

Janssen Research & Development, LLC

Advisory Committee Briefing Document

**Rivaroxaban for Reducing the Risk of Cardiovascular Events (Cardiovascular Death,
Myocardial Infarction and Stroke) After Acute Coronary Syndrome (ACS)**

JNJ-39039039; BAY 59-7939 (rivaroxaban)

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TABLE OF CONTENTS

TABLE OF CONTENTS	2
LIST OF IN-TEXT TABLES	4
LIST OF IN-TEXT FIGURES	7
LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS	9
EXECUTIVE SUMMARY	10
1. INTRODUCTION.....	15
1.1. Acute Coronary Syndrome: A Highly Prevalent Public Health Problem with High Mortality and Morbidity.....	15
1.2. Current Management After Acute Coronary Syndrome.....	15
1.3. Unmet Medical Need.....	16
2. PRECLINICAL DATA.....	17
2.1. Rivaroxaban Mechanism of Action, Preclinical Pharmacology and Chemical Class	17
2.2. Biological Basis for the Use of Rivaroxaban in Patients with ACS	20
2.3. Discussion.....	22
3. CLINICAL PHARMACOLOGY.....	22
4. OVERVIEW OF THE ACS CLINICAL DEVELOPMENT PROGRAM	27
4.1. Phase 2 Study ATLAS ACS TIMI 46.....	28
4.1.1. Results Relevant to Phase 3 Study Dose Selection.....	28
4.1.2. Efficacy and Safety of Rivaroxaban in ATLAS ACS TIMI 46.....	34
4.2. Phase 3 Study ATLAS ACS 2 TIMI 51.....	35
4.2.1. Key Aspects of Study Design	35
4.2.2. Statistical Methods.....	39
5. DEMOGRAPHICS AND DISPOSITION – ATLAS ACS 2 TIMI 51	46
5.1. Population Studied	46
5.2. Disposition.....	49
5.2.1. Premature Discontinuation From Study.....	51
5.2.2. Premature Discontinuation From Study Treatment	54
6. CLINICAL EFFICACY – ATLAS ACS 2 TIMI 51	57
6.1. Statistical Testing Results	57
6.2. Primary Efficacy Endpoint Analyses	59
6.2.1. Sensitivity Analysis of the Primary Efficacy Endpoint.....	63
6.2.1.1. Sensitivity Analysis in Different Analysis Sets.....	63
6.2.1.2. Sensitivity Analysis Using Imputed Events for Missing Data	64
6.2.1.3. Sensitivity Analysis by Actual Antiplatelet Agent Use	69
6.3. Secondary Efficacy Endpoints	76
6.3.1. Secondary Efficacy Endpoint 1: Composite of All-Cause Death, MI, or Stroke	76
6.3.2. Secondary Efficacy Endpoint 2: Net Clinical Outcome.....	76
6.3.3. Other Composite Secondary Efficacy Endpoints	76
6.4. Components of Composite Efficacy Endpoints.....	79
6.4.1. Cardiovascular Death and All Cause Death	79
6.4.2. Myocardial Infarction.....	81
6.4.3. Stroke.....	81
6.5. Efficacy in Subgroups	84
6.6. Off-Treatment Cardiovascular Events.....	88
6.7. Efficacy in Stratum 1	90
6.8. Summary of Clinical Benefits	92
6.9. Efficacy Discussion	94

6.9.1.	The Differential Effect Between the Dose Groups.....	94
6.9.2.	The Effect of Rivaroxaban on Stroke.....	96
6.9.3.	Time Course of Efficacy Benefit	96
6.9.4.	Outcome in Subgroups	97
7.	CLINICAL SAFETY – ATLAS ACS 2 TIMI 51	98
7.1.	Extent of Exposure.....	98
7.1.1.	Exposure to Study Drug.....	98
7.1.2.	Exposure to Concomitant Standard Care.....	99
7.2.	Bleeding Events	100
7.2.1.	Primary Safety Endpoint.....	102
7.2.1.1.	Sensitivity Analyses of the Primary Safety Endpoint.....	106
7.2.2.	Fatal Bleeding	106
7.2.3.	Intracranial Bleeding	107
7.2.4.	Bleeding Events by Location of Bleeding	108
7.2.5.	TIMI Life-Threatening Bleeding Events	110
7.2.6.	Treatment-Emergent Bleeding Using TIMI, ISTH and GUSTO Scales.....	112
7.2.7.	Bleeding-Related Treatment Emergent Adverse Events.....	113
7.2.8.	Bleeding in Subgroups.....	116
7.3.	Adverse Events Overall.....	119
7.3.1.	Most Common Adverse Events	119
7.3.2.	Other Adverse Events.....	119
7.3.3.	Deaths.....	119
7.3.4.	Adverse Events that Occurred Within 30 Days Prior to Permanent Discontinuation of Study Drug.....	120
7.4.	Safety in Stratum 1.....	121
7.5.	Dose Response.....	122
7.6.	Safety Across Studies In The Rivaroxaban Clinical Development Program	122
7.7.	Summary of Clinical Risks	123
7.8.	Safety Discussion.....	126
8.	BENEFIT-RISK ANALYSIS – ATLAS ACS 2 TIMI 51.....	126
8.1.	Quantitative Benefit-Risk Assessment.....	126
8.1.1.	Excess Number of Events and NNT/NNH	127
8.1.2.	Temporal Course of Benefit-Risk	129
8.2.	Quantitative Benefit-Risk Assessment Conclusions	134
9.	OVERALL SUMMARY	134
	REFERENCES.....	136

LIST OF IN-TEXT TABLES

Table 1:	Comparison of the Primary Efficacy Endpoint and Secondary Efficacy Endpoint 1 in the 2.5 mg b.i.d. and 5 mg b.i.d. Treatment Groups in All Strata and Stratum 2 (Study RIVAROXACS3001: mITT (Excluding Sites 091001, 091019 and 091026) Analysis Set).....	12
Table 2:	Comparison of Key Bleeding Results of the 2.5 mg b.i.d. and 5 mg b.i.d. Treatment Groups in All Strata and Stratum 2 (Study RIVAROXACS3001: Treatment-Emergent Safety Analysis Set).....	13
Table 3:	Rivaroxaban in Vitro Pharmacology Profile	18
Table 4:	Rivaroxaban Effect on Platelet Aggregation	19
Table 5:	Predicted Rivaroxaban PK Parameters in ACS Patients for 2.5 mg bid or 5 mg bid Dosing Regimens Based on Final PK Model and Total Study Population (n=2290) in Phase 2 Study ATLAS ACS TIMI 46 [Median (5 th to 95th Percentiles)]	25
Table 6:	Treatment Effect of Primary and Key Secondary Efficacy Endpoints by Dose Level Against Pooled Placebo Group as Adjudicated by Clinical Events Committee (Study ATLAS ACS TIMI 46: Intent-to-Treat Analysis Set).....	30
Table 7:	Treatment Effect of Primary Efficacy and Key Secondary Endpoints by Each Dose-Level Panel(s) as Adjudicated by Clinical Events Committee (Study ATLAS ACS TIMI 46: Intent-to-Treat Analysis Set).....	31
Table 8:	Treatment Effect of Treatment-Emergent Primary Bleeding Endpoints by Dose Level Against Pooled Placebo Group as Adjudicated by CEC (Study ATLAS ACS TIMI 46: Safety Analysis Set).....	32
Table 9:	Treatment Effect of Net Clinical Benefit Endpoints by Each Dose-Level Panel(s) as Adjudicated by Clinical Events Committee (Study ATLAS ACS TIMI 46: Intent-to-Treat Analysis Set).....	33
Table 10:	Predicted Rivaroxaban PK Parameters in ACS patients for 2.5 mg bid or 5 mg bid Dosing Regimens Versus Bleeding and Efficacy Results in ATLAS ACS TIMI 46	34
Table 11:	Description of Analysis Sets Used to Analyze Efficacy Data (Study RIVAROXACS3001)	41
Table 12:	Description of Analysis Sets Used to Analyze Safety Results (Study RIVAROXACS3001)	42
Table 13:	(TSUB06A) Description of ACS Index Events (Study RIVAROXACS3001: All Randomized Subjects).....	48
Table 14:	(TSUB08A) Primary Reasons for Premature Discontinuation from Study (Study RIVAROXACS3001; All Randomized Subjects).....	52
Table 15:	(TSUB10) Consent Withdrawal Effort (Study RIVAROXACS3001; All Randomized Subjects).....	53
Table 16:	(TSUB28A) Status for Consent Withdrawn Subjects at End of Study (Study RIVAROXACS3001; All Randomized Subjects).....	54
Table 17:	(TSUB07B) Primary Reasons for Premature Discontinuation From Double-Blind Treatment Period (Study RIVAROXACS3001: Safety Analysis Set)	56
Table 18:	(TEFF02A) Effect of Rivaroxaban Compared with Placebo on the Primary Efficacy Endpoint as Adjudicated by the CEC (First Occurrence of Cardiovascular Death, MI, Stroke) (Study RIVAROXACS3001; mITT (Excluding Sites 091001, 091019 and 091026) Analysis Set).....	60
Table 19:	(TSUBPH01a) Summary of Missing Follow-up Duration As a Proportion of Total Study Duration, to the Global Treatment End Date (Study RIVAROXACS3001; All Randomized Subjects Analysis Set).....	65
Table 20:	Comparison of Baseline Characteristics of Subjects with Unknown Vital Status vs Subjects Who Died or Who were Alive at the Global Treatment End Date (Study: JNJ39039039C-ACS3001: All Randomized Subjects).....	66
Table 21:	(TEFF1855 and TAE0072) Incidence of Efficacy and Safety Events as Adjudicated by the CEC in the 30 Days Prior to the Last Contact date for Subjects who had Unknown Vital Status at Global Treatment End Date (Study RIVAROXACS3001: All Randomized Subjects).....	66
Table 22:	(TEFFPHCO01) Hazard Ratio of the Primary Efficacy Endpoint (Adjudicated by the CEC) after Imputing Event Rates for Missing Data (Study: JNJ39039039C-ACS3001: Intent-to-Treat (Excluding Sites 091001, 091019 and 091026) Analysis Set).....	68

