SYNOPSIS

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Name of Sponsor/Company	Janssen Research & Development*
Name of Finished Product	Rivaroxaban
Name of Active Ingredient(s)	JNJ-39039039; BAY-59-7939

*Rivaroxaban (BAY-59-7939, JNJ-39039039) is being co-developed under a collaboration and license agreement between Bayer HealthCare AG (BHC) and Ortho McNeil Pharmaceuticals, Inc. (OMP) dated October 1, 2005. As determined by the parties, both BHC and OMP may use affiliated corporate entities to conduct this clinical trial. On behalf of OMP, such affiliates may include Johnson & Johnson Pharmaceutical Research & Development L.L.C. and Janssen-Cilag International N.V. Janssen Research & Development is a global organization that operates through different legal entities in various countries. Therefore, the legal entity acting as the sponsor for Janssen Research & Development studies may vary, such as, but not limited to Centocor Ortho Biotech Inc.; Centocor Ortho Biotech Products, L.P.; Janssen Biologics, B.V.; Janssen-Cilag International N.V.; Janssen, Inc; or Johnson & Johnson Pharmaceutical Research & Development, L.L.C. The term "sponsor" is used to represent these various legal entities as identified on the Contact Information page that accompanies the protocol.

Protocol No.: RIVAROXACS3001 (BAY59-7939/13194)

Title of Study: A Randomized, Double-Blind, Placebo-Controlled, Event-Driven Multicenter Study to Evaluate the Efficacy and Safety of Rivaroxaban in Subjects With a Recent Acute Coronary Syndrome

Study Name: The ATLAS ACS 2 TIMI 51 Trial (The second trial of Anti-Xa Therapy to Lower cardiovascular events in Addition to standard therapy in Subjects with Acute Coronary Syndrome)

EudraCT Number: 2008-002708-25

NCT No.: NCT00809965

Clinical Registry No.: CR014710

Coordinating Investigator: C. Michael Gibson, MD, Beth Israel Deaconess Medical Center, Harvard Medical School, [redacted], [redacted] United States

Study Center(s): Seven hundred sixty-six sites in 44 countries worldwide randomized subjects in this study.

Number of Sites Randomizing by Country
(Study RIVAROXACS3001)

Country	Sites Randomizing n	Country	Sites Randomizing n	Country	Sites Randomizing n
ARGENTINA	33	GREECE	4	PORTUGAL	10
AUSTRALIA	16	HUNGARY	13	ROMANIA	10
BELGIUM	8	INDIA	53	RUSSIAN FED.	70
BRAZIL	20	ISRAEL	11	SERBIA	8
BULGARIA	23	ITALY	19	SLOVAKIA	4
CANADA	17	JAPAN	49	SOUTH KOREA	7
CHILE	13	LATVIA	5	SPAIN	22
CHINA	32	LITHUANIA	7	SWEDEN	9
COLOMBIA	14	MALAYSIA	5	THAILAND	5
CROATIA	3	MEXICO	14	TUNISIA	6
CZECH REPUBLIC	19	MOROCCO	3	TURKEY	14
DENMARK	7	NETHERLANDS	15	UKRAINE	29
EGYPT	6	NEW ZEALAND	6	UNITED KINGDOM	17
FRANCE	11	PHILIPPINES	5	UNITED STATES	62
GERMANY	23	POLAND	39		

NOTE: Russian Fed. = Russian Federation
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Publication (Reference):

Study Design: Gibson CM, Mega JL, Burton P, Goto S, Verheugt F, Bode C, Plotnikov A, Sun X, Cook-Bruns N, Braunwald E. Rationale and design of the Anti-Xa Therapy to Lower cardiovascular events in Addition to standard therapy in Subjects with Acute Coronary Syndrome– Thrombolysis in Myocardial Infarction 51 (ATLAS-ACS 2 TIMI 51) trial: A randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of rivaroxaban in subjects with acute coronary syndrome. Am Heart J. 2011; 161:815-821.

Results: Mega JL, Braunwald E, Wiviott SD, Bassand JP, Bhatt DL, Bode C, Burton P, Cohen M, Cook-Bruns N, Fox KAA, Goto S, Murphy SA, Plotnikov AN, Schneider D, Sun X, Verheugt FWA, and Gibson CM, for the ATLAS ACS 2–TIMI 51 Investigators. Rivaroxaban in Patients with a Recent Acute Coronary Syndrome. N. Engl. J. Med. 2011 Published online November 13, 2011, http://www.nejm.org/doi/pdf/10.1056/NEJMoa1112277, Last accessed November 14, 2011.

Study Period: 26 November 2008 – 19 September 2011.

Phase of Development: Phase 3

Objectives: The primary objective of this study was to determine whether rivaroxaban in addition to standard care reduces the risk of the composite of cardiovascular (CV) death, MI, or stroke in subjects with a recent ACS compared with placebo in addition to standard care.

The secondary objectives of this study were 1) to determine whether rivaroxaban reduces the risk of the composite of all cause death, MI, or stroke in subjects with a recent ACS compared with placebo in addition to standard care, 2) to examine the effect of rivaroxaban on net clinical outcome, defined as the composite of CV death, MI, ischemic stroke, or a Thrombolysis in Myocardial Infarction (TIMI) major bleeding event not associated with coronary artery bypass graft (CABG) surgery, 3) to determine whether rivaroxaban reduces the risk of the composite of CV death, MI, stroke, or severe recurrent ischemia requiring revascularization in subjects with a recent ACS compared with placebo in addition to standard care, and 4) to determine whether rivaroxaban reduces the risk of the composite of CV death, MI, stroke,

or severe recurrent ischemia leading to hospitalization in subjects with a recent ACS compared with placebo in addition to standard care.

The safety objectives of this study were to assess TIMI major bleeding events not associated with CABG surgery (i.e., non-CABG TIMI Major bleeding) as the primary safety endpoint, and to assess overall safety by examining other bleeding events, serious adverse events, adverse events leading to discontinuation of study drug, and adverse events of special interest.

Methodology: The ATLAS ACS 2 TIMI 51 study was a randomized, double-blind, placebo-controlled, event-driven, multicenter study designed to evaluate the efficacy and safety of rivaroxaban in subjects with a recent ACS (STEMI, NSTEMI, or UA) who were receiving standard care.

