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 CV185030

TITLE OF STUDY: A Phase 3, Active (Warfarin)-Controlled, Randomized, Double-blind, Parallel Arm Study to Evaluate Efficacy and Safety of Apixaban in Preventing Stroke and Systemic Embolism (SE) in Subjects with Non-valvular Atrial Fibrillation (AF)

INVESTIGATORS/STUDY CENTERS: 1,053 sites in 40 countries enrolled subjects (1,034 sites randomized at least 1 subject)

PUBLICATION: Lopes RD, Alexander JH, Al-Khatib SM, et al. Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) trial: Design and Rationale. Am Heart J 2010;159:331-339.

STUDY PERIOD: First Subject First Visit: 19-Dec-2006 **CLINICAL PHASE:** 3

Last Subject Last Visit: 25-May-2011

OBJECTIVES:

Primary Objective: To determine if apixaban was non-inferior (NI) to warfarin (international normalized ratio [INR] target range 2.0 - 3.0) for the combined endpoint of stroke (ischemic or hemorrhagic or of unspecified type) and SE, in subjects with AF and at least one additional risk factor for stroke.

Secondary Objectives: To determine, in subjects with AF and at least one additional risk factor for stroke**,** if apixaban was superior to warfarin (INR target range 2.0-3.0) for,

- the combined endpoint of stroke (hemorrhagic, ischemic, or of unspecified type) and SE
- major bleeding (International Society on Thrombosis and Hemostasis [ISTH] criteria)
- all-cause death.

Other secondary objectives were:

To compare, in subjects with AF and at least one additional risk factor for stroke, apixaban and warfarin with respect to:

- the composite endpoint of stroke (ischemic, hemorrhagic or of unspecified type), SE and major bleeding, in warfarin-naïve subjects
- the composite endpoint of stroke (ischemic, hemorrhagic or of unspecified type), SE and major bleeding

- the composite endpoint of stroke (ischemic, hemorrhagic or of unspecified type), SE and all-cause death
- the composite endpoint of stroke (ischemic, hemorrhagic or of unspecified type), SE, major bleeding and all-cause death
- the composite endpoint of stroke (ischemic, hemorrhagic or of unspecified type), SE, myocardial infarction (MI), and all-cause death.

To assess the safety of apixaban in subjects with AF and at least one additional risk factor for stroke.

METHODOLOGY:

This was an active (warfarin)-controlled, randomized, double-blind, double-dummy, parallel group study comparing apixaban to warfarin, with titration of warfarin based on central monitoring of the INR.

Subjects (both warfarin-naïve and warfarin-experienced) with AF and at least one additional risk factor for stroke were screened for study eligibility. The eligible subjects were randomized in a 1:1 ratio to either apixaban or warfarin titrated to a target INR range 2.0 to 3.0. Subjects who were on warfarin or another Vitamin K antagonist (VKA) prior to randomization had their VKA discontinued prior to randomization. Randomization was stratified by investigative site and prior warfarin/VKA status (naïve and experienced).

Subjects received either apixaban and warfarin-placebo or apixaban-placebo and warfarin following randomization during a titration phase using a dosing algorithm consisting of two initial daily doses of up to 6 mg of warfarin (or warfarin placebo) and doses of apixaban (or apixaban-placebo) of 5 mg twice daily (BID) [or 2.5 mg BID in select subjects].

Subsequent warfarin doses were recommended based upon an algorithm, however, the final dosing decision rested with the investigator. INR monitoring began by the fourth day following initiation of drug administration and was performed twice a week for two weeks, once a week for two weeks, and monthly thereafter once a stable INR was attained. An investigator could increase the frequency of INR monitoring if it was considered clinically indicated, with titration of warfarin or warfarin-placebo based on central monitoring of INR measurements utilizing encrypted point of care (POC) devices and centralized dosing recommendations.

Study visits occurred monthly for INR monitoring. At the INR visits, only INR monitoring, assessment of outcomes, assessment of adverse events (AEs) and laboratory tests, and assessment of study medication compliance were performed. In addition, at the quarterly visits during the treatment period (Months 3, 6, 9, 15, 18, 21, 27, 30, 33, 39, 42, 45, 51, 54 and 57) assessment of changes in concomitant medications, vital signs and laboratory assessments were performed and at the yearly visits during the treatment period (Months 12, 24, 36 and 48) physical measurements, and 12 lead electrocardiograms (ECGs) were obtained. All subjects were followed for the development of stroke (ischemic, hemorrhagic, or of unspecified type), SE, MI, death, bleeding, hospitalization or treatment discontinuation until the end of the study.