Table 23:	(TEFFUS26A) Effect of Rivaroxaban Compared with Placebo on the Primary Efficacy Endpoint (First Occurrence of Cardiovascular Death, MI, Stroke) and its Components Occurring Up to the Last Dose of Thienopyridine as Adjudicated by the CEC (Study RIVAROXACS3001: Modified Intent-to-Treat (Excluding Sites 091001, 091019 and 091026) Analysis Set).....	70
Table 24:	(TEFFUS27) Incidence of the Primary Efficacy Endpoint and its Components Occurring after the Last Dose of Thienopyridine as Adjudicated by the CEC (Study RIVAROXACS3001: : Modified Intent-to-Treat (Excluding Sites 091001, 091019 and 091026) Analysis Set).....	71
Table 25:	(TSUB25B) Extent of Exposure to Concomitant Thienopyridine Between the First Dose of Study Drug and the Last Dose of Study Drug (Study RIVAROXACS3001: Safety Analysis Set).....	73
Table 26:	(TEFF05A) Effect of Rivaroxaban Compared With Placebo on Secondary Efficacy Endpoints as Adjudicated by the CEC (Study RIVAROXACS3001; mITT (Excluding Sites 091001, 091019 and 091026) Analysis Set)	77
Table 27:	(TAEPH02) Summary of Cardiovascular Deaths by Primary Cause as Adjudicated by the CEC (Study RIVAROXACS3001: Modified Intent-To-Treat (Excluding Sites 091001, 091019 and 091026) Analysis Set)	81
Table 28:	(TEFF00A) Stroke by Subcategories as Adjudicated by the CEC (Study RIVAROXACS3001: Modified Intent-To-Treat (Excluding Sites 091001, 091019 and 091026) Analysis Set).....	83
Table 29:	(TEFF1800) Cochran–Mantel–Haenszel Test by Modified Rankin Scale for Subjects Who Experienced Stroke as Reported by Investigator (Study RIVAROXACS3001; Modified Intent-to-Treat (Excluding Sites 091001, 091019 and 091026) Analysis Set).....	84
Table 30:	(TEFF1032B) Effect of Rivaroxaban 2.5 mg Compared with Placebo on First Occurrence of Primary Efficacy Events as Adjudicated by the CEC by Subgroup (Study RIVAROXACS3001: Modified Intent-to-Treat (Excluding Sites 091001, 091019 and 091026) Analysis Set).....	87
Table 31:	(TEFF33) Incidence of the Primary Efficacy Endpoint and Secondary Efficacy Endpoint after the Last Dose as Adjudicated by the CEC (Study RIVAROXACS3001; Rebound (Excluding Sites 091001, 091019 and 091026) Analysis Set).....	89
Table 32:	Comparison of Key Efficacy Results of the 2.5 mg b.i.d. and 5 mg b.i.d. Treatment Groups in All Strata and Stratum 2 (Study RIVAROXACS3001: mITT (Excluding Sites 091001, 091019 and 091026) Analysis Set)	93
Table 33:	(TEFF1040) Summary of Non-CABG TIMI Major Bleeding Events (adjudicated by CEC) Prior to Death (Study RIVAROXACS3001: Modified Intent-to-Treat (Excluding Sites 091001, 091019 and 091026) Analysis Set)	96
Table 34:	(TSUB17) Total Duration of Treatment (Including Any Study Drug Interruption) (Study RIVAROXACS3001; Safety Analysis Set).....	99
Table 35:	(from TBL21) Incidence of Treatment–Emergent Bleeding Events as Adjudicated by the CEC (Study RIVAROXACS3001; Treatment-Emergent Safety Analysis Set)	101
Table 36:	(TBL01) 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)	104
Table 37:	(TBL03D) Treatment-Emergent Fatal Bleeding using TIMI Scale by Location Reported by the CEC (Study RIVAROXACS3001; Treatment-Emergent Safety Analysis Set)	107
Table 38:	(TBL03A) Treatment–Emergent TIMI Major Bleeding Events by Location Reported by the CEC (Study RIVAROXACS3001; Treatment-Emergent Safety Analysis Set)	109
Table 39:	(TBL28) Incidence of Treatment-Emergent TIMI Life-Threatening Bleeding as Adjudicated by the CEC (Study RIVAROXACS3001; Treatment-Emergent Safety Analysis Set)	111
Table 40:	(TBL27) Incidence of Treatment-Emergent ISTH Major Bleeding as Adjudicated by the CEC (Study RIVAROXACS3001; Treatment-Emergent Safety Analysis Set)	113
Table 41:	(TAE19A) Treatment-Emergent Bleeding-Related Adverse Events in at Least 1% of Subjects in Any Treatment Group by System Organ Class and Preferred Term (Study RIVAROXACS3001; Safety Analysis Set).....	114

Table 42:	(TBLPH05B): Effect of Rivaroxaban 2.5 mg Compared with Placebo on Non-CABG TIMI Major Bleeding Events in Fragile Populations (Study RIVAROXACS3001: Treatment-Emergent Safety Analysis Set)	118
Table 43:	(TAE16A) Summary of All-Cause Deaths by Primary Cause as Adjudicated by CEC in All Strata (Study RIVAROXACS3001: Safety Analysis Set)	120
Table 44:	(TBL21) Incidence of Treatment-Emergent Bleeding Events as Adjudicated by the CEC in Stratum 1 (Study RIVAROXACS3001: Treatment-Emergent Safety Analysis Set)	122
Table 45:	Comparison of Key Safety Results of the 2.5 mg b.i.d. and 5 mg b.i.d. Treatment Groups in All Strata and Stratum 2 (Study RIVAROXACS3001: Treatment-Emergent Safety Analysis Set)	125
Table 46:	(RNCB055) Decomposition of Ischemic and Hemorrhagic Events for Rivaroxaban 2.5 mg BID Dose (Study RIVAROXACS3001: Modified Intent-to-Treat (Excluding Sites 091001, 091019 and 091026) Analysis Set)	130

LIST OF IN-TEXT FIGURES

Figure 1:	Factor Xa - a Pivotal Point in the Coagulation Pathway.....	18
Figure 2:	Chemical Characteristics of Rivaroxaban.....	20
Figure 3:	Prediction of rivaroxaban plasma-concentration - vs time profile at Steady-State in ACS patients treated with rivaroxaban 2.5 mg bid (left panel) or 5 mg bid (right panel), as used in Phase 3 (medians [5th - 95th percentiles]; n=2290)	25
Figure 4:	Observed Concentration-effect Relationship for Prothrombin Time in ACS Patients at Steady-state in the Phase 2 ATLAS ACS TIMI 46 trial / PK/PD Sub-study	26
Figure 5:	Diagram of Statistical Testing Procedure (Study RIVAROXACS3001).....	45
Figure 6:	Subject Disposition (Study RIVAROXACS3001).....	50
Figure 7:	Results of Statistical Testing Procedure (Study RIVAROXACS3001; mITT (Excluding Sites 091001, 091019 and 091026) Analysis Set)	58
Figure 8:	(Feff01a) Kaplan-Meier Estimates of The Primary Efficacy Endpoint (Cardiovascular Death, MI, Stroke) by Stratum as Adjudicated by the CEC (Study Rivaroxacs3001: mITT[Excluding Sites 091001, 091019 And 091026] Analysis Set)	61
Figure 9:	(FEFF00A) Log (-log) Plots of Survival Function Regarding the Primary Efficacy Endpoint (First Occurrence of Cardiovascular Death, MI, Stroke) as Adjudicated by the CEC in All Strata (Study: JNJ39039039C-ACS3001: Modified Intent-to-Treat (Excluding Sites 091001, 091019 and 091026) Analysis Set)	62
Figure 10:	(FEFF19A) Effect of Combined Rivaroxaban Compared with Placebo on the Primary Efficacy Endpoint (First Occurrence of Cardiovascular Death, MI, Stroke) in All Strata (Study RIVAROXACS3001; Excluding Sites 091001, 091019 and 091026 Analysis Set).....	63
Figure 11:	(FEFF19E) Effect of Rivaroxaban 2.5 mg BID Compared with Placebo on the Primary Efficacy Endpoint (First Occurrence of Cardiovascular Death, MI, Stroke) in Stratum 2 (Study RIVAROXACS3001; Excluding Sites 091001, 091019 and 091026 Analysis Set).....	64
Figure 12:	(FEFF1020) Kaplan-Meier Estimates of the Primary Efficacy Endpoint (First Occurrence of Cardiovascular Death, MI, Stroke) Up to the Last Dose of Thienopyridine as Adjudicated by the CEC in Stratum 2 (Study RIVAROXACS3001: Modified Intent-to-Treat (Excluding Sites 091001, 091019 and 091026) Analysis Set).....	72
Figure 13:	(FBSUBPH04): Kaplan-Meier Estimates of Thienopyridine Discontinuation During Study for All Strata (Study RIVAROXACS3001: All Randomized Subjects with Actual Thienopyridine Use).....	75
Figure 14:	(FEFF1060e) Effect of Rivaroxaban 2.5 mg BID Compared with Placebo on All Cause Death as Adjudicated by the CEC in Stratum 2 (Study RIVAROXACS3001)	80
Figure 15:	(FEFF20B) Hazard Ratios and Rates of the Primary Efficacy Endpoint (First Occurrence of Cardiovascular Death, MI, Stroke) by Subgroup for Rivaroxaban 2.5 mg BID Dose Group Compared With Placebo in Stratum 2 (Study RIVAROXACS3001; mITT (Excluding Sites 091001, 091019, and 091026) Analysis Set).....	86
Figure 16:	(FEFF4001g) Effect of Rivaroxaban Compared with Placebo on the Primary Efficacy Endpoint (First Occurrence of Cardiovascular Death, MI, or Stroke) as Adjudicated by the CEC in ASA Stratum (Integrated Summary of Efficacy of Study 39039039ACS2001 and Study RIVAROXACS3001: Modified Intent-to-Treat (Excluding Sites 091001, 091019 and 091026) Analysis Set)	91
Figure 17:	(FBL01A) Kaplan-Meier Estimates of the First Occurrence of Treatment-Emergent Non-CABG TIMI Major Bleeding Events as Adjudicated by the CEC (Study RIVAROXACS3001; Treatment-Emergent Safety Analysis Set)	105
Figure 18:	(FBL07A) Effect of Combined Rivaroxaban Compared with Placebo on First Occurrence of Non-CABG TIMI Major Bleeding Events in All Strata (Study RIVAROXACS3001)	106
Figure 19:	(FBL10h) Hazard Ratios and Rates of the First Occurrence of Treatment-Emergent Non-CABG related TIMI Major Bleeding Events by Subgroup for Rivaroxaban 2.5 mg B.I.D. Group Compared With Placebo in Stratum 2 (Study RIVAROXACS3001; Treatment-Emergent Safety Analysis Set)	117

