior to ending the study.

NUMBER OF SUBJECTS (Planned and Analyzed): Planned: 10,800 subjects (5400 in each group); randomized: 7392 (3705 on apixaban and 3687 on placebo); treated 7315 (3672 on apixaban and 3643 on placebo).

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION: Eligible **s**ubjects were males and females ≥ 18 years of age with a recent ST-segment elevation (STE) or non-ST- segment elevation (NSTE) ACS (including UA). Subjects were to have completed parenteral anticoagulation therapy for the index ACS event and to be clinically stable, receiving standard of care for ACS, including single (aspirin or a $P2Y_{12}$ antagonist) or dual (aspirin plus a $P2Y_{12}$ antagonist) antiplatelet therapy, at the discretion of the treating physician.

TEST PRODUCT, DOSE AND MODE OF ADMINISTRATION, DURATION OF TREATMENT, BATCH NUMBERS: Oral apixaban 5 mg or 2.5 mg tablets BID were administered for an average of 27 months. Apixaban 5 mg tablets batch numbers: 8L40941, 8L41121, 9F46089, 9M36608. Apixaban 2.5 mg tablets batch numbers: 8K43005, 9K50676.

REFERENCE THERAPY, DOSE AND MODE OF ADMINISTRATION, DURATION OF TREATMENT, BATCH NUMBERS: Oral placebo tablets identical in appearance to the apixaban 2.5 mg and 5 mg tablets were administered for an average of 28 months. The matching placebo for apixaban 5 mg tablets batch numbers: 8K46568, 9F53487, 9M36561. The matching placebo for apixaban 2.5 mg tablets batch numbers: 8M32676, 9E45739.

CRITERIA FOR EVALUATION: All suspected efficacy events and all non-minimal bleeding events were adjudicated by the Clinical Event Committee (CEC).

Efficacy: The primary efficacy endpoint was the time to first occurrence of CV death, MI, or ischemic stroke. The secondary efficacy endpoints were the time to first occurrence of:

- CV death, MI, UA, or ischemic stroke
- CV death, fatal bleeding, MI or stroke (ischemic or hemorrhagic)
- Death (all-cause), MI or stroke (ischemic or hemorrhagic)
- CV death
- MI
- Ischemic stroke
- UA
- Stent thrombosis

Safety: The primary safety endpoint was the time to first occurrence of TIMI major bleeding. The secondary safety endpoint was the time to first occurrence of International Society on Thrombosis and Hemostasis (ISTH) major, major or clinically relevant non-major (CRNM) bleeding, and all bleeding

events reported by investigator. Other safety outcome measures assessed included TIMI minor bleeding, Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO) (severe, major and minor) bleeding, other adverse events (AEs), electrocardiograms (ECGs), abnormal standard clinical laboratory test result. Though not pre-specified in the Statistical Analysis Plan (SAP), bleeding events according to GUSTO criteria were also assessed.

STATISTICAL CONSIDERATIONS:

Sample Size: This study was powered to detect a 20% risk reduction of apixaban versus placebo at the one-sided α=0.005 (equivalent to a two-sided 0.01 level). With 938 subjects with the confirmed primary efficacy endpoint, the study had 80% power to detect a 20% risk reduction of apixaban versus placebo when testing at the one-sided $\alpha = 0.005$ and ~ 93% power to detect the same risk reduction when testing at the one-sided $\alpha = 0.025$.

The sample size and length of follow-up required to achieve this number of events would have depended on the accrual rate and the annual event rates. With an accrual period of 2 years, an average follow-up of 1.25 years and assuming a primary efficacy event rate of 8 events per hundred-subject years, a total of 10,800 subjects randomized in a 1:1 ratio to placebo or apixaban would have been required to achieve the desired number of events. These calculations further assumed an incidence of 1% loss to follow-up.

Efficacy Analyses:

Censoring scheme: subjects who did not experience an efficacy endpoint were censored at the earliest of their death date (when death is not part of the endpoint), last contact date (for subjects who withdrew consent to be followed up or were lost to follow-up) or the efficacy cut-off date.

A test of superiority at the one-sided $\alpha = 0.025$ significance level for the primary efficacy outcome was performed using a Cox proportional hazards model including treatment group as a covariate and stratified by type of anti-platelet therapy at baseline (single versus dual anti-platelet therapies). A point estimate and two-sided 95% confidence interval (CI) for the relative risk (RR) as measured by the hazard ratio (HR) was calculated based on this Cox proportional hazards model.