Follow-up of subjects who discontinued study drug prior to the attainment of 448 primary efficacy events in the study were to occur quarterly by a telephone call; the final follow-up visit was to be in person, if at all possible, and was performed within approximately 30 days after the attainment of 448 primary efficacy events in the study. Subjects who completed double-blind treatment with study drug were to have had telephone contact approximately 30 days after the last dose of double-blind study drug. SAEs (that occurred within 30 days after the last dose of double-blind study drug) and study outcomes were documented at all follow-up contacts. Subjects were followed up to the later of efficacy cut-off date (30-Jan-2011) or 30 days after last dose date.

NUMBER OF SUBJECTS (Planned and Analyzed): Planned: 18,000 subjects (9,000 in each group); randomized: 18,201 (9,120 on apixaban and 9,081 on warfarin); treated: 18,140 (9,088 on apixaban and 9,052 on warfarin).

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION: Males and females ≥18 years of age with AF or flutter and one or more of the following additional risk factors for stroke: (1) age ≥75 years, (2) previous stroke, transient ischemic attack (TIA) or SE, (3) symptomatic congestive heart failure or left ventricular (LV) dysfunction with an LV ejection fraction (LVEF) ≤40%, (4) diabetes mellitus, or (5) hypertension requiring pharmacological treatment.

TEST PRODUCT, DOSE AND MODE OF ADMINISTRATION, DURATION OF TREATMENT, BATCH NUMBERS: Oral apixaban 5 mg or 2.5 mg tablets or matching placebo were administered for a mean duration of about 89 weeks. (1) Apixaban 5 mg oral tablets BID batch numbers: 6J19142, 6J14405, 6L21774. 6L21311, 6L20559, 6J19142, 7B22438, 7B29610, 7D29267, 8B35840, 8J34317, 8L41121, 9F46090, 9M36608, 0C61290, 0D59695; (2) Apixaban 5 mg matching placebo tablets BID batch numbers: 6J12329, 6L18668, 7C28836, 7G30556, 7H21579, 8L41233, 9F53462, 9M36561, 0C59651, 7G30557, 0E56747, 7A31474; (3) Apixaban 2.5 mg oral tablets BID batch numbers: 6E17717, 7B27015, 7B29116, 8B41849, 7H25317; and (4) Apixaban 2.5 mg matching placebo tablets BID batch numbers: 6E18428, 7A29111, 7C28811, 7H21577.

REFERENCE THERAPY, DOSE AND MODE OF ADMINISTRATION, DURATION OF TREATMENT, BATCH NUMBERS: Oral warfarin 2 mg tablets (titrated to a target INR range of 2.0 - 3.0) or matching placebo were administered for a mean duration of about 88 weeks. (1) Warfarin 2 mg oral tablets batch numbers: 6H18170. 6H16924, 6H12630, 7C29108, 8H36497, 9B46206, 9G51481, 9M39214, 0C65272, 0C65584, GH16928; and (2) Warfarin matching placebo oral tablets batch numbers: 6H18176, 6H12637, 6H12634, 7C29114, 8H36498, 9B46209, 9G51483, 9M39197, 0C65546, 0C65582.

CRITERIA FOR EVALUATION: An Adjudication Committee (also referred to as Clinical Event Committee [CEC]) adjudicated all incidences of death, stroke, SE, and MI, major bleeding events, and clinically relevant non-major bleeding events (CRNM). Adjudicated results were the basis for the primary analyses.

An independent Data Monitoring Committee (DMC), provided oversight of safety and efficacy considerations for the study, and gave recommendations to the Study Steering Committee.

Efficacy Endpoints: The primary efficacy endpoint was the time to first occurrence of confirmed stroke (ischemic, hemorrhagic, or of unspecified type) or SE, during the Intended Treatment Period.