The study was conducted in 3 phases: a 6-day screening phase, a double-blind treatment phase, and a follow up phase. Subjects who experienced a primary or secondary efficacy endpoint event (except for death and hemorrhagic stroke) continued to receive blinded study drug and completed all assessments at all scheduled visits, if possible. Subjects returned to the study center every 12 weeks until the global treatment end date; the projected date of accrual of approximately 983 primary efficacy endpoint events anticipated to be adjudicated as mITT events. The Executive Committee (EC) notified sites in advance of the global treatment end date via written communication, and study sites scheduled subjects for EOT visits as soon as possible on or after the date. Subjects were instructed not to discontinue their study drugs on the global treatment end date, but rather at the EOT visit; therefore, some subjects were treated with study drug after the global treatment end date. Thirty days after their last dose of study drug, subjects were to complete the final end-of-study (EOS) contact (either in person or by telephone) to assess efficacy and safety data.

Subjects who permanently discontinued the study drug before the specified number of primary efficacy endpoint events had occurred were to complete an end-of-treatment/early withdrawal visit at the time of treatment discontinuation. These subjects were to be contacted 30 days later, and continue to be contacted every 12 weeks thereafter until the study ended to assess efficacy and safety endpoint data.

Two oral doses of rivaroxaban (2.5 mg twice daily and 5 mg twice daily) were studied in comparison with placebo twice daily. Randomization was stratified by the intention to use thienopyridine (yes [Stratum 2] or no [Stratum 1]) as standard care, in addition to low-dose aspirin/acetylsalicylic acid (ASA) therapy (75 to 100 mg/day).

Within each stratum, subjects were randomly assigned in a 1:1:1 ratio to receive rivaroxaban 2.5 mg twice daily, rivaroxaban 5 mg twice daily or placebo twice daily. All study drug or placebo was to be taken orally, twice daily, once in the morning and once in the evening (approximately 12 hours apart).

Subjects were randomly assigned to study drug up to 7 calendar days after the subject had been hospitalized for the index ACS event (i.e., during the 6-day screening phase [Days –6 to –1] plus Day 1 of the double-blind treatment phase), when parenteral anticoagulant therapy would normally be discontinued. Randomization was to occur as soon as possible after the initial treatments for the index ACS event, including revascularization procedures, but could not occur during the first 24 hours following hospitalization.

The primary efficacy endpoint is the composite of CV death, MI, or stroke. The secondary efficacy endpoints are 1) assessments of the composite of all cause death, MI, or stroke, 2) net clinical outcome, defined as the composite of CV death, MI, ischemic stroke, or non-CABG TIMI Major bleeding event, 3) assessments of the composite of CV death, MI, stroke, or severe recurrent ischemia requiring revascularization, and 4) assessments of the composite of CV death, MI, stroke or severe recurrent ischemia requiring hospitalization.

All bleeding events were adjudicated by an independent Clinical Events Committee (CEC). The primary scale used to adjudicate bleeding events was the TIMI scale which has categories of major bleeding events, minor bleeding events, bleeding events requiring medical attention, and insignificant bleeding

events. Non-CABG TIMI Major bleeding events were assessed as the primary safety endpoint in this study. In addition to the TIMI scale, the rivaroxaban program uses the International Society on Thrombosis and Haemostasis (ISTH) bleeding event classification and has categories of major bleeding events, clinically relevant nonmajor bleeding events, and minimal bleeding events. For comparison with other studies outside the rivaroxaban clinical development program, bleeding events were also categorized using the Global Strategies for Opening Occluded Coronary Arteries (GUSTO) scale including severe, moderate and mild bleeding events. Safety was also assessed by evaluation of serious adverse events, adverse events leading to discontinuation of study drug, adverse events of special interest and clinical laboratory tests.

Number of Subjects (planned and analyzed): Originally, approximately 13,570 subjects (2,079 subjects in Stratum 1 and 11,491 subjects in Stratum 2) were estimated to be needed to reach the expected number of primary efficacy endpoint events and the targeted study power. The protocol allowed for the sample size to be increased to 16,000 subjects if planning assumptions were modified based on a blinded data review; since Stratum 1 enrollment was slower than originally projected, the final sample size was increased to approximately 15,500, in order to allow for accrual of a total of 983 clinical endpoint events. A total of 15,526 subjects (1,053 in Stratum 1 and 14,473 in Stratum 2) were actually randomized in the study. The efficacy population included all randomized subjects, without regard to treatment exposure and was used for the primary efficacy analysis (i.e., the modified Intent-to-Treat (mITT) analysis). The safety population included all randomized subjects who received at least one dose of study drug and was used for the primary safety analysis (i.e., the Treatment-Emergent Safety analysis). The numbers of subjects included in the efficacy and safety populations are shown in the table below. A total of 184 subjects from 3 sites ([redacted], and [redacted] were excluded from the efficacy analyses due to potential trial misconduct.

Table TSUB00: Number of Randomized Subjects
(Study RIVAROXACS3001: All Randomized Subjects Analysis Set)

	---------- Rivaroxaban ----------				
Subject Stratum	2.5 mg BID (N=5174)	5 mg BID (N=5176)	Combined (N=10350)	Placebo (N=5176)	Total (N=15526)
Population	n (%)	n (%)	n (%)	n (%)	n (%)
All Strata	5174	5176	10350	5176	15526
All Randomized Subjects	5174 (100)	5176 (100)	10350 (100)	5176 (100)	15526 (100)
All Randomized Subjects Excluding Selected Sites*	5114 (98.8)	5115 (98.8)	10229 (98.8)	5113 (98.8)	15342 (98.8)
Safety	5115 (98.9)	5110 (98.7)	10225 (98.8)	5125 (99.0)	15350 (98.9)
ASA	349	349	698	355	1053
All Randomized Subjects	349 (100)	349 (100)	698 (100)	355 (100)	1053 (100)
All Randomized Subjects Excluding Selected Sites*	349 (100)	348 (99.7)	697 (99.9)	353 (99.4)	1050 (99.7)
Safety	343 (98.3)	342 (98.0)	685 (98.1)	352 (99.2)	1037 (98.5)
ASA + Thieno	4825	4827	9652	4821	14473
All Randomized Subjects	4825 (100)	4827 (100)	9652 (100)	4821 (100)	14473 (100)
All Randomized Subjects Excluding Selected Sites*	4765 (98.8)	4767 (98.8)	9532 (98.8)	4760 (98.7)	14292 (98.7)
Safety	4772 (98.9)	4768 (98.8)	9540 (98.8)	4773 (99.0)	14313 (98.9)