Figure 20: Risk Differences (per 10,000 patient-years) of Ischemic and Hemorrhagic Events for Rivaroxaban 2.5 mg BID Dose in Stratum 2 (Study RIVAROXACS3001: Modified Intent-to-Treat (Excluding Sites 091001, 091019 and 091026) Analysis Set).....	132
Figure 21: (FNCB1008a) Cumulative Excess Number of Events Based on Kaplan-Meier Method for the Composite of Non-bleeding CV death, MI and Ischemic Stroke Versus Fatal Bleeding and Symptomatic ICH as Adjudicated by the CEC Rivaroxaban 2.5 mg b.i.d. Versus Placebo, Stratum 2 (Study RIVAROXACS3001: Modified Intent-to-Treat (Excluding Sites 091001, 091019 and 091026) Analysis Set)	133

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

ACC	American College of Cardiology
ACCF	American College of Cardiology Foundation
ACS	acute coronary syndrome
AHA	American Heart Association
ALT	alanine aminotransferase
ASA	acetyl salicylic acid
AUC	area under the plasma concentration vs time curve from zero to infinity after single (first) dose
b.i.d.	twice-daily
Bcrp	breast cancer resistance protein
CABG	coronary artery bypass graft
CEC	Clinical Events Committee
CHD	coronary heart disease
CHF	congestive heart failure
CI	confidence interval
C _{max}	maximum drug concentration in plasma after single dose administration
CRF	case report form
CV	cardiovascular
CVD	cardiovascular disease
DVT	deep venous thromboembolism
F1.2	prothrombin fragment 1 and 2
FXa	Factor Xa
GUSTO	Global Strategies for Opening Occluded Coronary Arteries
HR	hazard ratio
ICH	intracranial hemorrhage
ISTH	International Society on Thrombosis and Haemostasis
ITT	Intent-to-Treat
LFT	liver function test
MI	myocardial infarction
mITT	modified intent-to-treat
NCO	net clinical outcome
NNH	number needed to harm
NNT	number needed to treat
NSTEMI	non-ST-segment elevation myocardial infarction
OMP	Ortho McNeil Pharmaceuticals
PCI	percutaneous coronary intervention
PE	pulmonary embolism
P-gp	P-glycoprotein
PiCT	prothrombinase induced clotting time
PT	prothrombin time
q.d.	once daily
RRR	relative risk reduction
SAP	Statistical Analysis Plan
SRIH	severe recurrent ischemia leading to hospitalization
SRIR	severe recurrent ischemia requiring revascularization
STEMI	ST-segment elevation myocardial infarction
TAT	inhibited thrombin-antithrombin
TDD	total daily dose
TF	tissue factor
TIA	transient ischemic attack
TIMI	thrombolysis in myocardial infarction
t _{max}	time to reach maximum drug concentration in plasma after single (first) dose
U.S.	United States
UA	unstable angina
ULN	upper limit of normal
VTE	venous thromboembolism

EXECUTIVE SUMMARY

Rivaroxaban (XARELTO[®]) is an oral anticoagulant that acts by selective and direct inhibition of factor Xa (FXa). Rivaroxaban is being developed for the prevention and treatment of multiple thrombosis-mediated conditions through a joint collaboration agreement between Bayer HealthCare AG (Bayer) and Ortho McNeil Pharmaceuticals, Inc (OMP).

In the overall clinical development program, rivaroxaban has been assessed in multiple indications, with over 70,000 subjects enrolled, and over 40,000 subjects exposed to rivaroxaban in completed and ongoing clinical studies to date. Rivaroxaban is currently approved in the United States (U.S.) with the trade name XARELTO[®] for the following indications:

- Rivaroxaban 10 mg tablet once daily for the prophylaxis of deep vein thrombosis (DVT), which may lead to pulmonary embolism (PE) in patients undergoing knee or hip replacement surgery (NDA 22406, approved in July 2011);
- Rivaroxaban 20 mg and 15 mg tablet once daily to reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation (NDA 202439, approved in November 2011)

The subject of this briefing book is a supplemental New Drug Application (sNDA 202439, S002) that was submitted by Janssen Research & Development, LLC (hereafter referred to as the Sponsor) on behalf of Janssen Pharmaceuticals, Inc (successor in interest to OMP) on 29 December 2011, for the use of rivaroxaban 2.5 mg tablets twice a day in the following proposed indication:

To reduce the risk of thrombotic cardiovascular (CV) events in patients with acute coronary syndrome (ACS) (ST segment elevation infarction [STEMI], non-ST segment elevation myocardial infarction [NSTEMI], or unstable angina [UA]) in combination with aspirin alone or with aspirin plus a thienopyridine (clopidogrel or ticlopidine).

Rivaroxaban has been shown to reduce the risk of a combined endpoint of CV death, myocardial infarction (MI) or stroke. The difference between treatments was driven by CV death and MI.

This document provides the information necessary to assess the use of rivaroxaban as an anticoagulant in addition to standard care antiplatelet therapy in patients with recent ACS. The information is based primarily on the data from the global Phase 3 pivotal study ATLAS ACS 2 TIMI 51 (acronym for the second trial of Anti-Xa Therapy to Lower Cardiovascular Events in Addition to Aspirin with or without Thienopyridine Therapy in Subjects with Acute Coronary Syndrome; study number RIVAROXACS3001). A Phase 2 Study, ATLAS ACS TIMI 46 (acronym for Anti-Xa Therapy to Lower Cardiovascular Events in Addition to Aspirin with or without Thienopyridine Therapy in Subjects with Acute Coronary Syndrome), provided important supportive efficacy and safety data and the basis for dose selection in the Phase 3 study ATLAS ACS 2 TIMI 51.

ATLAS ACS 2 TIMI 51 was a large (15,526 subjects), randomized, double-blind, placebo-controlled, event-driven study. Randomization was stratified by the intention to use

thienopyridine as standard care in addition to low-dose acetyl salicylic acid (ASA). Subjects intended to be treated with ASA only as standard care were enrolled in Stratum 1, and subjects intended to be treated with ASA plus a thienopyridine as standard care were enrolled in Stratum 2. In this document, study results are presented primarily for data across Stratum 1 and Stratum 2 (i.e., for all randomized subjects, referred to as All Strata hereafter), and for Stratum 2 alone (i.e., for subjects who were intended to receive dual antiplatelet standard care of aspirin plus an thienopyridine). In discussions with the Food and Drug Administration (FDA, hereafter referred to as the Agency), the Agency indicated that Stratum 2 would be the relevant group for their review, as dual antiplatelet therapy is the indicated standard of care for ACS in the U.S.. The majority of subjects (93%) in the study were enrolled in Stratum 2, which will be the main focus of this briefing book. Data from subjects in Stratum 1 are also presented for completeness.

ATLAS ACS 2 TIMI 51 tested 2 rivaroxaban doses, 2.5 mg twice daily and 5 mg twice daily, compared with placebo, in addition to standard care. In summary, the efficacy data show:

- Pooled data across Stratum 1 and Stratum 2 (All Strata) showed that the rivaroxaban combined doses were superior to placebo at reducing the risk of the primary efficacy endpoint, the composite of CV death, MI or stroke (hazard ratio [HR]: 0.84, 95% confidence interval [CI]: 0.74, 0.96; $p=0.008$). The rivaroxaban combined doses were also superior for the primary efficacy endpoint in Stratum 2 (HR: 0.86, 95% CI: 0.75, 0.98; $p=0.024$).
- Rivaroxaban 2.5 mg twice daily dose demonstrated superiority to placebo for the primary efficacy endpoint in Stratum 2 (HR: 0.85, 95% CI: 0.72, 0.99; $p=0.039$), the result was primarily driven by a reduction in CV death (HR: 0.62, 95% CI: 0.47, 0.82). In addition, sensitivity analyses of all cause mortality showed nominal statistical significance for rivaroxaban 2.5 mg twice daily in all analysis sets tested, including the intent-to-treat (ITT) analysis set (nominal p -value <0.001 in Stratum 2). Rivaroxaban 5 mg twice daily dose did not demonstrate superiority for the primary efficacy endpoint in Stratum 2 (HR: 0.87, 95% CI: 0.74, 1.01; $p=0.075$). [Table 1](#) presents a comparison of the 2 rivaroxaban treatment groups in the primary efficacy endpoint and a secondary efficacy endpoint.
- Stratum 1 consisted of 7% of all enrolled subjects, and the number of events collected in Stratum 1 was small; the results of the primary efficacy endpoint in Stratum 1 were consistent with Stratum 2 and numerically favored treatment with rivaroxaban in those subjects receiving aspirin alone as background therapy.
- The robustness of the treatment effect of rivaroxaban in reducing the risk of the primary efficacy endpoint was shown by the consistency of the results in all sensitivity analyses performed. Importantly, while the pre-specified primary efficacy analysis population was the modified intent-to-treat (mITT) analysis set, the superiority finding was observed in all other analysis sets, including ITT and ITT total.
- Consistency of treatment effect of rivaroxaban in reducing the risk of the primary efficacy endpoint was seen across major subgroups.