The secondary efficacy endpoints included were the time to first occurrence of confirmed: stroke (hemorrhagic, ischemic or of unspecified type); SE; all-cause death; composite of stroke (ischemic, hemorrhagic, or of unspecified type), SE, major bleeding; composite of stroke (ischemic, hemorrhagic, or of unspecified type), SE, all-cause death; composite of stroke (ischemic, hemorrhagic, or of unspecified type), SE, major bleeding, all-cause death; composite of stroke (ischemic, hemorrhagic, or of unspecified type), SE, MI, all-cause death; composite of stroke (ischemic, hemorrhagic, or of unspecified type), SE, and major bleeding in warfarin- naïve subjects, during the Intended Treatment Period.

Safety Endpoints: The primary safety endpoint is the time from first dose of study drug to first occurrence of confirmed ISTH major bleeding during the Treatment Period. The secondary safety endpoints were the time from first dose of study drug to first occurrence, during the Treatment Period, of: composite of confirmed ISTH major bleeding and CRNM, and all bleeding events reported by the investigator. Other safety endpoints include the following during the Treatment Period: adjudicated bleeding events using GUSTO and TIMI guidelines, fractures, other AEs, abnormal standard clinical laboratory tests, vital signs, and ECGs.

STATISTICAL CONSIDERATIONS:

Sample size determination: Different regulatory agencies have different requirements for establishing the non-inferiority of apixaban to warfarin. Some Health Authorities require a more stringent control of the type I error (one-sided 0.005 level rather than one-sided 0.025 level) in the presence of a single supporting study. Others require a more stringent non-inferiority margin (1.38 rather than 1.44). Therefore,

1) in regulatory regions requiring a more stringent non-inferiority margin, the non-inferiority of apixaban relative to warfarin was demonstrated if the upper bound of the two-sided 95% confidence interval (CI) for relative risk (RR) was less than 1.38.
2) in regulatory regions requiring a more stringent control of the type I error, the non-inferiority of apixaban relative to warfarin was demonstrated if the upper bound of the two-sided 99% CI for RR was less than 1.44.

The number of events required to achieve 90% power and meet the criteria described in (1) is lower than the number of events required to achieve 90% power and meet the criteria described in (2). This study was sized to meet the more stringent criterion. With 448 subjects with confirmed strokes or systemic emboli, the study would have at least 90% power to meet both regulatory definitions of non-inferiority described above. With an average 2.1 years follow-up and assuming a stroke rate of 1.20 per hundred patient-years (pt-yrs), ~18,000 randomized subjects allocated in a 1:1 ratio to the apixaban or warfarin group would be needed to achieve the desired power. These calculations assumed an incidence of 1% loss to follow-up. Investigative sites were pooled to the geographic region level when including investigative sites as a stratification factor in a Cox proportional hazards model.

Statistical testing strategy: The 4 key objectives of the study were tested following a hierarchical testing strategy at a significance level adjusted for the formal interim test for superiority (the adjustment was small and did not impact the results). Overall type I error was preserved at ≤5%.

1) NI for the primary efficacy endpoint was assessed first (at NI margin=1.38 and one-sided α= 0.025; and at NI margin=1.44 and one-sided α= 0.005)

The following tests in the sequence are performed at the one-sided α= 0.025

- If NI for the primary efficacy endpoint (using a NI margin of 1.38) was demonstrated, then superiority for the primary efficacy endpoint is tested.
- If superiority for the primary efficacy endpoint was demonstrated then superiority for ISTH major bleeding is tested.
- If superiority for major bleeding was demonstrated then superiority for all-cause death is tested.

Primary efficacy analysis: An intention-to-treat analysis was performed on the Randomized Population based on adjudicated primary efficacy endpoint events occurring during the Intended Treatment Period.

Censoring scheme: subjects who did not experience an efficacy endpoint event were censored at the earlier 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 (30-Jan-2011).

Tests using each non-inferiority margin were performed using a Cox proportional hazards model including treatment group as a covariate and stratified by investigative site and prior warfarin/VKA status (experienced, naïve). If the primary objective was met then the hypotheses associated with key secondary objectives were tested in a sequential fashion.

Primary safety analysis:

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

For major bleeding, a point estimate and two-sided 95% CI for relative risk and a p-value for the test of equality of rates was calculated. The test was performed using a Cox proportional hazards model including treatment group as a covariate, and stratified by investigative site and prior warfarin/VKA status (experienced, naïve).