Note: All randomized subjects constitute the Intent-to-Treat population.
Note: The safety population includes all subjects who received at least one dose of study drug.
Note: * excluding sites [redacted] and [redacted]
Note: Percentages calculated with the number of subjects in each subject stratum and treatment group as denominator.
Note: ASA = Acetylsalicylic acid; Thieno = Thienopyridine.
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Index Event Diagnosis and Main Criteria for Inclusion: Men and women aged ≥18 years, currently receiving ASA therapy (75 to 100 mg/day) alone or in combination with a thienopyridine (clopidogrel or ticlopidine per national dosing recommendation), who had been hospitalized for symptoms suggestive of ACS that lasted at least 10 minutes at rest, and occurred 48 hours or less before hospital presentation, or who developed ACS while being hospitalized for an indication other than ACS and had a diagnosis of STEMI, NSTEMI or unstable angina. Subjects aged 18 to 54 years inclusive must also have had either diabetes mellitus or a prior MI in addition to the presenting ACS event. Subjects were excluded if anticoagulation therapy was indicated, e.g., atrial fibrillation, or if they had any condition that, in the opinion of the investigator, contraindicated anticoagulant therapy or would have an unacceptable risk of bleeding, or who had a serious concomitant disease (e.g., cardiogenic shock, ventricular arrhythmias refractory to treatment, CrCl <30 mL/min, known significant liver disease, prior hemorrhagic stroke [and for Stratum 2, prior ischemic stroke or TIA], Hb <10 g/dL, HIV positive).

Test Product, Dose and Mode of Administration, Batch No.: Rivaroxaban was supplied as 2.5 and 5 mg tablets for oral administration. The batch numbers of rivaroxaban were as follows: Rivaroxaban 2.5 mg: (BX02VCL, BX02VCH, BC02VCD, BX02VCD, BX035LS, BX035LT, BX036C7, BX036C8, BX036C9, BX036CC, BX036CA, BX036CD, BX036CE, BX036C6, BX036CB, AM076, AN115, AN116, AN148), Rivaroxaban 5 mg: (BX02NG1, BX02VC8, BX02VC7, BXA4CSB, BXA4CSC, BX035LU).

Reference Therapy, Dose and Mode of Administration, Batch No.: Matching placebo tablets were supplied for oral administration; there were no visible differences between the 2 rivaroxaban strengths and the matching placebo tablets. The batch numbers of placebo were: BX02P60, BX02VJR, BX02VJP, BXA4C7S, BXA4C7T, and BXA4C7U.

Duration of Treatment: The duration of the treatment period for a given subject depended on the time required to accrue the prespecified number of adjudicated primary efficacy endpoint events. The study was stopped based on the estimated accrual of 983 primary efficacy endpoints anticipated to be adjudicated as mITT events.

Criteria for Evaluation: The primary efficacy endpoint was the composite of CV death, MI, or stroke. The secondary efficacy endpoints were: 1) assessments of the composite of all cause death, MI, or stroke, 2) net clinical outcome, defined as the composite of CV death, MI, ischemic stroke, or non-CABG TIMI Major bleeding event, 3) assessments of the composite of CV death, MI, stroke, or severe recurrent ischemia requiring revascularization, and 4) assessments of the composite of CV death, MI, stroke or severe recurrent ischemia requiring hospitalization. Non-CABG TIMI Major bleeding events were assessed as the primary safety endpoint in this study. In addition, clinically significant bleeding events, including TIMI major, TIMI minor, and bleeding events requiring medical attention, were recorded, adjudicated, and analyzed. CEC adjudicators also classified bleeding according to the International Society on Thrombosis and Haemostasis (ISTH) scale and the Global Strategies for Opening Occluded Coronary Arteries (GUSTO) scale. Safety was also assessed by evaluation of serious adverse events, adverse events leading to discontinuation of study drug, adverse events of special interest and clinical laboratory tests.

Statistical Methods: This was an event-driven study. A total of 983 primary efficacy endpoint events were estimated to have approximately 96% power to detect a 22.5% relative reduction (i.e., hazard ratio=0.775) between pooled doses of rivaroxaban and placebo arms pooled across Stratum 1 and 2, with a 2-sided type I error rate of 0.05. The double-blind treatment period was to stop on the projected date of accrual of approximately 983 primary efficacy endpoint events anticipated to be adjudicated as mITT events (i.e., global treatment end date). Approximately 13,570 subjects were originally estimated to be needed to reach the expected number of primary efficacy endpoint events to compare the pooled rivaroxaban (2.5 mg twice daily and 5 mg twice daily) arms with the placebo arm in order to reach the targeted study power. The protocol allowed for the sample size to be increased to 16,000 subjects if planning assumptions were modified based on a blinded data review; since Stratum 1 enrollment was

slower than originally projected, the final sample size was increased to approximately 15,500, in order to allow for accrual of a total of 983 clinical endpoint events. A formal interim review of efficacy and safety data was performed when approximately 70% (688) of the required total number (983) of primary efficacy events, best available or adjudicated by the Clinical Events Committee, had occurred, in order to assess whether the study should be stopped for overwhelming superiority. Details on α adjustment calculation, as well as details of the interim stopping plan, are provided in the SAP. The data cut-off for the interim analysis was November 29, 2010, based on 704 total primary efficacy events. The IDMC met on January 12, 2011 to review the data. The study continued unaltered following that analysis.

The efficacy population included all randomized subjects, excluding subjects from sites [redacted] and [redacted],without regard to treatment exposure and was used for the primary efficacy analysis (i.e., the modified Intent-to-Treat (mITT) analysis). The mITT analysis set included all randomized subjects and the endpoint events that occurred from randomization up to the earlier date of the global treatment end date, or 30 days after last dose of study drug (for subjects who discontinued study drug prematurely), or 30 days after randomization (for subjects who were randomized but never treated). The safety population included all randomized subjects who received at least one dose of study drug and was used for the primary safety analysis (i.e., the Treatment-Emergent Safety analysis). The Treatment-Emergent Safety analysis set included all randomized subjects who received at least one dose of study drug and the events that occurred from first dose up to the date of last dose of study drug plus 2 days for each subject.

Unless otherwise stated, the efficacy analyses were based on adjudicated events.

Based on time from randomization to the first occurrence of the primary efficacy endpoint (i.e., composite of CV death, MI, or stroke), the objective of the primary efficacy analysis was to determine whether rivaroxaban is superior to placebo, in addition to standard care, in the reduction of the primary efficacy endpoint in subjects with a recent ACS. A stratified (stratified by the intention to use a thienopyridine [yes or no]) or unstratified (Stratum 2 alone) log-rank test was the primary analysis for hypothesis testing on the pooled rivaroxaban treatment groups versus placebo. A similar stratified log-rank test using the same stratum variable (or without stratum, if for Stratum 2 alone) was performed for the individual dose comparisons.