Table 1: Comparison of the Primary Efficacy Endpoint and Secondary Efficacy Endpoint 1 in the 2.5 mg b.i.d. and 5 mg b.i.d. Treatment Groups in All Strata and Stratum 2 (Study RIVAROXACS3001: mITT (Excluding Sites 091001, 091019 and 091026) Analysis Set)

	Rivaroxaban 2.5 mg b.i.d. (N=5114 for All Strata; N= 4765 for Stratum 2)	Rivaroxaban 5 mg b.i.d. (N=5115 for All Strata; N= 4767 for Stratum 2)	Placebo (N=5113 for All Strata; N= 4760 for Stratum 2)
Primary Efficacy Endpoint (the composite of cardiovascular death, MI or stroke)			
All Strata			
Event Incidence (n [%])	313 (6.1%)	313 (6.1%)	376 (7.4%)
HR (95% CI) vs Placebo	0.84 (0.72,0.97)	0.85 (0.73,0.98)	-
Stratum 2			
Event Incidence (n [%])	286 (6.0%)	289 (6.1%)	340 (7.1%)
HR (95% CI) vs Placebo	0.85 (0.72,0.99)	0.87 (0.74,1.01)	-
Secondary Efficacy Endpoint 1 (the composite of all-cause death, MI or stroke)			
All Strata			
Event Incidence (n [%])	320 (6.3%)	321 (6.3%)	386 (7.5%)
HR (95% CI) vs Placebo	0.83 (0.72,0.97)	0.84 (0.73,0.98)	-
Stratum 2			
Event Incidence (n [%])	292 (6.1%)	297 (6.2%)	350 (7.4%)
HR (95% CI) vs Placebo	0.84 (0.72,0.98)	0.87 (0.74,1.01)	-

Note: Endpoint events were adjudicated by the Clinical Endpoint Committee.

Note: MI=myocardial infarction; CI=confidence interval; HR=hazard ratio

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. Source outputs: DEFF02A, DEFF05A.

As expected, the use of rivaroxaban was associated with increased rates of bleeding events compared to placebo (Table 2).

- For all subjects cross strata, the occurrence of the primary safety endpoint (non-CABG TIMI major bleeding) was significantly higher in both the 2.5 mg twice daily dose group (1.3%; HR: 3.46, 95% CI: 2.08, 5.77; p<0.001) and the 5 mg twice daily dose group (1.6%; HR: 4.47, 95% CI: 2.71, 7.36; p<0.001) compared with placebo (0.4%).
- Rates of fatal bleeding in the rivaroxaban 2.5 mg twice daily dose group (6/5115) was numerically lower than that in the 5 mg twice daily dose group (15/5110), and similar to that in the placebo group (9/5125).
- Although intracranial hemorrhage (ICH) and hemorrhagic stroke rates were increased in the rivaroxaban groups compared with placebo, the incidence of fatal ICH was low overall, and similar in subjects receiving rivaroxaban 2.5 mg twice daily (5 cases) and placebo (4 cases).
- Other than the increase in bleeding risk, no off-target safety signal was identified in the rivaroxaban ACS clinical development program.

**Table 2: Comparison of Key Bleeding Results of the 2.5 mg b.i.d. and 5 mg b.i.d. Treatment Groups in All Strata and Stratum 2
(Study RIVAROXACS3001: Treatment-Emergent Safety Analysis Set)**

	Rivaroxaban 2.5 mg b.i.d. (N=5115 for All Strata; N= 4772 for Stratum 2)	Rivaroxaban 5 mg b.i.d. (N=5110 for All Strata; N= 4768 for Stratum 2)	Placebo (N=5125 for All Strata; N= 4773 for Stratum 2)
Primary Safety Endpoint (non-CABG TIMI major bleeding)			
All Strata			
Event Incidence (n [%])	65 (1.3%)	82 (1.6%)	19 (0.4%)
HR (95% CI) vs Placebo	3.46 (2.08,5.77)	4.47 (2.71,7.36)	-
Stratum 2			
Event Incidence (n [%])	63 (1.3%)	78 (1.6%)	19 (0.4%)
HR (95% CI) vs Placebo	3.35 (2.01,5.60)	4.26 (2.58,7.03)	-
Intracranial Bleeding			
All Strata			
Event Incidence (n)	14	18	5
- With Fatal Outcome	5/14	8/18	4/5
HR (95% CI) vs Placebo	2.83 (1.02,7.86)	3.74 (1.39,10.07)	-
Stratum 2			
Event Incidence (n)	13	16	5
- With Fatal Outcome	4/13	8/16	4/5
HR (95% CI) vs Placebo	2.63 (0.94,7.38)	3.34 (1.22,9.12)	-
Fatal Bleeding			
All Strata			
Event Incidence (n)	6	15	9
HR (95% CI) vs Placebo	0.67 (0.24,1.89)	1.72 (0.75,3.92)	-
Stratum 2			
Event Incidence (n)	5	15	8
HR (95% CI) vs Placebo	0.63 (0.21,1.93)	1.93 (0.82,4.56)	-

Note: Bleeding events were adjudicated by the Clinical Endpoint Committee.

Note: CABG=coronary artery bypass graft; TIMI= thrombolysis in myocardial infarction;

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: percentages were not shown for events with frequency < 1% in all treatment groups.

Source outputs: DBL01, DBL04.

The pre-defined Secondary Efficacy Endpoint 2 was Net Clinical Outcome (NCO), which was the composite of CV death, MI, ischemic stroke or non-CABG TIMI major bleeding. Although the HR numerically favored rivaroxaban, a statistically significant reduction compared with placebo in NCO was not seen.

In post hoc quantitative benefit-risk analyses using approaches that compare non-bleeding efficacy endpoint events against several different severity levels of bleeding events, including methodology proposed previously by the Agency⁴¹, rivaroxaban consistently prevented more fatal and irreversible non-bleeding CV events than bleeding events caused, confirming the positive benefit-risk profile of rivaroxaban as compared with placebo. Benefit exceeded harm early in treatment and continued to exceed harm throughout the course of treatment.

Taken together, these results led the Sponsor to recommend the 2.5 mg twice daily regimen for the sought indication. As a result, data presented in this document will primarily focus on the rivaroxaban 2.5 mg twice daily treatment group, compared with placebo.

1. INTRODUCTION

1.1. Acute Coronary Syndrome: A Highly Prevalent Public Health Problem with High Mortality and Morbidity

Coronary heart disease (CHD) is a common clinical and pathological condition. The incidence and prevalence rates of CHD remain high throughout the developed world. In the U.S., the American Heart Association reports that the prevalence of CHD in adults ≥ 20 years of age is 7.0%; CHD prevalence is 8.3% for men and 6.1% for women²⁹. Approximately 785,000 Americans will have a coronary event each year, and approximately 470,000 will have a recurrent event. For Americans over age 40, the lifetime risk of developing CHD is 49% for men and 32% for women²¹. While rates vary from country to country, the incidence and prevalence of CHD are also high in the European Union (EU) as well as in other countries^{27,40}.

Coronary heart disease is the major cause of death in adults in the U.S. and in most countries in Europe^{27,29,40}. In 2007, CHD mortality in the U.S. was 571,402, and the American Heart Association estimates that approximately once every minute someone in the U.S. will die of a coronary event²⁹. In 2006, the Euro Heart Survey reported that the average age-standardized CV mortality ratio across Europe was 5.1 per 1,000 inhabitants for men, and 3.4 per 1,000 inhabitants for women^{27,32}.

The clinical manifestations of CHD are for the most part the result of atherosclerotic plaque rupture and thrombosis. Hence, atherothrombosis is the major pathophysiological process responsible for the occurrence of severe ischemic events in patients with CHD. The most severe clinical manifestation of CHD is referred to as acute coronary syndrome (ACS), a term which includes conditions of unstable angina (UA), non-ST-elevation myocardial infarction (NSTEMI) and ST-elevation MI (STEMI).

1.2. Current Management After Acute Coronary Syndrome

Following an ACS event, patients are at high risk of another morbid event of ACS or stroke or dying from a CV cause. The incidence, prevalence and severity of clinical consequences for patients with ACS drove a rapid increase in clinical development activities over the past 3 decades that ultimately resulted in the approval of parenteral, short acting antiplatelet agents for use in the acute setting, oral antiplatelet agents for chronic use, and parenteral anticoagulants also for use in the acute setting. The aim of all of these therapies is preventing thrombus formation at the site of rupture of an atherosclerotic plaque and subsequent adverse cardiovascular events.

An important component of the current standard care for post-ACS patients is the long-term use of antiplatelet agents, principally ASA with or without the addition of a thienopyridine, such as clopidogrel^{3,47}. Ticlopidine was the first thienopyridine used historically in secondary prevention after ACS and has been largely replaced by clopidogrel attributable to the less favorable adverse reactions profile of ticlopidine; however, it remains to be a medication of choice in some countries and patients who are intolerant to clopidogrel. Clopidogrel has been extensively studied for the prevention of CV events in ACS patients. Clopidogrel is a prodrug and its platelet inhibition effect is modest due to the slow and variable conversion of the prodrug into its active

metabolite^{20,43}. The 2 newer antiplatelet agents, prasugrel⁴³ and ticagrelor⁴², were not approved for use at the outset of the pivotal ATLAS ACS 2 TIMI 51 trial of rivaroxaban in ACS patients and were therefore not included in this trial.

1.3. Unmet Medical Need

Despite the widespread use of antiplatelet agents in the acute and chronic setting, the incidence of CV events such as CV death, MI or stroke in the post-ACS population remains high. For example, the results of the multinational GRACE registry of ACS patients has reported a 6-month mortality rate of approximately 12% for patients presenting with a STEMI or NSTEMI ACS event^{8, 12}. Even with newer antiplatelets, such as ticagrelor, the CV event rate was 9.8% at 12 months in the PLATO trial⁴². In the ATLAS ACS 2 TIMI 51 trial, subjects receiving placebo in addition to standard care antiplatelet treatment for ACS had over a 4% risk of dying within 2 years of their index ACS event, and over a 10% risk of dying from a cardiovascular cause, having another MI or stroke.