SUMMARY OF RESULTS:

Disposition and Baseline/Demographic Characteristics:

The mean duration of exposure to double-blind study drug was approximately 1.7 years in each treatment group. A total of 20,998 subjects were enrolled in the study; of these subjects, 18,201 (86.7%) were randomized to receive study treatment. A total of 8,043 (88.2%) subjects in the apixaban group and 7,933 (87.4%) subjects in the warfarin group completed the study. The most common reasons for not completing the Treatment Period were subject's request to discontinue study treatment (10.1 and 10.9%, respectively), AE (7.4 and 8.1%, respectively), and death (3.6 and 3.8%, respectively) for apixaban and warfarin groups.

The median TTR for subjects randomized to warfarin, a pre-specified analysis that included all INRs (those obtained during titration, interruption or on treatment) was 60.5%; the boundary between the 1st and 2nd quartiles was 46.6%, and the boundary between the 3rd and 4th quartiles was 71.4%. The median TTR for subjects randomized to warfarin, excluding the first 7 days of the study and excluding warfarin interruptions, was 66.0%; the boundary between the 1st and 2nd quartiles was 52.4%, and the boundary between the 3rd and 4th quartiles was 76.5%.

The treatment groups were well balanced for baseline demographic and disease characteristics with no clinically relevant differences in these characteristics (Table 1).

Table 1: Baseline Demographic and Disease Characteristics - Randomized Subjects

	Apixaban N = 9120	Warfarin N = 9081	Total N = 18201
AGE (YRS)			
MEAN	69.1	69.0	69.1
MIN , MAX	21 , 95	19 , 97	19 , 97
STANDARD DEVIATION	9.61	9.74	9.68
AGE CATEGORY (%)			
<65	2731 (29.9)	2740 (30.2)	5471 (30.1)
65-<75	3539 (38.8)	3513 (38.7)	7052 (38.7)
>=75	2850 (31.3)	2828 (31.1)	5678 (31.2)
GENDER (%)			
MALE	5886 (64.5)	5899 (65.0)	11785 (64.7)
FEMALE	3234 (35.5)	3182 (35.0)	6416 (35.3)
RACE (%)			
WHITE	7536 (82.6)	7493 (82.5)	15029 (82.6)
BLACK/AFRICAN AMERICAN	125 (1.4)	102 (1.1)	227 (1.2)
ASIAN	1310 (14.4)	1332 (14.7)	2642 (14.5)
AMERICAN INDIAN/ ALASKA NATIVE	26 (0.3)	24 (0.3)	50 (0.3)
NATIVE HAWAIIAN/ OTHER PACIFIC ISLANDER	2 (<0.1)	2 (<0.1)	4 (<0.1)
OTHER	121 (1.3)	127 (1.4)	248 (1.4)
NOT REPORTED	0	1 (<0.1)	1 (<0.1)

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

Approximately 57% of randomized subjects were warfarin/VKA experienced and 43% were warfarin/VKA naïve, in each treatment group. Most subjects randomized to apixaban were assigned to 5 mg BID dose (95.4%), and 4.6% were assigned to the 2.5 mg BID dose (Table 2).

Baseline risk factors for stroke were similar for the apixaban and warfarin groups. The mean $CHADS_2$ score was 2.1 in each treatment group. The majority of subjects (66.9%) in both treatment groups had ≥2 risk factors at baseline. Treated hypertension was the most common risk factor (87.4%), followed by CHF (35.4%), and age ≥75 years (31.2%). Overall, 19.4% of subjects had a prior stroke, TIA, or SE.

Table 2: Summary of Apixaban/Matching Placebo Dose at Randomization and Risk Factors - Randomized Subjects