For each secondary efficacy endpoint, a Cox proportional hazards model including treatment group as a covariate was used to estimate RR and two-sided 95% CIs for RR within each stratum associated with type of antiplatelet therapy at randomization (single, dual).

Safety Analyses:

Censoring scheme: subjects who did not experience a bleeding endpoint were censored at the earlier of 2 days after discontinuation of study drug, death date, last contact date (for subjects who withdraw consent to be followed up or are lost to follow-up).

A point estimate and two-sided 95% CI for RR, as measured by the HR, and a p-value for the test of equality of rates (HR = 1) was calculated for the primary safety outcome. The test was performed using a Cox proportional hazards model including treatment group as a covariate and stratified by type of anti-platelet therapy at baseline (single or dual anti-platelet therapies).

Similar analyses to those performed for the primary safety endpoint were performed for each of the secondary bleeding endpoints.

SUMMARY OF RESULTS:

Disposition and Baseline/Demographic Characteristics: The mean duration of exposure to study drug was approximately 27 weeks for subjects in the apixaban group and 28 weeks for subjects in the placebo group. A total of 7484 subjects were enrolled in the study; of these subjects, 7392 (98.8%) were randomized to receive study treatment. All subjects discontinued the study following the decision of Steering Committee chairman and the sponsors' decision to terminate the study.

This study enrolled globally a high risk post-ACS population as characterized by advanced age and multiple cardiac and non-cardiac co-morbidities, e.g., diabetes, heart failure. The treatment groups were balanced for baseline demographic characteristics, qualifying events, and ACS treatments for index events (Table 1). Most subjects (91.5%) randomized to the apixaban group received the apixaban 5 mg BID dose.

Most subjects were randomized following non-STEMI (42.8%) or STEMI (38.4%), while only 18.8% were randomized following unstable angina. Aspirin (98.6%), clopidogrel (84.7%), unfractionated heparin [UFH] (47.6%), low molecular weight heparin [LMWH] (42.5%), and PCI (44%) were the most commonly reported treatments for the index ACS event at baseline. Comparison of frequency of ACS treatments for index events between apixaban and placebo groups showed no differences that were deemed to be clinically relevant, overall and within each antiplatelet therapy (dual or single) stratum.

Table 1: Baseline Demographic and Disease Characteristics - Randomized Subjects

	Placebo N=3687	Apixaban N=3705	Total N=7392
Age (yrs)			
Mean (SD)	65.4 (11.05)	65.3 (10.89)	65.4 (10.97)
Median	67.0	67.0	67.0
Min, Max	21.0 - 93.0	24.0 - 98.0	21.0 - 98.0
Gender (n, %)			
Male	2518 (68.3)	2496 (67.4)	5014 (67.8)
Female	1169 (31.7)	1209 (32.6)	2378 (32.2)
Race (n, %)			
White	2802 (76.0)	2781 (75.1)	5583 (75.5)
Black/African-American	82 (2.2)	91 (2.5)	173 (2.3)
Asian	649 (17.6)	669 (18.1)	1318 (17.8)
American Indian or Alaska Native	33 (0.9)	41 (1.1)	74 (1.0)
Native Hawaiian or Pacific Islander	2 (<0.1)	0	2 (<0.1)
Other	119 (3.2)	123 (3.3)	242 (3.3)
Characteristic of index event (%)			
STEMI	1412 (38.3)	1426 (38.5)	2838 (38.4)
NSTEMI	1582 (42.9)	1581 (42.7)	3163 (42.8)
Unstable angina	693 (18.8)	698 (18.8)	1391 (18.8)
Type of risk factors at enrollment (%)			
Age ≥65 years	2175 (59.0)	2179 (58.8)	4354 (58.9)
Diabetes mellitus	1732 (47.0)	1804 (48.7)	3536 (47.8)
Prior MI	996 (27.0)	899 (24.3)	1895 (25.6)
Ischemic cardiovascular disease	364 (9.9)	375 (10.1)	739 (10.0)
Peripheral vascular disease	674 (18.3)	664 (17.9)	1338 (18.1)
Heart failure or LVEF <40% with index ACS event	1871 (50.7)	1847 (49.9)	3718 (50.3)
Impaired renal function	599 (16.2)	582 (15.7)	1181 (16.0)
No revascularization for index ACS event	2034 (55.2)	2061 (55.6)	4095 (55.4)

Efficacy Results:

Due to the early termination of the study, only 572 (61% of the target 938) of the primary efficacy endpoints were accrued. Apixaban, on a background of antiplatelet therapy (80% dual), did not demonstrate a statistically significant reduction nor did it show a clinically meaningful reduction in recurrent ischemic events in high-risk, post-ACS subjects (Table 2).