A stratified (stratified by the intention to use a thienopyridine [yes or no]) or unstratified (Stratum 2 alone) Cox proportional hazards regression model was used with treatment group (rivaroxaban vs. placebo) as the covariate to provide a point estimate and 95% confidence interval for the treatment effect of the relative risk reduction (RRR) (RRR=100 X [1 – hazard ratio]%). A similar stratified Cox model using the same stratum variable (or without stratum if for Stratum 2 alone) was performed for the individual dose comparisons.

Kaplan Meier curves were prepared to display the cumulative proportions of events by treatment group.

Two simultaneous evaluation strategies were selected on the basis of advice from health authorities in different regions and were employed for the primary endpoint analyses. The primary evaluation strategy was based on data combined across both strata. A second evaluation strategy was similarly carried out based on data from subjects in Stratum 2 only.

Based on time from randomization to the first occurrence of the primary efficacy endpoint, the primary efficacy analysis was performed between the pooled rivaroxaban groups and the placebo group; due to a small adjustment necessitated by the interim efficacy analysis, a 2-sided α=0.0499982 was used for the primary efficacy analysis. If the pooled rivaroxaban groups were found to be superior to placebo, then each rivaroxaban individual dose was simultaneously tested versus placebo at a 2-sided significance level of 0.050. If the superiority of a dose group was declared, the secondary efficacy endpoints were tested for that dose group, at the same 2-sided significance level of 0.050, in the sequential order below:

1. Secondary Efficacy Endpoint 1: Composite of all-cause death, MI, or stroke

2. Secondary Efficacy Endpoint 2 (Net Clinical Outcome): Composite of CV death, MI, ischemic stroke, or non-CABG TIMI Major bleeding event

3. Secondary Efficacy Endpoint 3: Composite of CV death, MI, stroke, or severe recurrent ischemia requiring revascularization

4. Secondary Efficacy Endpoint 4: Composite of CV death, MI, stroke, or severe recurrent ischemia leading to hospitalization

Each subsequent ordered secondary endpoint could be tested only for the dose that was significant for the previous endpoints. If an individual test during any step was not statistically significant, further testing could continue but significance could not be claimed.

Sensitivity analyses were performed on the primary efficacy endpoint using the same approach as in the primary efficacy analysis (i.e., mITT analysis set) based on the ITT analysis set (all adjudicated events of CV death, MI, and stroke observed after randomization up to the global treatment end date), Treatment-Emergent Safety analysis set, and ITT-Total analysis set (all adjudicated events of CV death, MI, and stroke occurring after randomization). The analysis methods mirrored that proposed for the primary efficacy analysis. For the primary efficacy endpoint, investigator-reported events as compared to adjudicated events were also summarized.

The component events of the various composite endpoints were also analyzed using the same methods as those used for the primary efficacy endpoint, including log-rank test, Cox model, and Kaplan-Meier estimates. Stent thrombosis and its sub-categories were summarized by treatment group.

Time from first dose to the first occurrence of the primary safety endpoint (non-CABG TIMI Major bleeding event) was analyzed and tested in the primary Treatment-Emergent Safety analysis set, as well as in the mITT approach Safety and Safety analysis sets. Similarly to the primary efficacy endpoint analyses, a stratified (stratified by the intention to use a thienopyridine [yes or no]) or unstratified (Stratum 2 alone) log-rank test was the primary analysis for hypothesis testing. A stratified (stratified by the intention to use a thienopyridine [yes or no]) or unstratified (Stratum 2 alone) Cox proportional hazards regression model was also used to provide a point estimate and 95% confidence interval for the treatment effect of the relative risk reduction (RRR) (RRR=100 X [1 – hazard ratio]) with treatment group as a class covariate with placebo as reference. Kaplan Meier curves were provided for the cumulative proportions of events by treatment group.

Other bleeding endpoints included:

- TIMI major and/or TIMI minor
- Clinically significant bleeding, i.e. the composite of TIMI major, TIMI minor, or bleeding events requiring medical attention
- Bleeding events according to the ISTH criteria
- Bleeding events according to the GUSTO criteria
- All bleeding events according to TIMI classification

For these bleeding event endpoints, similar analyses were performed as for the primary safety endpoint.

Death was summarized by CV, non-CV, unknown, and sub-categories specified in the CRF. Treatment emergent adverse events (TEAE) were defined as those events starting between the first study drug administration and 2 days after the last study drug administration, inclusive. The number and percentage of subjects with TEAEs, Treatment-emergent Serious Adverse Events (TESAE) and TEAEs resulting in permanent discontinuation of study drug were summarized for each treatment group by system organ class and dictionary-derived term. In particular, liver-related TEAEs and bleeding TEAEs were identified and summarized using Standardized MedDRA Queries (SMQ).

The frequency of ALT >3x ULN (during the first 24 weeks of treatment) was summarized and compared across treatment groups. In addition, analyses of the time to first occurrence of an ALT >3x ULN comparing treatment groups were evaluated. Abnormal ALT and total bilirubin was tabulated as eDISH plot. Concurrent and non-concurrent ALT > 3x ULN and total bilirubin > 2x ULN were summarized by treatment group.

RESULTS:

STUDY POPULATION: Of the 15,526 subjects randomized, 13,124 (84.5%) subjects completed the study. Subjects who completed the follow-up period were considered to have completed the study. The percentages of subjects who completed the study were similar across treatment groups and strata. The most common reason for not completing the study was consent withdrawn (1294 [8.3%]); the percentage of subjects that withdrew consent was slightly higher in the 2.5 mg b.i.d. and 5 mg b.i.d. groups compared with placebo. Of the 1,294 subjects who withdrew consent, 177 (13.7%) subjects were confirmed to be alive. Vital status remained unknown for 1,117 (86.3%) subjects who withdrew consent; the sponsor was denied permission to collect vital status information on 1,111 of these subjects, leaving only 6 subjects for which the sponsor had permission but was unable to collect vital status information at study end. The total number of subjects lost to follow-up at the global study end was low (45 [0.3%]). The percentage of missing time in the follow-up period to global study end due to subjects who discontinued prematurely from the study for reasons other than death was 5.9%, 5.9%, and 5.3% in the rivaroxaban 2.5 mg b.i.d., 5 mg b.i.d., and placebo groups, respectively. Of 15,350 treated subjects, the total numbers of subjects who prematurely discontinued study drug were 1376 (26.9%) rivaroxaban 2.5 mg b.i.d. subjects, 1504 (29.4%) rivaroxaban 5 mg b.i.d. subjects and 1351 (26.4%) placebo subjects. The most common reasons for premature discontinuation of study treatment were Other, adverse event, and consent withdrawn. Within the category of "Other", the most common sub-classification was "Subject choice/Non compliance," which includes subjects that did not want to continue taking study drug or attend clinic visits but were willing to be contacted at the global study end and did not formally withdraw consent. In All Strata, the Kaplan-Meier estimated cumulative discontinuation rates at 6 months and 1 year were 17.85% and 24.11% for the 2.5 mg b.i.d. group, 20.34% and 26.83% for the 5 mg b.i.d. group and 17.30% and 22.61% for the placebo group, respectively.