	Apixaban N = 9120	Warfarin N = 9081	Total N = 18201
APIXABAN OR MATCHING PLACEBO DOSE (%)			
2.5 MG BID	428 (4.7)	403 (4.4)	831 (4.6)
5.0 MG BID	8692 (95.3)	8678 (95.6)	17370 (95.4)
TYPE OF RISK FACTOR AT ENROLLMENT (%)			
AGE >= 75 YEARS	2850 (31.3)	2828 (31.1)	5678 (31.2)
PRIOR STROKE, TIA, OR SYSTEMIC EMBOLISM	1748 (19.2)	1790 (19.7)	3538 (19.4)
PRIOR STROKE	1045 (11.5)	1082 (11.9)	2127 (11.7)
PRIOR TIA	603 (6.6)	654 (7.2)	1257 (6.9)
PRIOR SYSTEMIC EMBOLISM	142 (1.6)	129 (1.4)	271 (1.5)
SYMP CHF WITHIN 3 MONTHS OR LVEF <= 40%	3235 (35.5)	3216 (35.4)	6451 (35.4)
SYMPTOMATIC CHF	2784 (30.5)	2757 (30.4)	5541 (30.4)
LVEF <=40%	1324 (14.5)	1301 (14.3)	2625 (14.4)
DIABETES MELLITUS	2284 (25.0)	2263 (24.9)	4547 (25.0)
HYPERTENSION WITH PHARMACOLOGICAL Tx	7962 (87.3)	7954 (87.6)	15916 (87.4)
NUMBER OF RISK FACTORS(%)			
<= 1	3025 (33.2)	3000 (33.0)	6025 (33.1)
>= 2	6095 (66.8)	6081 (67.0)	12176 (66.9)
CHADS-2 SCORE AT ENROLLMENT (%)			
<= 1	3100 (34.0)	3083 (34.0)	6183 (34.0)
2	3262 (35.8)	3254 (35.8)	6516 (35.8)
>= 3	2758 (30.2)	2744 (30.2)	5502 (30.2)
MEAN (SD)	2.1 (1.10)	2.1 (1.11)	2.1 (1.10)
MEDIAN	2.0	2.0	2.0
MIN, MAX	(0.0, 6.0)	(0.0, 6.0)	(0.0, 6.0)

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

Efficacy Results:

Apixaban was superior to warfarin for prevention of stroke (hemorrhagic or ischemic) and SE (two-sided p=0.0114, HR=0.79) [Table 3].

According to the sequential testing strategy, since, superiority of apixaban compared to warfarin was demonstrated for both the primary efficacy endpoint (Table 3) and ISTH major bleeding (Table 7), superiority for all-cause death was tested. Apixaban was superior to warfarin for prevention of all-cause death (two-sided p=0.0465, HR =0.89, Table 4). This was also supported by the numerical reduction observed for both CV and non-CV deaths. The incidence of other efficacy endpoints, including hemorrhagic stroke, ischemic or unspecified stroke, SE, and MI, was lower on apixaban than warfarin (Table 5).

Approximately 1.4% of subjects in each treatment group were censored due to loss to follow-up and approximately 3% of subjects in each treatment group were censored due to withdrawal of consent. Apixaban had its largest effect relative to warfarin on hemorrhagic stroke with an observed HR = 0.51 and 95% CI = (0.35, 0.75). Furthermore, a statistically significant and large magnitude of effect for reduction in stroke events by apixaban was observed for clinically important fatal or disabling strokes (Fatal: p=0.0172 and Rankin score 3 to 6: p=0.0178).

Sensitivity analyses assessed the robustness of the primary efficacy results. Statistically significant and clinically relevant reductions were observed after including covariates of clinical relevance and also after excluding protocol deviations expected to affect the primary efficacy endpoint. Numerical decreases in

stroke/SE event rates were observed across all levels of INR control. These analyses further support the superiority conclusion for the primary efficacy endpoint.

Table 3: Summary of Primary Efficacy Endpoint During the Intended Treatment Period - Randomized Subjects

	Apixaban N = 9120	Warfarin N = 9081
STROKE/SYSTEMIC EMBOLISM, n (%)	212 (2.32)	265 (2.92)
EVENT RATE (%/YR)	1.27	1.60
HAZARD RATIO (APIXABAN/WARFARIN)	0.79	
95% CI FOR HAZARD RATIO	(0.66, 0.95)	
99% CI FOR HAZARD RATIO	(0.62, 1.00)	
1-SIDED P-VALUE FOR NI TEST (NI MARGIN = 1.38)	<.0001	
1-SIDED P-VALUE FOR NI TEST (NI MARGIN = 1.44)	<.0001	
2-SIDED P-VALUE FOR SUPERIORITY TEST	0.0114	
FIRST EVENT, n (%)		
ISCHEMIC OR UNSPECIFIED STROKE	159 (1.74)	173 (1.91)
HEMORRHAGIC STROKE	38 (0.42)	76 (0.84)
SYSTEMIC EMBOLISM	15 (0.16)	16 (0.18)
CENSORED, n (%)	8908 (97.68)	8816 (97.08)
DEATH DURING INTENDED TREATMENT PERIOD	514 (5.64)	547 (6.02)
WITHDREW CONSENT TO BE FOLLOWED-UP	292 (3.20)	304 (3.35)
LOST TO FOLLOW-UP	130 (1.43)	124 (1.37)
COMPLETED INTENDED TREATMENT PERIOD	7972 (87.41)	7841 (86.35)
FIRST EVENT AFTER COMPLETING ITP	27 (0.30)	10 (0.11)