Table 2: Summary of Primary Efficacy Endpoint During the Intended Treatment Period - Randomized Subjects

	Placebo N=3687	Apixaban N=3705
ALL RANDOMIZED SUBJECTS		
CV DEATH/MI/ISCHEMIC STROKE	293 (7.95)	279 (7.53)
EVENT RATE (%/YR)	13.96	13.20
HAZARD RATIO (APIXABAN/PLACEBO)		0.95
95% CI FOR HAZARD RATIO		(0.80, 1.11)
TWO-SIDED P-VALUE		0.5094
FIRST EVENT, n (%)		
CV DEATH	79 (2.14)	82 (2.21)
MI	183 (4.96)	179 (4.83)
ISCHEMIC STROKE	31 (0.84)	18 (0.49)
CENSORED, n (%)	3394 (92.05)	3426 (92.47)
DEATH (CAUSE OTHER THAN CV) DURING ITP	31 (0.84)	44 (1.19)
WITHDREW CONSENT TO BE FOLLOWED	40 (1.08)	41 (1.11)
LOST TO FOLLOW-UP	19 (0.52)	31 (0.84)
COMPLETED ITP	3304 (89.61)	3310 (89.34)
FIRST EVENT AFTER COMPLETING ITP	14 (0.38)	32 (0.86)
BY TYPE OF ANTIPLATELET THERAPY		
DUAL, n/N(%)	222/ 2965 (7.49)	213/ 2968 (7.18)
EVENT RATE (%/YR)	13.95	13.28
HAZARD RATIO (APIXABAN/PLACEBO)		0.95
95% CI FOR HAZARD RATIO		(0.79, 1.15)
TWO-SIDED P-VALUE		0.6255
SINGLE, n/N(%)	71/ 722 (9.83)	66/ 737 (8.96)
EVENT RATE (%/YR)	13.99	12.97
HAZARD RATIO (APIXABAN/PLACEBO)		0.92
95% CI FOR HAZARD RATIO		(0.66, 1.29)
TWO-SIDED P-VALUE		0.6324

Apixaban, compared with placebo, did not show a clinically meaningful reduction in the secondary composite or individual efficacy endpoints, overall or within each antiplatelet therapy stratum other than possibly for stent thrombosis; the observed HR for stent thrombosis was 0.73 with a 95% CI of (0.47, 1.12). The incidence of all-cause death was similar in both treatment groups, overall and within each antiplatelet therapy (dual or single) stratum. However, the event rate in non-CV death was higher in apixaban than placebo (1.46 per 100-pt yrs [32]) in apixaban and (0.83 per 100-pt yrs [18]) in placebo, mainly driven by hemorrhagic stroke (9 [0.24%] subjects in apixaban group and none in placebo group).

Table 3: Summary of Individual Efficacy Endpoints During the Intended Treatment Period - Randomized Subjects