Since many of the clinical events that occur in ACS patients are due to acute and subacute thrombosis, one additional management strategy is the use of an anticoagulant either instead of or in addition to antiplatelet therapy (ASA and thienopyridine). As proof of principle, a meta-analysis of 10 studies³⁰ (n=5,938 subjects), showed that compared with ASA alone, warfarin plus ASA treatment had lower annual rates of MI (2.2% versus 4.1%, respectively), ischemic stroke (0.4% versus 0.8%, respectively), and revascularization (11.5% versus 13.5%, respectively). Subjects receiving warfarin plus ASA had an increased risk of major bleeding compared with subjects on ASA alone (1.5% versus 0.6%, respectively). Warfarin has been shown to significantly reduce mortality and cerebrovascular events after MI compared with placebo in a clinical study of 1214 patients³⁴. In another trial of 3620 patients, warfarin alone or in combination with aspirin was superior to aspirin alone in reducing the incidence of the composite endpoint of death, nonfatal reinfarction or thromboembolic cerebral stroke¹⁸.

Because of difficulties inherent with warfarin treatment, including variations in the dose response, the need for frequent coagulation monitoring and dose adjustments to ensure that a therapeutic level of anticoagulation is achieved, multiple drug and food interactions, and a heightened risk for bleeding, especially when administered in combination with ASA therapy, there remains an unmet medical need for safer, efficacious, and convenient oral anticoagulants that do not depend on vitamin K antagonism for the treatment of subjects with ACS.

The ESTEEM study was a Phase 2 study assessing the efficacy and safety of ximelagatran, an oral direct thrombin inhibitor in preventing recurrent ACS in 1833 patients within 14 days of myocardial infarction (MI)⁴⁴. The primary endpoint (a composite of recurrent nonfatal MI, recurrent ischemia, or death) occurred in 12.7% and 16.3% of ximelagatran plus aspirin- or aspirin alone-treated patients. This trial suggested that the addition of anticoagulant to aspirin may reduce the rate of death and/or cardiovascular thrombotic outcomes.

This hypothesis has now been more extensively investigated in the Factor Xa (FXa) inhibitor class of oral anticoagulants. A variety of FXa inhibitors have recently been tested in ACS patients. The short term inhibition of FXa with fondaparinux was found to be safe and associated

with improved clinical outcome in both NSTEMI/UA (OASIS 5)⁴⁹ and STEMI (OASIS 6)⁵⁰ patients. Several new inhibitors of FXa have also been investigated in Phase 2 studies in patients with a recent acute coronary event including the parenteral agent otomixaban in the SEPIA ACS 1 TIMI 42 study³¹, darexaban in the RUBY-1 trial³⁶, and the oral FXa inhibitor apixaban in the APPRAISE 1 study. Apixaban was subsequently tested in the Phase 3 APPRAISE 2 study in subjects with a recent acute coronary event, but the study was terminated prematurely due to excess bleeding not offset by a reduction in efficacy events².

To further explore the potential of FXa inhibitors in treating ACS patients, the Sponsor tested rivaroxaban, a potent and highly selective direct FXa inhibitor that is orally bioavailable, in the ATLAS ACS clinical development program, the results of which are presented in this briefing book.

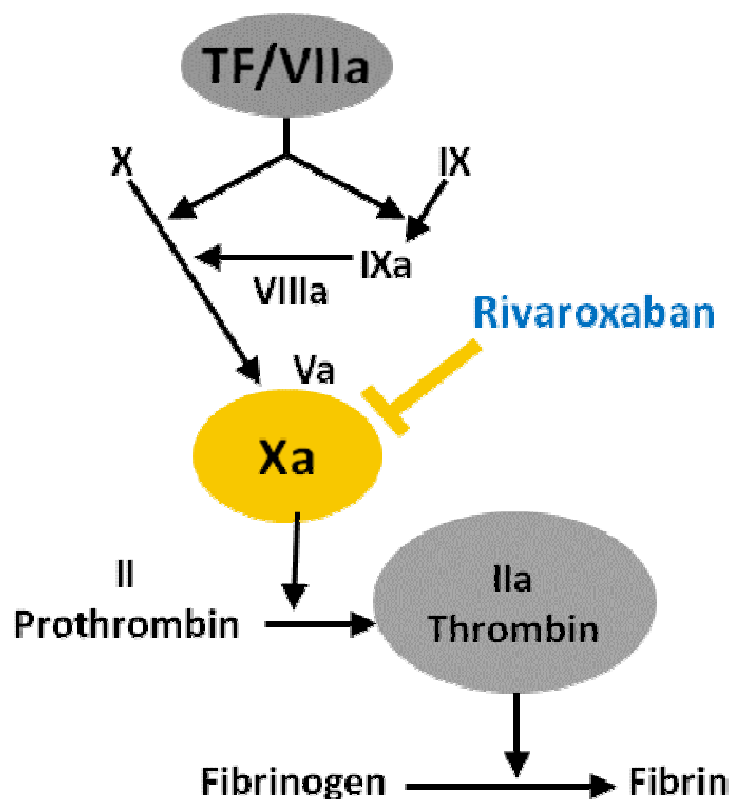
2. PRECLINICAL DATA

2.1. Rivaroxaban Mechanism of Action, Preclinical Pharmacology and Chemical Class

Activation of FX to FXa via the intrinsic and extrinsic pathway plays a central role in the cascade of blood coagulation by mediating thrombin formation (Figure 1). FXa directly converts prothrombin to thrombin through the prothrombinase complex, and ultimately, this reaction leads to fibrin clot formation and activation of platelets by thrombin. One molecule of FXa is able to generate more than 1000 molecules of thrombin due to the amplification nature of the coagulation cascade. The reaction rate of prothrombinase-bound FXa increases 300,000-fold compared with that of free FXa and causes an explosive burst of thrombin generation. Thrombin has several functions in blood coagulation, including the conversion of fibrinogen to fibrin, the activation of platelets, and the feedback activation of other coagulation factors, resulting in the amplification of its own formation.

Essentially, rivaroxaban produces antithrombotic effects by decreasing the amplified generation of thrombin, thus diminishing thrombin-mediated activation of both coagulation and platelets, without affecting the activity of thrombin or platelets. The remaining low levels of thrombin would be sufficient to ensure primary hemostasis, which could result in a favorable efficacy to safety (bleeding) margin for rivaroxaban (Figure 1).

Figure 1: Factor Xa - a Pivotal Point in the Coagulation Pathway



Rivaroxaban is a selective orally administered direct FXa inhibitor that does not require metabolic conversion or a cofactor to exert its activity. Rivaroxaban was selected as a drug candidate based on its in vitro potency, its selectivity against FXa, its anticoagulant activity in clotting assays in human plasma, absence of a direct effect on platelet aggregation, and its in vivo antithrombotic activity in animal models of both venous and arterial thrombosis (for details see Table 3 and Table 4). No off-target interactions were observed in extended receptor and enzyme screening. Metabolites of rivaroxaban do not contribute to a relevant extent to the human pharmacological activity of rivaroxaban.

Table 3: Rivaroxaban in Vitro Pharmacology Profile

FXa enzymatic assay	K_i 0.4±0.02 nM k_{on} 1.7×10 ⁷ M ⁻¹ s ⁻¹ k_{off} 5×10 ⁻³ s ⁻¹
Inhibition of prothrombinase (inhibition of thrombin generation)	IC ₅₀ 2.1±0.4 nM (0.0009 mg/L)
Inhibition of endogenous FXa in human plasma	IC ₅₀ 21±1 nM (0.009 mg/L)
Inhibition of clot-associated FXa*	IC ₅₀ 92±4 nM (0.040 mg/L)

*Reference: Depasse 2005⁸

Table 4: Rivaroxaban Effect on Platelet Aggregation

Human plasma inhibition platelet aggregation	
- collagen	Inactive at 200 μ M
- U46619 (thromboxane mimetic)	Inactive at 200 μ M
- ADP	Inactive at 200 μ M
- TRAP-6 (thrombin receptor activating peptide-6)	Inactive at 200 μ M
γ -thrombin	IC ₅₀ 81 μ M

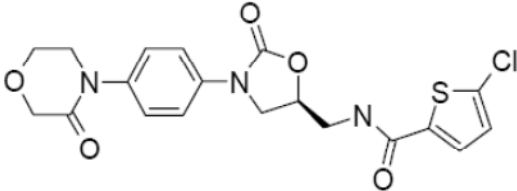
200 μ M = 87 mg/L; 81 μ M = 35 mg/L

In animal models bleeding times are not significantly affected at doses required for antithrombotic efficacy. At higher doses, bleeding times are dose-dependently prolonged. Concomitant use of rivaroxaban with antiplatelet or anticoagulant drugs revealed an additive effect on rat bleeding times. In a rat model of tissue factor (TF)-induced hypercoagulability, rivaroxaban dose-dependently inhibited thrombin-antithrombin (TAT) generation over a broad dose range.

In primate and rat, the antihemostatic effect of rivaroxaban could be partially antagonized with the pro-coagulative active drugs recombinant activated factor VII (r-FVIIa, NovoSeven[®]), a prothrombin complex concentrate (PCC, Beriplex[®]) or an activated prothrombin complex concentrate (APCC; FEIBA NF 1000E[®]). In the rat, administration of activated charcoal 15 minutes after an oral rivaroxaban dose reduced rivaroxaban plasma exposure.

The chemical name, structural formula and chemical characteristics of rivaroxaban are shown in [Figure 2](#). Rivaroxaban is chemically and mechanistically distinct from unfractionated and low molecular weight heparins (LMWH), fondaparinux, Vitamin K antagonists and direct thrombin inhibitors. Rivaroxaban active pharmaceutical ingredient is a stable molecule that is not prone to rapid degradation or decomposition. Rivaroxaban immediate-release tablets were used in Phase 3 studies and are stable in both bottle and blister packages and do not require any special storage conditions, desiccants or handling requirements.