Subjects are counted once per category but may be counted in multiple categories of events.
Stroke includes ischemic stroke, hemorrhagic stroke, ischemic stroke with hemorrhagic conversion, and stroke of uncertain type
ITP=Intended Treatment Period

Table 4: Summary of Adjudicated Causes of Death During the Intended Treatment Period - Randomized Subjects

	Apixaban N = 9120	Warfarin N = 9081
ALL-CAUSE DEATH, n (%)	603 (6.61)	669 (7.37)
EVENT RATE (%/YR)	3.52	3.94
HAZARD RATIO (APIXABAN/WARFARIN)	0.89	
95% CI FOR HAZARD RATIO	(0.80, 1.00)	
P-VALUE	0.0465	
CARDIOVASCULAR DEATH, n (%)	308 (3.38)	344 (3.79)
EVENT RATE (%/YR)	1.80	2.02
HAZARD RATIO (APIXABAN/WARFARIN)	0.89	
95% CI FOR HAZARD RATIO	(0.76, 1.04)	
NON-CARDIOVASCULAR DEATH, n (%)	196 (2.15)	208 (2.29)
EVENT RATE (%/YR)	1.14	1.22
HAZARD RATIO (APIXABAN/WARFARIN)	0.93	
95% CI FOR HAZARD RATIO	(0.77, 1.13)	
UNKNOWN CAUSE OF DEATH, n (%)	99 (1.09)	117 (1.29)
EVENT RATE (%/YR)	0.58	0.69
HAZARD RATIO (APIXABAN/WARFARIN)	0.84	
95% CI FOR HAZARD RATIO	(0.64, 1.09)	

Table 5: Summary of Individual Efficacy Endpoints During the Intended Treatment Period - Randomized Subjects

	Apixaban N = 9120	Warfarin N = 9081
ISCHEMIC OR UNSPECIFIED STROKE, n (%)	162 (1.78)	175 (1.93)
EVENT RATE (%/YR)	0.97	1.05
HAZARD RATIO (APIXABAN/WARFARIN)	0.92	
95% CI FOR HAZARD RATIO	(0.74, 1.13)	
HEMORRHAGIC STROKE, n (%)	40 (0.44)	78 (0.86)
EVENT RATE (%/YR)	0.24	0.47
HAZARD RATIO (APIXABAN/WARFARIN)	0.51	
95% CI FOR HAZARD RATIO	(0.35, 0.75)	
SYSTEMIC EMBOLISM, n (%)	15 (0.16)	17 (0.19)
EVENT RATE (%/YR)	0.09	0.10
HAZARD RATIO (APIXABAN/WARFARIN)	0.87	
95% CI FOR HAZARD RATIO	(0.44, 1.75)	
MI, n (%)	90 (0.99)	102 (1.12)
EVENT RATE (%/YR)	0.53	0.61
HAZARD RATIO (APIXABAN/WARFARIN)	0.88	
95% CI FOR HAZARD RATIO	(0.66, 1.17)	

Safety Results:

Overall Safety Summary: For events other than bleeding, the overall safety profile of apixaban was similar to that of warfarin based on the incidence of deaths (based on SAEs with outcome of death), AEs, SAEs, and discontinuation due to AEs (Table 6). The event rates for bleeding-related AEs were substantially lower for the apixaban group than the warfarin group.

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

	Apixaban N = 9088	Warfarin N = 9052
AE (%)	7406 (81.5)	7521 (83.1)
SAE (%)	3182 (35.0)	3302 (36.5)
BLEEDING AE (%)	2288 (25.2)	2961 (32.7)
DISCONTINUATIONS DUE TO AE (%)	688 (7.6)	758 (8.4)
DEATHS (%)	429 (4.7)	468 (5.2)

Bleeding Assessment: Apixaban was superior to warfarin for the primary safety endpoint of adjudicated ISTH major bleeding (HR 0.69 [95% CI: 0.60, 0.80]; p <0.0001, Table 7). The observed event rates (%/year) for major bleeding during the Treatment Period were 2.13% in the apixaban group vs. 3.09% in the warfarin group. A total of 10 (rate of 0.06%/year) fatal bleeding events (8 fatal bleeds, and 2 fatal hemorrhagic strokes) occurred in the apixaban group, compared with 37 (rate of 0.24%/year) fatal bleeding events in the warfarin group (11 fatal bleeds and 26 fatal hemorrhagic strokes). Intracranial bleeding events occurred in 52 (rate of 0.33%/year) vs. 122 (0.8%/year) subjects, respectively.