	Placebo (N=3687)	Apixaban (N=3705)
MI, n (%)	194 (5.26)	182 (4.91)
EVENT RATE (%/YR)	9.20	8.59
HAZARD RATIO (APIXABAN/PLACEBO)		0.93
95% CI FOR HAZARD RATIO		(0.76, 1.14)
TWO-SIDED P-VALUE		0.5086
MI TYPES, n (%)		
STEMI	36 (0.98)	29 (0.78)
NSTEMI	131 (3.55)	122 (3.29)
UNKNOWN MI TYPE	27 (0.73)	30 (0.81)
UNSTABLE ANGINA, n (%)	90 (2.44)	85 (2.29)
EVENT RATE (%/YR)	4.21	3.95
HAZARD RATIO (APIXABAN/PLACEBO)		0.94
95% CI FOR HAZARD RATIO		(0.70, 1.26)
TWO-SIDED P-VALUE		0.6702
STROKE, n (%)	40 (1.08)	36 (0.97)
EVENT RATE (%/YR)	1.85	1.65
HAZARD RATIO (APIXABAN/PLACEBO)		0.90
95% CI FOR HAZARD RATIO		(0.57, 1.40)
TWO-SIDED P-VALUE		0.6311
STROKE TYPE, n (%)		
PRIMARY HEMORRHAGIC	1 (0.03)	9 (0.24)
CEREBRAL PARENCHYMA	0	5 (0.13)
SUBARACHNOID	1 (0.03)	1 (0.03)
INTRAVENTRICULAR	0	2 (0.05)
SUBDURAL HEMATOMA	0	1 (0.03)
ISCHEMIC	34 (0.92)	23 (0.62)
INFARCTION WITH HEMORRHAGIC CONVERS	2 (0.05)	3 (0.08)
UNCERTAIN	3 (0.08)	2 (0.05)
STENT THROMBOSIS, n (%)	48 (1.30)	35 (0.94)
EVENT RATE (%/YR)	2.21	1.60
HAZARD RATIO (APIXABAN/PLACEBO)		0.73
95% CI FOR HAZARD RATIO		(0.47, 1.12)
TWO-SIDED P-VALUE		0.1502

Each type of event was counted once per subject, but subjects could have been counted in multiple categories.

Safety Results:

The overall safety profile of apixaban was similar to that of placebo based on the incidence of deaths, SAEs, discontinuation due to AEs, and AEs. The event rates for bleeding-related AEs were higher for the apixaban group than the placebo group (19.7% and 9.2%, respectively) for all randomized subjects (Table 4).

Table 4: Summary of Safety during the Treatment Period -Treated Subjects

	ALL TREATED		DUAL ANTIPLATELET		SINGLE ANTIPLATELET	
	Placebo N = 3643	Apixaban N = 3672	Placebo N = 2925	Apixaban N = 2939	Placebo N = 718	Apixaban N = 733
AE (%)	2102 (57.7)	2168 (59.0)	1692 (57.8)	1746 (59.4)	410 (57.1)	422 (57.6)
SAE (%)	884 (24.3)	894 (24.3)	718 (24.5)	720 (24.5)	166 (23.1)	174 (23.7)
BLEEDING AE (%)	336 (9.2)	722 (19.7)	293 (10.0)	638 (21.7)	43 (6.0)	84 (11.5)
D/C DUE TO AE (%)	216 (5.9)	245 (6.7)	172 (5.9)	200 (6.8)	44 (6.1)	45 (6.1)
DEATHS (%)	127 (3.5)	128 (3.5)	88 (3.0)	83 (2.8)	39 (5.4)	45 (6.1)

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

Bleeding Assessment: Compared with placebo, the event rates for all bleeding endpoints were significantly higher on apixaban than on placebo, overall and within each antiplatelet therapy stratum (dual and single) [Table 5].

The primary safety outcome was time from first dose of study drug to first occurrence of confirmed TIMI major bleeding during the Treatment Period. The observed event rate for TIMI major bleeding was 2.40 per 100-patient years (pt yrs) in the apixaban group and 0.91 per 100-pt yrs in the placebo group. This increased risk on apixaban (HR = 2.59) was statistically significant (p = 0.0006).

This increased risk on apixaban was observed for all bleeding endpoints using the TIMI, ISTH and GUSTO criteria, overall and within each of the type of antiplatelet strata

There were 5 fatal bleeding events (all intracranial) during the Treatment Period. All the fatal events occurred in apixaban-treated subjects with more than 2 risk factors.

Intracranial critical site bleeding occurred in 12 (0.33%) subjects in the apixaban group and in 3 (0.08%) subjects in the placebo group. Retroperitoneal bleeds occurred in 77 (2.10%)subjects in the apixaban group and 32 (0.88%) subjects in the placebo group, and gastrointestinal bleeds occurred in 57 (1.55%) subjects on apixaban versus 19 (0.52%) in the placebo group.