Figure 2: Chemical Characteristics of Rivaroxaban

Structural formula	
Chemical name	5-chloro-N-(((5S)-2-oxo-3-[4-(3-oxomorpholin-4-yl)phenyl]-1,3-oxazolidin-5-yl)methyl)thiophene-2-carboxamide
Molecular formula	C ₁₉ H ₁₈ ClN ₃ O ₅ S
Molecular weight	435.89 g/mol
JNJ No.	JNJ-39039039
CAS No.	366789-02-8
Chirality/Stereochemistry	Rivaroxaban has one chiral center
Other names	Rivaroxaban, BAY 59-7939

2.2. Biological Basis for the Use of Rivaroxaban in Patients with ACS

Acute coronary syndromes occur as the result of coronary atherosclerosis with subsequent thrombus formation at or near the site of plaque rupture in an coronary artery. It is thought that the stimulus for thrombus formation is rupture of the cap of the atherosclerotic plaque. Caps that rupture typically have a thin fibrous cap, large lipid cores, a high content of macrophages and show signs of active inflammation. This set of characteristics meets all of the classically defined requirements for thrombosis described by Virchow's triad: alterations (a decrease) in *blood flow*, injury to the vessel wall resulting in *inflammation* and a shift in the balance of anticoagulant and procoagulant factors resulting in a *hypercoagulable* state. Thus plaque rupture provides a nidus for the formation of platelet rich thrombi and a source of tissue factor to activate the extrinsic pathway of the coagulation cascade as well as an exposed surface to activate the intrinsic pathway. Activation of either the extrinsic or the intrinsic pathway of the coagulation cascade leads to the recruitment of activated FXa. As FXa cleaves prothrombin to thrombin and thrombin cleaves fibrinogen to fibrin that ultimately forms a clot, the activity of FXa is a critical regulatory point in the coagulation cascade. The rate of thrombin generation by FXa is increased some 300,000-fold by its subsequent association with FVa on the exposed anionic surface to form the prothrombinase complex²². Formation of the prothrombinase complex results in an explosive burst in the formation of thrombin at the site of the plaque rupture and can result in occlusion of the coronary vessel at the site of atherosclerotic stenosis or embolization of clot fragments with diffuse ischemia downstream from the site.

In addition to converting fibrin to fibrinogen, thrombin mediated cleavage of protease activated receptors results in activation of these receptors with subsequent platelet activation and pro-inflammatory action that link coagulation to inflammation⁷. Despite advances in the treatment of acute coronary syndrome the risk of recurrence of coronary events remains high. For example the risk of CV death, MI and stroke in patients with ACS in recent trials of anti-platelet drugs remains near 10% per annum⁴².

The increased risk of subsequent thrombotic events in ACS may be related to persistent activation of the coagulation cascade after the initial event. Merlini et al²⁶ first demonstrated the persistent increase in FXa among patients with ACS as compared with patients with stable syndromes by measurement of plasma concentrations of prothrombin fragment 1 and 2 (F_{1.2}) that circulates after FXa acts on thrombin in patients with unstable angina or myocardial infarction.

In a substudy of the Phase 2 ATLAS ACS TIMI 46 study¹⁴, 1,006 subjects were included to assess the effect of rivaroxaban on markers of coagulation – prothrombin fragment 1 and 2 (F_{1.2}) and D-dimer (DD) in ACS patients. At baseline, F_{1.2} and DD concentrations were similar in the placebo, rivaroxaban b.i.d., and rivaroxaban q.d. dosing groups (F_{1.2}: 241, 251, 259 pMol/L; DD: 0.69, 0.79, 0.76 µg/ml). Compared with placebo, rivaroxaban was associated with a significant early reduction in F_{1.2} levels 8–24 hrs after administration in both the b.i.d. (240 vs 209 pMol/L, P<0.01) and q.d. (240 vs 177 pMol/L, P<0.001) groups. DD at baseline vs 8–24 hrs was significantly increased in placebo patients (0.69 vs 0.75 µg/ml, P<0.05), but unchanged in patients receiving rivaroxaban.

These data demonstrate that in patients with ACS, rivaroxaban is associated with a significant, early reduction in F_{1.2}, which may translate into early therapeutic advantage at the time when patients are at high risk for recurrent ischemic events. These findings are important given the finding that thrombin generation persists following an ACS event. The use of rivaroxaban is predicted to effectively ameliorate the circulating prothrombotic environment that accompanies ACS.

Rivaroxaban has been evaluated for prevention of stent thrombosis in a porcine arteriovenous extracorporeal circuit model (Report No.: PH-36605)⁵. Rivaroxaban was administered alone at doses of 0.11, 0.33 or 1 µg/kg/min or on the background of single anti-platelet therapy in the form of aspirin or on the background of dual anti-platelet therapy in the form of aspirin and clopidogrel. The mass of the thrombus formed in the stent was reduced by rivaroxaban in a dose-dependent fashion (33, 48 and 67%, respectively). The same dosing regimen was more effective with the addition of aspirin (48, 72 and 86%, respectively) and even more effective with dual anti-platelet therapy (59, 91 and 98%, respectively). The addition of rivaroxaban to dual anti-platelet therapy was also more effective than dual anti-platelet therapy alone (61, 73 and 76%, respectively). Steady state plasma concentrations in this porcine model were 19, 60 and 180 µg/L. These values are relevant to interpretation of ATLAS ACS TIMI 46 and ATLAS ACS 2 TIMI 51 as the plasma concentrations of rivaroxaban obtained from the sparse PK data collection at doses of 2.5 and 5 mg bid from ATLAS ACS TIMI 46 study were 46/17 and 78/29 µg/L (C_{Max}/C_{Min})²⁸. The background therapy for both ATLAS ACS TIMI 46 and ATLAS ACS 2 TIMI 51, as with the porcine stent thrombosis study, was single or dual antiplatelet therapy.

Rivaroxaban has also been evaluated for effects on plaque stability in Apo-E deficient mice with established atherosclerotic lesions⁵¹. Rivaroxaban was shown to increase the thickness of the protective fibrous caps of the atherosclerotic lesion and fewer medial erosions and fewer lateral xanthomas were noted in the innominate artery. Evaluation of expression of inflammatory genes in the thoracic aorta of the same animals showed a reduction in the expression of key

inflammatory mediators such as IL-6, TNF- α , MCP-1, and Egr-1 in rivaroxaban treated mice. Together these findings suggest that rivaroxaban could support plaque stability and reduces vascular inflammation, both of which could be beneficial in an ACS population.

2.3. Discussion

Rivaroxaban is an effective and well characterized anticoagulant. By inhibiting FXa, rivaroxaban acts at the confluence of both the intrinsic and extrinsic pathways of coagulation and at the same time exerts control at the critical thrombin generation amplification point.

In recent years it has become apparent that thrombin generation continues for many months following an ACS event. Thrombin is a highly potent activator of the platelet and as such drives thrombus formation through 2 pathways. First, by activating platelets and inducing their aggregation, and second, by driving fibrin formation which binds the platelets together. Interestingly, thrombin also appears to have additional pleiotropic functions in that it is capable of inducing apoptosis in a variety of cell types including neurons and cardiac myocytes, and anti-thrombin agents have been shown to prevent apoptosis.

3. CLINICAL PHARMACOLOGY

According to the criteria of the Biopharmaceutical Classification System, rivaroxaban is a low-solubility, high-permeability compound (i.e. Class 2). Rivaroxaban is rapidly absorbed after oral administration of immediate-release (IR) tablets with a C_{max} occurring on average 2 – 4 h after dosing. The absolute bioavailability of the 5 mg IR tablet was complete and the absolute bioavailability of a 10 mg tablet is estimated to range from 80 – 100% under fasted conditions. At the lower tablet doses (from 1.25 mg to 15 mg) investigated under fasting conditions in a small number of subjects in the single ascending-dose study, rivaroxaban pharmacokinetics behaved linearly with dose. In a subsequent dose-proportionality study, the 2.5 mg, 5 mg and 10 mg tablets demonstrated dose-proportionality under fasting conditions by fulfilling the bioequivalence criteria when comparing dose-normalized AUC values (AUC/D), however, dose-proportionality was not demonstrated for dose-normalized C_{max} (C_{max}/D), suggesting that rivaroxaban may begin to exhibit solubility-limited absorption at 5 mg under fasting conditions. With tablet doses above 15 mg under fasting conditions, dose-dependent but less than dose-proportional increases in exposure were seen (with small increases beyond 40 mg). A ceiling effect with no further increase in average exposure was reached at a rivaroxaban dose of 50 mg, even when taken with food. The reduction in bioavailability at higher tablet strengths is best explained by a decrease in absorption, as a result of the limited aqueous solubility of rivaroxaban. Food enhances solubility and thus the absorption of rivaroxaban at higher doses.

Considering the lack of a relevant food effect observed with the 10 mg rivaroxaban tablet and similar results obtained from an exploratory pooled PK analysis across Phase 1 studies for doses less than 10 mg, a dedicated food effect study was not conducted on lower strength formulations, in particular the 2.5 mg tablet strength. The above mentioned results supported the administration of the 2.5 mg tablet without regard to meals in the pivotal Phase 3 ATLAS ACS 2 TIMI 51 study, and further support the proposed label, that rivaroxaban 2.5 mg tablets can be taken with or without food.

Plasma protein binding for rivaroxaban in human plasma is approximately 92% to 95%, with serum albumin being the main binding component, and fully reversible. Steady-state is generally achieved after the third day of dosing and rivaroxaban accumulates in plasma less than 40% after twice-daily administration.

Rivaroxaban is eliminated via hepatic metabolism as well as by renal and biliary/fecal excretion. Approximately 32% of a rivaroxaban dose undergoes CYP-mediated hepatic metabolism (18% by CYP3A4/3A5 and 14% by CYP2J2) and approximately 14% undergoes non-CYP mediated hydrolysis of the amide bonds. Unchanged rivaroxaban is the most abundant moiety in human plasma with no major or active circulating metabolites present.

Following administration of a [^{14}C]-rivaroxaban dose, approximately 66% of the radioactive dose was recovered in urine, 36% as unchanged drug (30% excreted by active tubular secretion via the efflux transporter proteins P-glycoprotein (P-gp) and ABCG2 (also abbreviated as Bcrp) and 6% by glomerular filtration) and 30% as metabolites. Approximately 28% of the radioactive dose was recovered in feces, approximately 21% as metabolites and approximately 7% as unchanged drug.