Of 15,526 randomized subjects in All Strata, approximately 3 of every 4 subjects were men (74.7%) and the mean age was 61.8 years (range 22 to 98 years). The majority of subjects were white (73.5%) and 20.8% were Asian; there were few black (107 [0.7%]) subjects. There were relatively few subjects enrolled with moderate to severe renal impairment (1086 [7.1%] subjects with baseline CrCl <50 mL/min). The majority of subjects had CV risk factors, such as hypertension, DM, history of MI, hypercholesterolemia. As expected in a study of this size, there were no important imbalances in baseline demographic or disease characteristics. Approximately half of the subjects randomized had ST-segment elevation ACS (STEMI) and half of subjects were randomized with an index event other than STEMI (i.e., NSTEMI and UA); NSTEMI and UA each comprised about 25% of the ACS index events. On average, subjects were randomized 4.7 days following the index event. There were 9387 (60.5%) subjects who had a revascularization procedure for the index event; the vast majority of these procedures were PCI. The overall low incidence of subjects with prior ischemic stroke (286 [1.8%]) and prior TIA (141 [0.9%]) was expected since the protocol excluded subjects with a history of hemorrhagic stroke and subjects with a history of ischemic stroke or TIA were eligible only for randomization in Stratum 1 (ASA only).

In All Strata, the median total duration of treatment (from the first dose of study drug administration to the last dose of study drug administration including days both on and off study drug) was 397.0 days and 376.5 days in the rivaroxaban 2.5 mg b.i.d. and 5 mg b.i.d. groups, respectively, and 399.0 days in the placebo group for subjects in the safety population. Since this was an event-driven study, subjects were exposed to study drug for varying lengths of time, depending on when they were enrolled. Across all treatment groups, more than 75% of subjects were exposed to study drug for ≥6 months, more than half for ≥12 months, and almost one-third were exposed for ≥18 months. Total exposure was 5542.4, 5394.8,

and 5611.2 patient-years in the 2.5 mg b.i.d., 5 mg b.i.d. and placebo groups, respectively. Duration of exposure to study drug was similar to the duration of exposure to concomitant ASA (median of 390.0 days) during the double-blind treatment period, while exposure to concomitant thienopyridine was slightly lower (median of 334.0 days).

EFFICACY RESULTS: The results showed that the study met its primary efficacy objective. In All Strata, the combined rivaroxaban groups were superior to placebo in reducing the occurrence of the primary efficacy endpoint (HR 0.84; 95% CI 0.74-0.96; P=0.008); further, both doses of rivaroxaban were individually superior to placebo in the primary efficacy analysis. The result in the 2.5 mg b.i.d. group was driven by a nominally significant reduction in CV deaths (HR: 0.66, 95% CI: 0.51, 0.86), including a numerical reduction in fatal MIs. While a small numerical reduction in CV deaths was observed in the 5 mg b.i.d. group, the result in this group was primarily driven by a reduction in MIs (HR: 0.79, 95% CI: 0.65, 0.97). Further, for All Strata, both the 2.5 mg b.i.d. and the 5 mg b.i.d. doses of rivaroxaban were individually superior to placebo, in addition to standard care, in reducing the occurrence of Secondary Efficacy Endpoint 1 events (i.e., composite of all-cause death, MI or stroke).; however, there was no significant reduction in the occurrence of the Secondary Efficacy Endpoint 2 in either of the rivaroxaban dose groups compared with placebo (i.e., composite of CV death, MI, ischemic stroke, or non-CABG TIMI major bleeding). As a result, the hierarchical testing for the rest of the secondary endpoints in All Strata was stopped.

The simultaneous analysis in Stratum 2 closely mirrored the results of All Strata. In Stratum 2, the combined rivaroxaban doses were superior to placebo in reducing the occurrence of the primary efficacy endpoint (HR 0.86; 95% CI 0.75, 0.98; P=0.024). However, between the 2 dose groups, only the 2.5 mg b.i.d. group achieved statistical significance for the primary efficacy endpoint. This result was, as noted above, driven by a substantial, nominally significant reduction in CV death (HR: 0.62, 95% CI: 0.47, 0.82). The results in the 5 mg b.i.d. rivaroxaban group were numerically better than those of the placebo group, but were not statistically significant. The hierarchical testing for the 5 mg b.i.d. group was then halted. Continuing the hierarchical testing for the 2.5 mg b.i.d. group in Stratum 2, rivaroxaban 2.5 mg b.i.d. was superior to placebo, in addition to standard care, in reducing the occurrence of the composite of all-cause death, MI or stroke, driven by a substantial and nominally statistically significant reduction in all-cause mortality (HR 0.64; 95% CI: 0.49, 0.83). Numerically lower rates of MIs and numerically higher rates of stroke compared with placebo were also observed in the 2.5 mg b.i.d. group. Consistent with the results of All Strata, rivaroxaban 2.5 mg b.i.d. was not significantly different compared with placebo on net clinical outcome (i.e., composite of CV death, MI, ischemic stroke, or non-CABG TIMI major bleeding), as prospectively defined in the SAP. As a result, the hierarchical testing for the 2.5 mg b.i.d. group in the remaining secondary endpoints in Stratum 2 was also stopped.