Table 5: Summary of Bleeding Endpoints During the Treatment Period

	ALL TREATED		DUAL ANTIPLATELET		SINGLE ANTIPLATELET	
	Placebo N=3643	Apixaban N=3672	Placebo N=2925	Apixaban N=2939	Placebo (N=718)	Apixaban (N=733)
FATAL BLEEDING, n(%)	0	5 (0.14)	0	2 (0.07)	0	3 (0.41)
EVENT RATE (%/YR)	0	0.26	0	0.14	0	0.64
TIMI CRITERIA						
MAJOR, n(%)	18 (0.49)	46 (1.25)	17 (0.58)	38 (1.29)	1 (0.14)	8 (1.09)
EVENT RATE (%/YR)	0.91	2.40	1.14	2.63	0.21	1.70
HAZARD RATIO (APIX/PLA)		2.59		2.27		8.03
95% CI FOR HAZARD RATIO		(1.50, 4.46)		(1.28, 4.02)		(1.00, 64.23)
TWO-SIDED P-VALUE		0.0006		0.0050		0.0495
MAJOR OR MINOR, n(%)	29 (0.80)	80 (2.18)	27 (0.92)	67 (2.28)	2 (0.28)	13 (1.77)
EVENT RATE (%/YR)	1.47	4.19	1.82	4.64	0.41	2.77
HAZARD RATIO (APIX/PLA)		2.79		2.52		6.55
95% CI FOR HAZARD RATIO		(1.83, 4.27)		(1.61, 3.93)		(1.48, 29.01)
TWO-SIDED P-VALUE		< 0.0001		< 0.0001		0.0134
ISTH CRITERIA						
MAJOR, n(%)	40 (1.10)	98 (2.67)	37 (1.26)	85 (2.89)	3 (0.42)	13 (1.77)
EVENT RATE (%/YR)	2.04	5.13	2.50	5.91	0.62	2.77
HAZARD RATIO (APIX/PLA)		2.48		2.33		4.37
95% CI FOR HAZARD RATIO		(1.72, 3.58)		(1.58, 3.43)		(1.24, 15.32)
TWO-SIDED P-VALUE		< 0.0001		< 0.0001		0.0214
MAJOR OR CRNM, n(%)	45 (1.24)	117 (3.19)	41 (1.40)	102 (3.47)	4 (0.56)	15 (2.05)
EVENT RATE (%/YR)	2.29	6.15	2.77	7.11	0.83	3.20
HAZARD RATIO (APIX/PLA)		2.64		2.53		3.78
95% CI FOR HAZARD RATIO		(1.87, 3.72)		(1.76, 3.63)		(1.25, 11.39)
TWO-SIDED P-VALUE		< 0.0001		< 0.0001		0.0182

Major (ISTH), major (TIMI), and severe (GUSTO) include deaths with bleeding as an adjudicated cause

Table 5: Summary of Bleeding Endpoints During the Treatment Period

	ALL TREATED		DUAL ANTIPLATELET		SINGLE ANTIPLATELET	
	Placebo N=3643	Apixaban N=3672	Placebo N=2925	Apixaban N=2939	Placebo (N=718)	Apixaban (N=733)
GUSTO CRITERIA						
SEVERE, n(%)	12 (0.33)	35 (0.95)	12 (0.41)	28 (0.95)	0	7 (0.95)
EVENT RATE (%/YR)	0.61	1.82	0.80	1.93	0	1.49
HAZARD RATIO (APIX/PLA)		2.96		2.37		NOT ESTIMABLE
95% CI FOR HAZARD RATIO		(1.54, 5.70)		(1.21, 4.66)		NOT ESTIMABLE
TWO-SIDED P-VALUE		0.0012		0.0124		
SEVERE OR MODERATE, n(%)	25 (0.69)	81 (2.21)	24 (0.82)	70 (2.38)	1 (0.14)	11 (1.50)
EVENT RATE (%/YR)	1.27	4.24	1.61	4.85	0.21	2.35
HAZARD RATIO (APIX/PLA)		3.29		2.96		11.08
95% CI FOR HAZARD RATIO		(2.10, 5.15)		(1.86, 4.71)		(1.43, 85.84)
TWO-SIDED P-VALUE		< 0.0001		< 0.0001		0.0213
ALL BLEEDING, n(%)	304 (8.34)	677 (18.44)	265 (9.06)	599 (20.38)	39 (5.43)	78 (10.64)
EVENT RATE (%/YR)	16.33	39.98	18.99	47.75	8.38	17.78
HAZARD RATIO (APIX/PLA)		2.36		2.40		2.07
95% CI FOR HAZARD RATIO		(2.06, 2.70)		(2.08, 2.78)		(1.41, 3.04)
TWO-SIDED P-VALUE		< 0.0001		< 0.0001		0.0002