Rivaroxaban is a low clearance drug (CL is approximately 10 L/h or 0.14 L/h/kg) and does not undergo any relevant first-pass metabolism. The terminal elimination half-life of rivaroxaban ranges from 5 to 9 hours in healthy young male subjects and from 11 to 13 hours in healthy elderly subjects.

Key results from the assessment of intrinsic (i.e. age, gender, body weight, ethnicity, renal and hepatic function) and extrinsic factors (i.e. drug and food interactions) can be found in the current approved label. However, it should be noted that for the ACS indication, at the proposed dose of 2.5mg b.i.d., no dosage adjustment is required for subjects with mild or moderate renal impairment and the use of rivaroxaban should be avoided in patients with severe renal impairment ($\text{CrCl} < 30 \text{ mL/min}$) due to the limited experience in this sub-population and the expected increase in rivaroxaban exposure and pharmacodynamic effects.

A dose adjustment for those patients with a CrCl between 30 to 50 mL/min is not warranted in this patient population based on the safety results from both the Phase 2 and 3 ATLAS ACS trials. Support for this recommendation can be found specifically in the ATLAS ACS 2 TIMI 51 trial, where the incidence of both bleeding and non-bleeding adverse events was similar for the subjects with varying degrees of renal impairment and balanced between the treatment groups. Additionally, the primary efficacy endpoint was comparable between the patients with different renal function.

Only a few additional clinical pharmacology studies have been conducted since the review and approval of rivaroxaban for the prophylaxis of DVT, which may lead to pulmonary embolism (PE) in patients undergoing hip or knee replacement surgery (VTE prevention indication, 10 mg dose strength) and for the reduction of risk for stroke and non CNS systemic embolism in patients with non-valvular atrial fibrillation (Afib indication, 15 mg and 20 mg dose strengths). These studies include: (1) a dose proportionality study assessing rivaroxaban dose

strengths of 2.5 mg, 5 mg and 10 mg, in healthy subjects; (2) Study 14883, a study assessing the pharmacodynamic changes when switching from warfarin to rivaroxaban in healthy Japanese subjects; and (3) Study 12606, a study assessing the potential pharmacokinetic interactions when coadministering rivaroxaban with fluconazole in healthy subjects. Additionally, population pharmacokinetic (PK) / pharmacodynamic (PD) analyses from the Phase 2 ATLAS ACS TIMI 46 study are also included in this submission, and briefly summarized below.

In the Phase 2 ATLAS ACS TIMI 46 study, eligible patients were randomized to the following treatment groups: oral rivaroxaban at 2.5, 5, 7.5, or 10 mg b.i.d. (5, 10, 15, or 20 mg total daily dose [TDD]); oral rivaroxaban at 5, 10, 15, or 20 mg q.d. in the evening (with a placebo dose in the morning); or placebo. Study drug was taken with or without food.

Both sparse PK/PD and intensive PK samples were taken during the trial. The structural population PK model that was developed for rivaroxaban for the DVT treatment indication was used for this analysis. The PK/PD analyses were conducted in a subgroup of patients where time matched PK and PD samples were collected. The PD measurements include prothrombin time (PT) and prothrombinase induced clotting time (PiCT). Matched samples imply that the PD blood samples to determine coagulation characteristics (PT and PiCT) were taken at the same times as PK blood samples were collected. Previously identified structural models along with the covariates were used in the current analysis to confirm whether the models were adequate to describe the PK/PD relationships of rivaroxaban in the ACS population and to estimate the PK/PD parameter values for the current population.

The results of this analysis confirmed that the PK data in the ACS patient population can be adequately described by a one-compartment model with first-order absorption and first-order elimination, coinciding with the results obtained with the previously developed structural population PK model established for VTE-prevention, DVT-treatment, and Afib patient populations. In turn, the PK parameter estimates for ACS patients were comparable to those for VTE prevention, DVT treatment, and Afib patients.

The demographic covariates identified as affecting rivaroxaban pharmacokinetics (apparent oral clearance [CL/F] and apparent volume of distribution [V/F]) were age, renal function (assessed via serum creatinine) and body weight (expressed as calculated lean body mass). The covariate estimates were consistent with those estimated in VTE-prevention, DVT-treatment, and Afib patients. Model-based simulations showed that the influences of renal function and age on the exposure to rivaroxaban in the ACS population were similar to the findings from Phase 1 special population studies. The effect of lean body mass on the drug exposure was minimal and was also consistent with previously reported data.

With the population PK model, rivaroxaban clearance was estimated to be approximately 6.5 L/h in ACS patients (compared with approximately 10 L/h on average in healthy young subjects), with an inter-individual variability of approximately 30%. Volume of distribution was estimated to be approximately 58 L, with inter-individual variability of approximately 10%, similar to that observed with healthy subjects. No time-dependent effects on rivaroxaban PK were detected in patients over the 180-day course of the phase 2 dose-finding study.

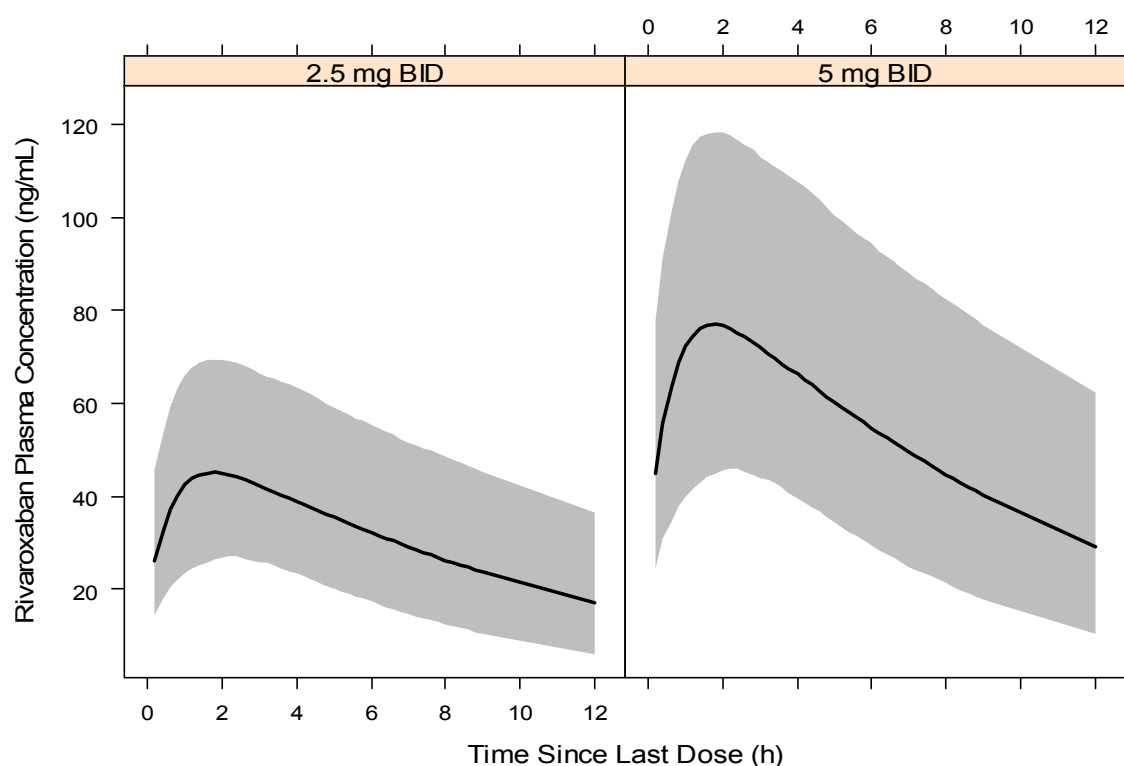
Table 5 provides the predicted rivaroxaban exposure data for the 2.5 mg and the 5 mg bid dose regimens tested in the Phase 2 ATLAS ACS TIMI 46 study, while Figure 3, depicts the respective estimated plasma-concentration vs time profiles.

Table 5: Predicted Rivaroxaban PK Parameters in ACS Patients for 2.5 mg bid or 5 mg bid Dosing Regimens Based on Final PK Model and Total Study Population (n=2290) in Phase 2 Study ATLAS ACS TIMI 46 [Median (5th to 95th Percentiles)]

Parameter	2.5 mg bid	5 mg bid
AUC ₀₋₁₂ (µg*h/L)	376 (213-641)	639 (363-1090)
C _{max} (µg/L)	46 (28.3-70)	78.3 (48.2-119)
C _{trough} (µg/L)	17.2 (6.11-36.6)	29.3 (10.4-62.3)

Source: ATLAS ACS TIMI 46 Population PK/PD Report [R-8642], in Module 5.3.3.5\Appendix 16

Figure 3: Prediction of rivaroxaban plasma-concentration - vs time profile at Steady-State in ACS patients treated with rivaroxaban 2.5 mg bid (left panel) or 5 mg bid (right panel), as used in Phase 3 (medians [5th - 95th percentiles]; n=2290)