Rivaroxaban 2.5 mg b.i.d. was superior to placebo in reducing CV deaths and all-cause deaths; the incidence of CV deaths in the rivaroxaban 5 mg b.i.d. group was not significantly different compared with placebo. The majority of all-cause deaths were CV deaths. A greater reduction in the incidence of MIs was observed with rivaroxaban 5 mg b.i.d. compared with the 2.5 mg b.i.d. dose; however, a numerically higher percentage of MIs in the 5 mg b.i.d. group were fatal. There was a higher incidence of stroke in the rivaroxaban treatment groups compared with placebo. Neither rivaroxaban dose appeared to modify the risk of ischemic stroke, although the rates of ischemic stroke were low; in All Strata, the incidence of ischemic stroke was 0.6% in the 2.5 mg b.i.d. group, 0.7% in the 5 mg b.i.d. group, and 0.6% in the placebo group. The incidence of hemorrhagic strokes was numerically higher in the rivaroxaban groups (0.3% and 0.4%), compared with placebo (0.1%). For those subjects with available data, the proportion of subjects with moderate to severe disability following their stroke was nominally statistically significantly lower in the 2.5 mg b.i.d. group compared with the placebo group. Fewer cases of definite or probable stent thrombosis fulfilling the ARC definitions were observed in both the rivaroxaban 2.5 mg b.i.d. and 5 mg b.i.d. rivaroxaban groups compared with placebo.

The results for the primary efficacy endpoint and Secondary Efficacy Endpoint 1 and the components of both composite endpoints are summarized in the table below:

Table TEFF04-DERIVED: Effect of Rivaroxaban Compared with Placebo on Primary Efficacy Endpoint and Secondary Efficacy Endpoint 1 and Components as Adjudicated by the CEC
(Study RIVAROXACS3001: Modified Intent-to-Treat (Excluding Sites [redacted] and [redacted] Analysis Set)

	Rivaroxaban				-- 2.5 mg BID --	--- 5 mg BID ---	--- Combined ---
	2.5 mg BID	5 mg BID	Combined	Placebo	------ vs. -----	------ vs. -----	------ vs. -----
Subject Stratum	(N=5114)	(N=5115)	(N=10229)	(N=5113)	---- Placebo ---	---- Placebo ---	---- Placebo ---
Parameter	n(%)	n(%)	n(%)	n(%)	HR (95% CI)	HR (95% CI)	HR (95% CI)
All Strata	5114	5115	10229	5113			
Primary	313(6.1)	313(6.1)	626(6.1)	376(7.4)	0.84 (0.72,0.97)	0.85 (0.73,0.98)	0.84 (0.74,0.96)
Dth/MI/St	320(6.3)	321(6.3)	641(6.3)	386(7.5)	0.83 (0.72,0.97)	0.84 (0.73,0.98)	0.84 (0.74,0.95)
CV_Dth	94(1.8)	132(2.6)	226(2.2)	143(2.8)	0.66 (0.51,0.86)	0.94 (0.75,1.20)	0.80 (0.65,0.99)
Death	103(2.0)	142(2.8)	245(2.4)	153(3.0)	0.68 (0.53,0.87)	0.95 (0.76,1.19)	0.81 (0.66,1.00)
MI	205(4.0)	179(3.5)	384(3.8)	229(4.5)	0.90 (0.75,1.09)	0.79 (0.65,0.97)	0.85 (0.72,1.00)
Stroke	46(0.9)	54(1.1)	100(1.0)	41(0.8)	1.13 (0.74,1.73)	1.34 (0.90,2.02)	1.24 (0.86,1.78)
ASA	349	348	697	353			
Primary	27(7.7)	24(6.9)	51(7.3)	36(10.2)	0.74 (0.45,1.22)	0.64 (0.38,1.07)	0.69 (0.45,1.05)
Dth/MI/St	28(8.0)	24(6.9)	52(7.5)	36(10.2)	0.77 (0.47,1.26)	0.64 (0.38,1.07)	0.70 (0.46,1.07)
CV_Dth	12(3.4)	9(2.6)	21(3.0)	10(2.8)	1.20 (0.52,2.77)	0.89 (0.36,2.20)	1.04 (0.49,2.21)
Death	13(3.7)	9(2.6)	22(3.2)	10(2.8)	1.30 (0.57,2.96)	0.89 (0.36,2.20)	1.09 (0.52,2.31)
MI	16(4.6)	10(2.9)	26(3.7)	22(6.2)	0.72 (0.38,1.37)	0.44 (0.21,0.93)	0.58 (0.33,1.02)
Stroke	2(0.6)	8(2.3)	10(1.4)	7(2.0)	0.28 (0.06,1.37)	1.13 (0.41,3.12)	0.71 (0.27,1.86)
ASA + Thieno	4765	4767	9532	4760			
Primary	286(6.0)	289(6.1)	575(6.0)	340(7.1)	0.85 (0.72,0.99)	0.87 (0.74,1.01)	0.86 (0.75,0.98)
Dth/MI/St	292(6.1)	297(6.2)	589(6.2)	350(7.4)	0.84 (0.72,0.98)	0.87 (0.74,1.01)	0.85 (0.75,0.97)
CV_Dth	82(1.7)	123(2.6)	205(2.2)	133(2.8)	0.62 (0.47,0.82)	0.95 (0.74,1.21)	0.78 (0.63,0.97)
Death	90(1.9)	133(2.8)	223(2.3)	143(3.0)	0.64 (0.49,0.83)	0.95 (0.75,1.21)	0.79 (0.64,0.98)
MI	189(4.0)	169(3.5)	358(3.8)	207(4.3)	0.92 (0.75,1.12)	0.83 (0.68,1.02)	0.88 (0.74,1.04)
Stroke	44(0.9)	46(1.0)	90(0.9)	34(0.7)	1.31 (0.84,2.05)	1.39 (0.89,2.16)	1.35 (0.91,2.00)

Note: The data shown are for all randomized subjects and the endpoint events occurring at or after randomization and the earliest date of the global treatment end date, 30 days after study drug was prematurely discontinued and 30 days after randomization for those subjects who were randomized but not treated.

Note: A subject could have more than one component event.
Note: n = number of subjects with events; N = number of subjects at risk; % = 100 * n / N.
Note: Primary: first occurrence of cardiovascular death including unknown death, MI, or stroke; CV_Dth: Cardiovascular death including unknown death; Dth/MI/St (Secondary Efficacy Endpoint 1): first occurrence of all cause death, MI or stroke; MI: Myocardial infarction.
Note: HR (95% CI): Hazard ratios (95% confidence interval) as compared to placebo arm are based on the (stratified, only for all strata) Cox proportional hazards model.
Note: ASA = Acetylsalicylic acid; Thieno = Thienopyridine.
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In general, rivaroxaban treatment was consistently associated with improved outcomes on the primary efficacy endpoint across all major subgroups. For the majority of analyses, interaction p values were >0.05. The benefit of rivaroxaban was consistently demonstrated whether subjects had STEMI, NSTEMI or unstable angina as their index event. There was a benefit across doses and strata in subjects with a history of CHF compared to those without prior CHF.