Apixaban was also superior to warfarin for the secondary endpoints of the composite of major or CRNM bleeding and all bleeding. Event rates were consistently and significantly lower in the apixaban compared with the warfarin group for all bleeding endpoints using GUSTO and TIMI criteria.

Table 7: Summary of Adjudicated Bleeding Endpoints (ISTH and All Bleeds) During the Treatment Period - Treated Subjects

	Apixaban N = 9088	Warfarin N = 9052
ISTH MAJOR, n (%)	327 (3.60)	462 (5.10)
EVENT RATE (%/YR)	2.13	3.09
HAZARD RATIO (APIXABAN/WARFARIN)	0.69	
95% CI FOR HAZARD RATIO	(0.60, 0.80)	
P-VALUE	<.0001	
FATAL BLEED AND HEMORRHAGIC STROKE, n (%)	10 (0.11)	37 (0.41)
EVENT RATE (%/YR)	0.06	0.24
FATAL BLEED, n (%)	8 (0.09)	11 (0.12)
EVENT RATE (%/YR)	0.05	0.07
FATAL HEMORRHAGIC STROKE, n (%)	2 (0.02)	26 (0.29)
EVENT RATE (%/YR)	0.01	0.17
BLEEDING INTO A CRITICAL SITE, n (%)	91 (1.00)	158 (1.75)
INTRACRANIAL	52 (0.57)	122 (1.35)
INTRAARTICULAR	6 (0.07)	10 (0.11)
INTRAOCULAR	28 (0.31)	19 (0.21)
PERICARDIAL	0	0
INTRASPINAL	2 (0.02)	2 (0.02)
INTRAMUSCULAR W/ COMPARTMENT SYNDROME	1 (0.01)	1 (0.01)
RETROPERITONEAL	2 (0.02)	5 (0.06)
DECREASE IN HGB >= 2G/DL OVER 24 HRS	165 (1.82)	222 (2.45)
TRANSFUSION OF >= 2 UNITS OF PRBC	70 (0.77)	101 (1.12)
ISTH MAJOR OR CRNM, n (%)	613 (6.75)	877 (9.69)
EVENT RATE (%/YR)	4.07	6.01
HAZARD RATIO (APIXABAN/WARFARIN)	0.68	
95% CI FOR HAZARD RATIO	(0.61, 0.75)	
P-VALUE	<.0001	
ALL BLEEDING, n (%)	2356 (25.92)	3060 (33.80)
EVENT RATE (%/YR)	18.08	25.82
HAZARD RATIO (APIXABAN/WARFARIN)	0.71	
95% CI FOR HAZARD RATIO	(0.68, 0.75)	
P-VALUE	<.0001	

Major (ISTH), severe (GUSTO) and Major (TIMI) bleeds include deaths with bleeding as an adjudicated cause Components of ISTH major bleed are as reported by the Investigator (not adjudicated)

Hepatic Safety: The hepatic safety of apixaban was assessed by evaluating LFTs, including concurrent elevations of ALT >3xULN and total bilirubin >2xULN on the same date, and AEs by both the Sponsor and an independent, blinded, panel of 3 hepatologists. The cases of concurrent elevations of ALT >3xULN and total bilirubin >2xULN on the same date and/or pre-selected hepatic SAEs (jaundice, hepatitis, and hepatic failure) were assessed by an independent, blinded, panel of 3 hepatologists. The hepatic safety findings summarized below suggest that apixaban has a hepatic safety profile that is similar to that of warfarin:

- Laboratory Values: The frequency of subjects with LFT elevations, including concurrent elevations of ALT >3xULN and total bilirubin >2xULN on the same date, was low, and similar in the apixaban and warfarin groups (Table 8). The frequency of subjects with LFT elevations, including concurrent elevations of ALT >3xULN, total bilirubin >2xULN, and ALP<2xULN on the same date was balanced between the 2 groups and indicate that small fraction of these elevations had cholestatic component. Almost all cases had other potentially contributing factors, including concomitant medications. The number of cases assessed as possible or probable relationship to the study drug by the independent, blinded, panel of hepatologists was low and balanced between the 2 groups.
- Liver-related AEs, SAEs (including deaths), and Discontinuations: The frequency of these events was low, and similar in the apixaban and warfarin groups. Most subjects with SAEs related to elevations in LFT with outcome of death had underlying liver disease conditions, e.g., hepatic malignancy.
- Other Events: A small number of cases did not meet the criterion of concurrent elevations of ALT >3xULN and total bilirubin >2xULN on the same date. These cases were assessed by the independent, blinded, panel of hepatologists as these subjects had SAEs of hepatitis, jaundice, or hepatic failure; the relationship to the study drug was assessed as possible or probable to the study drug for 3 subjects in the apixaban group and 1 subject in the warfarin group.

Table 8: Summary of Hepatic Safety of Apixaban During the Treatment Period - Treated Subjects with Available Measurements

	Apixaban N = 9088 n(%)	**Warfarin N = 9052 n(%)**
ALT>3xULN and TBili>2xULN[a]	32 (0.4)	27 (0.3)
ALT>3xULN and TBili>2xULN on same date	23 (0.3)	22 (0.3)
Possible relationship per external hepatologists	3	3
Probable relationship per external hepatologists	0	0
ALT>3xULN AND TBILI >2xULN AND ALP<2xULN on same date	13 (0.1)	16 (0.2)
Possible relationship per external hepatologists	1	3
Probable relationship per external hepatologists	0	0
Liver AEs, SAEs (including deaths), and Discontinuations (per liver SMQs)		
AEs	445 (4.9)	475 (5.2)
SAEs[a]	50 (0.6)	48 (0.5)
SAEs with outcome of death	5 (< 0.1) [b]	5 (< 0.1) [b]
Liver transplant	0	0
AEs leading to Discontinuations	26 (0.3)	35 (0.4)
SAEs of hepatitis, jaundice, and liver failure for subjects who did not meet the criteria for ALT>3xULN and TBili>2xULN on same date		
Possible relationship per external hepatologists	3	1
Probable relationship per external hepatologists	0	0

[a] Includes data from the first dose through 30 days after the last dose of study drug
[b] 2 of 5 deaths occurred during the Follow-up Period
SMQ = standardized MedDRA query

Net-Clinical Benefit: The net-clinical benefit profile of apixaban, assuming equal weighting of the primary efficacy and safety endpoints, was favorable to that of warfarin based on the composite endpoint of efficacy (stroke and SE) and safety (ISTH major bleeding) events when counting events during the Treatment Period for the Treated Subject Population (Table 9).

Table 9: Net-clinical Benefit During the Treatment Period - Treated Subjects

	Apixaban N=9088	Warfarin N=9052
NET-CLINICAL BENEFIT, n (%)	459 (5.05)	608 (6.72)
EVENT RATE (%/YR)	3.01	4.09
HAZARD RATIO (APIXABAN/WARFARIN)	0.74	
95% CI FOR HAZARD RATIO	(0.65, 0.83)	
P-VALUE	<.0001	

Net-Clinical Benefit = Composite of stroke, systemic embolism and ISTH major bleeding
The denominator to calculate each percentage is the total number of treated subjects in the treatment group(s).

CONCLUSIONS:

In subjects with AF and at least one additional risk factor for stroke:

- Apixaban was superior to warfarin for the prevention of stroke (hemorrhagic or ischemic) and systemic embolism.
- Apixaban was superior to warfarin with regard to ISTH major bleeding, and apixaban resulted in fewer intracranial hemorrhages and fewer fatal hemorrhages than warfarin.
- Apixaban was superior to warfarin for the prevention of death due to any cause.
- The incidence of each individual efficacy endpoint (including hemorrhagic stroke, ischemic or unspecified stroke, systemic embolism, and MI) was lower on apixaban than warfarin.
- For events other than bleeding, the safety profile of apixaban was similar to that of warfarin based on the incidence of SAEs, discontinuation due to AEs, and LFT increases.
- Apixaban has better efficacy and less bleeding than warfarin, demonstrating a strongly favorable profile compared to warfarin.

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