Major (ISTH), major (TIMI), and severe (GUSTO) include deaths with bleeding as an adjudicated cause

Elevations in Liver Function Tests (LFTs) and Liver-related AEs: The frequency of subjects with LFT elevations (ALT, AST, ALP, and total bilirubin) was low and similar for the apixaban and placebo treatment groups, overall and within each antiplatelet therapy (dual or single) stratum (Table 6). Furthermore, the number of subjects with concurrent elevations of ALT >3xULN and total bilirubin >2xULN was low and similar in both treatment groups (both <0.1%). Among all treated subjects, the frequency of subjects with liver-related AEs (serious or non-serious) was similar in the apixaban group (2.3%) and the placebo group (2.4%). Serious AEs and discontinuations related to liver were infrequent in the apixaban and placebo groups.

Table 6: Summary of Liver-Related Elevations During the Treatment Period - Treated Subjects With Available Measurements

	Placebo	Apixaban
AT AND TBILI ELEVATION ON SAME DATE, n/N (%)		
(ALT>3XULN OR AST>3XULN)&TBILI>2XULN	2 / 3117 (<0.1)	2 / 3098 (<0.1)
(ALT>3XULN OR AST>3XULN)&TBILI>2XULN&ALP<2XULN	0 / 3109	1 / 3090 (<0.1)
ALT AND TBILI ELEVATION ON SAME DATE, n/N (%)		
ALT > 3X ULN & TBILI >2X ULN	1 / 3116 (<0.1)	2 / 3097 (<0.1)
ALT > 3X ULN & TBILI >2X ULN & ALP<2XULN	0 / 3109	1 / 3089 (<0.1)
ALT ELEVATION, n/N (%)		
>3X ULN	39 / 3132 (1.2)	40 / 3116 (1.3)
>5X ULN	20 / 3132 (0.6)	21 / 3116 (0.7)
>10X ULN	8 / 3132 (0.3)	3 / 3116 (<0.1)
>20X ULN	2 / 3132 (<0.1)	0 / 3116
AST ELEVATION, n/N (%)		
>3X ULN	35 / 3131 (1.1)	34 / 3110 (1.1)
>5X ULN	15 / 3131 (0.5)	17 / 3110 (0.5)
>10X ULN	6 / 3131 (0.2)	6 / 3110 (0.2)
>20X ULN	3 / 3131 (<0.1)	2 / 3110 (<0.1)
BOTH AST AND AST ELEVATION ON SAME DATE, n/N (%)		
>3X ULN	25 / 3128 (0.8)	21 / 3108 (0.7)
>5X ULN	8 / 3128 (0.3)	12 / 3108 (0.4)
>10X ULN	4 / 3128 (0.1)	2 / 3108 (<0.1)
>20X ULN	2 / 3128 (<0.1)	0 / 3108
TOTAL BILIRUBIN (TBILI) ELEVATION, n/N (%)		
>2X ULN	10 / 3126 (0.3)	9 / 3108 (0.3)

The denominator to calculate percentages for each event is the total number of treated subjects with available laboratory results for that analyte within each treatment group

CONCLUSIONS:

- APPRAISE-2 enrolled globally a high risk post-ACS population as characterized by advanced age and multiple cardiac and non-cardiac co-morbidities, e.g., diabetes, heart failure.
- Compared with placebo, on a background of antiplatelet therapy (80% dual):
  - Apixaban showed a significant increase in bleeding events compared with placebo in subjects receiving single or dual antiplatelet therapy. This led to early termination of the study.
  - With 61% of the expected events accrued, apixaban did not show a clinically meaningful reduction in recurrent ischemic events overall or in subjects receiving single or dual antiplatelet therapy.
- The incidence of liver-related abnormalities and AEs, other than bleeding, was similar for apixaban and placebo.
- Apixaban did not show a favorable risk-benefit profile for prevention of recurrent ischemic events in high-risk, post-ACS subjects receiving single or dual antiplatelet therapy.

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