SAFETY RESULTS: In All Strata, the occurrence of the primary safety endpoint was significantly higher in the combined rivaroxaban groups compared with the placebo group (1.4% rivaroxaban vs. 0.4% placebo; HR: 3.96, 95% CI: 2.46, 6.38; p<0.001). Further, the occurrence of the primary safety endpoint was significantly higher in both the 2.5 mg b.i.d. group (1.3% 2.5 mg b.i.d. vs. 0.4% placebo; HR: 3.46, 95% CI: 2.08, 5.77; p<0.001) and in the 5 mg b.i.d. group (1.6% 5 mg b.i.d. vs. 0.4% placebo; HR: 4.47, 95% CI: 2.71, 7.36; p<0.001) compared with placebo.

In Stratum 2, the occurrence of the primary safety endpoint was significantly higher in the combined rivaroxaban groups compared with the placebo group (1.5% rivaroxaban vs. 0.4% placebo; HR: 3.80, 95% CI: 2.35, 6.14; p<0.001). Further, the occurrence of the primary safety endpoint was significantly higher in both in both the 2.5 mg b.i.d. group (1.3% 2.5 mg b.i.d. vs. 0.4% placebo; HR: 3.35, 95% CI: 2.01, 5.60; p<0.001) and in the 5 mg b.i.d. group (1.6% 5 mg b.i.d. vs. 0.4% placebo; HR: 4.26, 95% CI: 2.58, 7.03; p<0.001) compared with placebo.

Numerically higher incidence rates in both rivaroxaban groups compared with placebo were seen in most of the bleeding categories in All Strata, in Stratum 2, and Stratum 1.

Table TBL01-DERIVED: Effect of Rivaroxaban Compared with Placebo on Treatment-Emergent Bleeding using TIMI scale as Adjudicated by the CEC (Study RIVAROXACS3001: Treatment-Emergent Safety Analysis Set)

	---------- Rivaroxaban ----------						
Subject Stratum	2.5 mg BID (N=5115)	5 mg BID (N=5110)	Combined (N=10225)	Placebo (N=5125)	-- 2.5 mg BID vs. Placebo --	--- 5 mg BID vs. Placebo --	-- Combined vs. Placebo --
Parameter	n(%)	n(%)	n(%)	n(%)	HR (95% CI)	HR (95% CI)	HR (95% CI)
All Strata	5115	5110	10225	5125			
Primary	65(1.3)	82(1.6)	147(1.4)	19(0.4)	3.46 (2.08,5.77)	4.47 (2.71,7.36)	3.96 (2.46,6.38)
Clinical Sig.	586(11.5)	748(14.6)	1334(13.0)	327(6.4)	1.84 (1.61,2.11)	2.43 (2.13,2.76)	2.13 (1.89,2.40)
TIMI Ma or Mi	100(2.0)	132(2.6)	232(2.3)	46(0.9)	2.20 (1.55,3.11)	2.96 (2.12,4.14)	2.58 (1.88,3.54)
TIMI Major	68(1.3)	85(1.7)	153(1.5)	27(0.5)	2.55 (1.63,3.98)	3.25 (2.11,5.02)	2.90 (1.92,4.36)
TIMI Minor	32(0.6)	49(1.0)	81(0.8)	20(0.4)	1.62 (0.92,2.82)	2.52 (1.50,4.24)	2.07 (1.27,3.37)
TIMI Med. Attent.	492(9.6)	637(12.5)	1129(11.0)	282(5.5)	1.79 (1.55,2.07)	2.39 (2.08,2.75)	2.09 (1.83,2.38)
ASA	343	342	685	352			
Primary	2(0.6)	4(1.2)	6(0.9)	0			
Clinical Sig.	19(5.5)	23(6.7)	42(6.1)	11(3.1)	1.77 (0.84,3.71)	2.10 (1.02,4.31)	1.93 (0.99,3.75)
TIMI Ma or Mi	3(0.9)	4(1.2)	7(1.0)	2(0.6)	1.53 (0.26,9.16)	2.00 (0.37,10.94)	1.77 (0.37,8.50)
TIMI Major	2(0.6)	4(1.2)	6(0.9)	2(0.6)	1.02 (0.14,7.22)	2.00 (0.37,10.94)	1.51 (0.30,7.47)
TIMI Minor	1(0.3)	0	1(0.1)	0			
TIMI Med. Attent.	16(4.7)	19(5.6)	35(5.1)	9(2.6)	1.82 (0.81,4.13)	2.13 (0.96,4.70)	1.97 (0.95,4.10)
ASA + Thieno	4772	4768	9540	4773			
Primary	63(1.3)	78(1.6)	141(1.5)	19(0.4)	3.35 (2.01,5.60)	4.26 (2.58,7.03)	3.80 (2.35,6.14)
Clinical Sig.	567(11.9)	725(15.2)	1292(13.5)	316(6.6)	1.84 (1.61,2.12)	2.44 (2.14,2.78)	2.14 (1.89,2.42)
TIMI Ma or Mi	97(2.0)	128(2.7)	225(2.4)	44(0.9)	2.23 (1.56,3.18)	3.01 (2.13,4.23)	2.62 (1.89,3.61)
TIMI Major	66(1.4)	81(1.7)	147(1.5)	25(0.5)	2.67 (1.68,4.23)	3.35 (2.14,5.25)	3.01 (1.97,4.60)
TIMI Minor	31(0.6)	49(1.0)	80(0.8)	20(0.4)	1.56 (0.89,2.74)	2.52 (1.50,4.24)	2.04 (1.25,3.33)
TIMI Med. Attent.	476(10.0)	618(13.0)	1094(11.5)	273(5.7)	1.79 (1.54,2.07)	2.40 (2.08,2.77)	2.09 (1.83,2.39)

Note: The data shown are for all subjects who received at least one dose of study drug and the endpoint events occurring between the first study drug administration and 2 days after the last study drug administration, inclusive.
Note: A subject could have more than one component event.
Note: n = number of subjects with events; N = number of subjects at risk; % = 100 * n / N.
Note: Primary: Non-CABG related TIMI major bleeding; Clinical Sig.: first occurrence of any TIMI major, TIMI minor, or bleed requiring medical attention;
TIMI Ma or Mi: TIMI major or TIMI minor bleeding; TIMI Med. Attent.: TIMI bleeding requiring medical attention.
Note: HR (95% CI): Hazard ratios (95% confidence interval) as compared to placebo arm are based on the (stratified, only for all strata) Cox proportional hazards model.
Note: ASA = Acetylsalicylic acid; Thieno = Thienopyridine; CABG = Coronary artery bypass grafting.
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Of note, the overall incidence of treatment-emergent fatal bleeding in the study was low, and importantly, was not increased in the rivaroxaban 2.5 mg b.i.d. group compared with placebo, and numerically higher in the rivaroxaban 5 mg b.i.d. group compared with placebo [6 (0.1%) 2.5 mg b.i.d. rivaroxaban, 15 (0.3%) 5 mg b.i.d. rivaroxaban, and 9 (0.2%) placebo subjects] for All Strata. The rates of intracranial

hemorrhage and hemorrhagic stroke were low overall, but incidence rates were higher in the combined rivaroxaban groups compared to the placebo group (0.3% vs. 0.1%), particularly in Stratum 2. However, fatal intracranial bleeding was balanced between the 2.5 mg b.i.d. group (5 [0.1%]) and the placebo group (4 [0.1%]), but the incidence of fatal intracranial bleeding was numerically higher in the 5 mg b.i.d. group (8 [0.2%]). The most frequently reported sites of treatment-emergent TIMI Major bleeding were gastrointestinal [88 (0.9%) subjects in the combined rivaroxaban groups and 13 (0.3%) placebo subjects] and intracranial bleeding [32 (0.3%) subjects in the combined rivaroxaban groups and 5 (0.1%) placebo subjects].

The results of the subgroup analyses were generally consistent with the results of the overall primary safety endpoint analysis; there were no significant treatment interactions in any of the subgroups based on demographics, baseline characteristics, medical history, index event or region. The results using the ISTH and GUSTO scales confirmed the findings for TIMI life-threatening bleeding. The majority of life-threatening bleeding events in the rivaroxaban 2.5 mg b.i.d. group included bleeding that led to decreases in hemoglobin and blood transfusions; bleeding events that required intravenous inotropic support or surgical intervention were balanced between the 2.5 mg b.i.d. group and placebo. In the 5 mg b.i.d. group, all categories of life-threatening bleeding were numerically higher than those in the placebo group, with the exception of those requiring surgical intervention.

Across all treatment groups, the most common bleeding-related adverse events were in gastrointestinal and respiratory disorders. More treatment-emergent bleeding-related adverse events occurred in the 5 mg b.i.d. group compared with the 2.5 mg b.i.d. and placebo dose groups. Gingival bleeding was the most common gastrointestinal bleeding-related adverse event and epistaxis was the most common respiratory bleeding-related adverse event. The rates of clinical and laboratory markers of liver safety were balanced across all treatment groups and all strata.

STUDY LIMITATIONS: No notable study limitations were identified by the Sponsor.

CONCLUSION(S): The following conclusions can be drawn from the ATLAS ACS 2 TIMI 51 trial:

- The addition of rivaroxaban to standard care antiplatelet therapy was effective in reducing the occurrence of the composite primary endpoint of cardiovascular death, myocardial infarction or stroke compared with placebo in subjects with a recent ACS.
  - Both the 2.5 mg b.i.d. and the 5 mg b.i.d. doses were effective in reducing the occurrence of the primary efficacy endpoint.
  - In general, rivaroxaban treatment was consistently associated with improved outcomes on the primary efficacy endpoint across all subgroups.
  - The addition of rivaroxaban at doses of 2.5 mg b.i.d. and 5 mg b.i.d. to standard care antiplatelet therapy was effective in reducing the occurrence of secondary efficacy endpoint 1 (i.e., composite of all-cause death, MI or stroke) compared with placebo in subjects with a recent ACS.
- The 2.5 mg b.i.d. dose of rivaroxaban in addition to standard care antiplatelet therapy was nominally statistically significant in reducing the incidence of cardiovascular deaths, and 5 mg b.i.d. was nominally statistically significant in reducing the incidence of myocardial infarctions, particularly in subjects intended to be treated with ASA only as standard antiplatelet therapy. The effect of the 2.5 mg b.i.d. dose on MI and the effect of the 5 mg b.i.d. dose on CV deaths were directionally consistent. Neither dose modified the risk of stroke.
- The risk of stent thrombosis was nominally significantly reduced with rivaroxaban 2.5 mg b.i.d.
- Overall, the rates of the primary safety endpoint (treatment-emergent non-CABG TIMI major bleeding) were low. The addition of either rivaroxaban 2.5 mg b.i.d. or 5 mg b.i.d. to standard care

antiplatelet therapy increased the incidence of the primary safety endpoint compared with placebo (standard care antiplatelet therapy alone).

  - The results of the subgroup analyses were generally consistent with the results of the overall primary safety endpoint analysis; there were no significant treatment interactions in any of the subgroups based on demographics, baseline characteristics, medical history, index event or region.

- The rates of intracranial bleeding and hemorrhagic stroke were low overall, but incidence rates were higher in the rivaroxaban treatment groups compared with placebo and incidence rates for those with fatal intracranial bleeding events were similar among placebo subjects and rivaroxaban 2.5 mg b.i.d. subjects.
- The overall incidence of fatal bleeding events in the study was low; there were numerically fewer fatal bleeding events in subjects treated with 2.5 mg b.i.d. than in subjects treated with placebo, but numerically more fatal bleeding events were observed with the 5 mg b.i.d. dose.
- The results using the ISTH and GUSTO scales confirmed the findings for TIMI life-threatening bleeding. The majority of life-threatening bleeding events in the rivaroxaban 2.5 mg b.i.d. group included bleeding that led to decreases in hemoglobin and blood transfusions; bleeding events that required intravenous inotropic support or surgical intervention were balanced between the 2.5 mg b.i.d. group and placebo. In the 5 mg b.i.d. group, all categories of life-threatening bleeding were numerically higher than those in the placebo group, with the exception of those requiring surgical intervention.
- Across all treatment groups, the most common bleeding-related adverse events were in gastrointestinal and respiratory disorders. More treatment-emergent bleeding-related adverse events occurred in the 5 mg b.i.d. group compared with the 2.5 mg b.i.d. and placebo dose groups. Gingival bleeding was the most common gastrointestinal bleeding-related adverse event and epistaxis was the most common respiratory bleeding-related adverse event.
- The rates of clinical and laboratory markers of liver safety were balanced across all treatment groups and all strata.
- Overall, the incidence of non-bleeding adverse events, including treatment-emergent adverse events/SAEs, adverse events with an onset greater than 2 days after discontinuation of study drug, and adverse events leading to permanent discontinuation of study drug, was similar across treatment groups and strata.

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