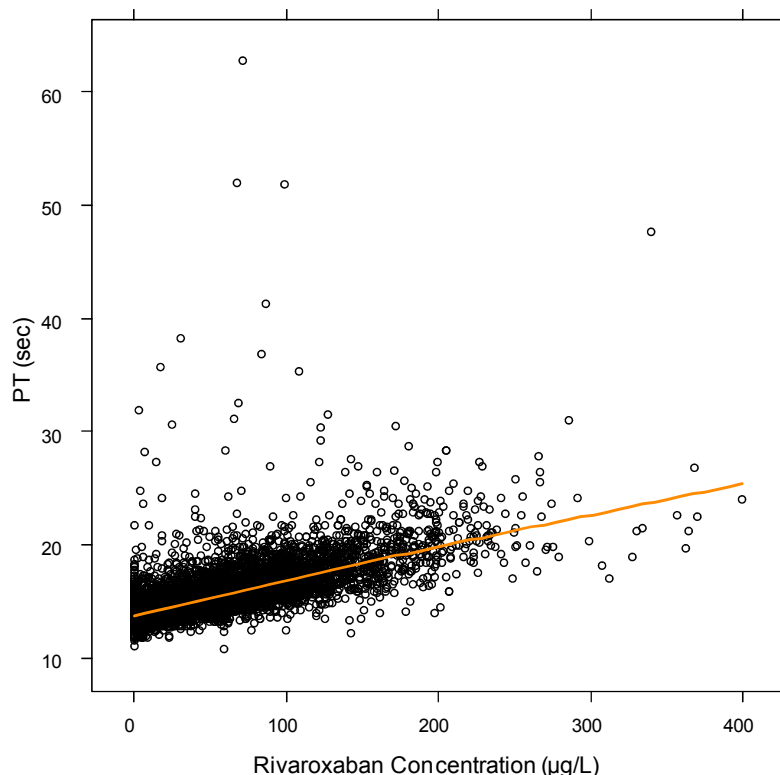


Source: ATLAS ACS TIMI 46 Population PK/PD Report [R-8642], in Module 5.3.3.5\Appendix 15

Similar to the results obtained from the population PK/PD analyses in VTE prevention, DVT treatment, and atrial fibrillation patients, rivaroxaban plasma concentrations exhibited a close-to-linear relationship with PT in the ACS population (Figure 4). At steady-state, the baseline PT was estimated to be 14 seconds and the slope of the correlation between PT and rivaroxaban

plasma concentrations was 3.2 seconds/ 100 $\mu\text{g/L}$ drug concentration. The residual variability was low (7.6%).

Figure 4: Observed Concentration-effect Relationship for Prothrombin Time in ACS Patients at Steady-state in the Phase 2 ATLAS ACS TIMI 46 trial / PK/PD Sub-study



Source: Module 5.3.3.5\ATLAS ACS TIMI 46 Population PK/PD Report\Figure 10

Note: The orange lines represent a LOWESS smoother

The majority of the parameter estimates for the current ACS patient population are similar to those reported for the DVT treatment and atrial fibrillation populations originally used to construct the PT response-concentration model. The estimated mean slope (3.2 sec per 100 $\mu\text{g/L}$) reflecting the sensitivity of this coagulation marker towards increases in rivaroxaban drug exposure is similar to what was observed in the DVT treatment patients (3.6 sec per 100 $\mu\text{g/L}$), and atrial fibrillation patients (4.3 sec per 100 $\mu\text{g/L}$). As previously stated, there is a close-to-linear relationship between rivaroxaban plasma concentrations and PT, thus providing evidence that PT Neoplastin plus[®] may be a suitable tool to indirectly estimate rivaroxaban exposure if necessary.

4. OVERVIEW OF THE ACS CLINICAL DEVELOPMENT PROGRAM

Overall Rivaroxaban Clinical Development Program

Rivaroxaban has been under development for the treatment and prevention of a number of thrombosis-mediated conditions, with over 70,000 subjects enrolled, and over 40,000 subjects exposed to rivaroxaban in completed and ongoing clinical studies in the overall clinical development program as of 31 December 2011.

Rivaroxaban is currently approved in the U.S. with the trade name XARELTO® in the following indications:

- Rivaroxaban 10 mg tablet once daily for the prophylaxis of deep vein thrombosis (DVT), which may lead to PE in patients undergoing knee or hip replacement surgery (NDA 22406, approved in July 2011);
- Rivaroxaban 20 mg and 15 mg tablet once daily to reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation (NDA 202439, approved in November 2011).

Worldwide, XARELTO 10 mg tablet once daily is currently marketed in over 100 countries, including the member countries of the European Union (EU), for the prevention of venous thromboembolism (VTE) in patients undergoing hip or knee replacement. XARELTO 20 mg and 15 mg tablet once daily have recently (December 2011) also been approved for marketing in the European Union for the prevention of stroke and systemic embolism in adult patients with nonvalvular atrial fibrillation with one or more risk factors, such as congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, prior stroke or transient ischemic attack, and for the treatment of DVT, and prevention of recurrent DVT and PE following an acute DVT in adults.

Rivaroxaban ACS Clinical Development Program

The rivaroxaban ACS program is a large, multinational clinical development program to evaluate the efficacy and safety of rivaroxaban 2.5 mg and 5 mg twice daily in combination with standard care of ASA alone or with ASA plus a thienopyridine, compared with placebo plus standard care, for the prevention of CV events (CV death, MI and stroke) in patients with ACS. The rivaroxaban ACS program included 2 clinical studies as described below in Sections 4.1 and 4.2.

Other Ongoing Rivaroxaban Clinical Development Programs

In addition to the ACS indication, rivaroxaban is under development for the treatment or prevention of the following thrombosis-mediated conditions, including:

- Prophylaxis of DVT and PE in hospitalized medically ill patients (pivotal clinical study completed)
- Treatment and secondary prevention of DVT (pivotal clinical studies completed)
- Treatment and secondary prevention of PE (pivotal clinical studies completed)

Rivaroxaban Postmarketing Experience Worldwide

Worldwide postmarketing exposure to XARELTO on the 10 mg tablet for prevention of VTE following elective hip or knee replacement surgery since the first approval of rivaroxaban in Canada on 15 September 2008 until a cutoff date of 31 December 2011 was estimated at 1,553,600 patients (excluding clinical and observational studies). In addition, data were collected from over 18,000 patients (with over 9,000 subjects exposed to rivaroxaban) in a Phase 4 postmarketing observational study (XAMOS study 13802). In the indication of stroke and systemic embolism prevention in patients with nonvalvular atrial fibrillation, based on one 20 mg or 15 mg tablet of XARELTO per patient per day, the cumulative exposure to XARELTO since the start of marketing approval through 31 December 2011 was estimated to be 92,132 person-months or 7,678 person-years in the United States.

4.1. Phase 2 Study ATLAS ACS TIMI 46

The hypothesis that FXa inhibition with rivaroxaban can result in a reduction in CV events was initially tested in the Phase 2 ATLAS ACS TIMI 46 study (Study number 39039039ACS2001 or BAY-59-7939/11898). This randomized, multicenter, double-blind, placebo-controlled, dose-escalation study evaluated the safety and efficacy of rivaroxaban in subjects with a recent ACS who received standard care background ASA therapy, or ASA plus a thienopyridine.

The primary goal of the Phase 2 study was to guide the selection of rivaroxaban doses for testing in a definitive Phase 3 study by assessing the safety (bleeding) via a dose escalation design. The secondary goal was to evaluate the safety and efficacy of rivaroxaban in subjects with a recent acute coronary event who received standard care antiplatelet therapy.

The ATLAS ACS TIMI 46 study consisted of a 6-month double-blind treatment period and 1-month follow up period and compared once-daily dosing with twice-daily dosing within the same total daily dose (TDD). A total of 3491 subjects were randomized to various rivaroxaban dose groups starting at 5 mg and escalating to 20 mg TDD. Randomization was stratified by the intention to use thienopyridine as standard care (Stratum 1 = no, Stratum 2 = yes) in addition to low-dose ASA. Dose panels were tested per the Executive Committee guidance. The results demonstrated that rivaroxaban increases the risk of bleeding in a dose dependent manner; however, a TDD of 5 or 10 mg appeared to have an acceptable safety profile, had less bleeding than the higher doses, and produced a numerical reduction in the risk of the composite of CV death, MI or stroke. Results of ATLAS ACS TIMI 46 are summarized in more detail below.

4.1.1. Results Relevant to Phase 3 Study Dose Selection

The dose selection for the pivotal Phase 3 study ATLAS ACS 2 TIMI 51 was based on the review of safety, efficacy and the resulting net clinical outcome data from of the Phase 2 ATLAS ACS TIMI 46 study. The TDD of rivaroxaban studied in ATLAS ACS TIMI 46 were 5 mg, 10 mg, 15 mg and 20 mg, administered as either once-daily or twice-daily regimens.

In ATLAS ACS TIMI 46, for the primary efficacy endpoint, the composite of all cause death, MI, stroke, or severe recurrent ischemia requiring revascularization, the HR for the pooled rivaroxaban 5 mg, 10 mg, 15 mg, and 20 mg TDD groups, as compared with the pooled placebo

group in the intent-to-treat (ITT) analysis set were 0.85 (95% CI: 0.53-1.36), 0.75 (95% CI: 0.53-1.05), 1.28 (95% CI: 0.82-2), and 0.78 (95% CI: 0.53-1.16), respectively. For the key secondary efficacy endpoint, the composite of all-cause death, MI or stroke, the HR for the pooled rivaroxaban 5 mg, 10 mg, 15 mg, and 20 mg TDD groups, as compared with the pooled placebo group were 0.77 (95% CI: 0.45-1.31), 0.69 (95% CI: 0.47-1.03), 1.38 (95% CI: 0.83-2.3), and 0.59 (95% CI: 0.36-0.96), respectively (Table 6). The higher rivaroxaban TDDs did not appear to have increased efficacy.

Within the 5 mg and 10 mg TDD regimens, rivaroxaban 2.5 mg and 5 mg b.i.d. appeared to be numerically more efficacious than the once-daily doses. The 2.5 mg and 5 mg b.i.d. rivaroxaban doses resulted in 46% (HR: 0.54; 95% CI: 0.25-1.2) and 37% (HR: 0.63; 95% CI: 0.37-1.05) relative reductions respectively in the risk of the composite endpoint of all cause death, MI or stroke, while rivaroxaban doses of 5 mg and 10 mg administered once-daily resulted in 8% (HR: 0.92; 95% CI: 0.48-1.76) and 24% (HR: 0.76; 95% CI: 0.47-1.24) relative risk reductions (RRRs) in the same endpoint. This trend was observed in both Stratum 1 and Stratum 2 (Table 7).

Rivaroxaban in addition to standard care increased the risk of bleeding for each dose level, with a strong positive dose relationship for both strata. In Stratum 1, the incidence rates of treatment-emergent clinically significant bleeding events for rivaroxaban 5 mg, 10 mg, and 20 mg TDD groups were 1.3% (HR [95% CI]: 0.84 [0.15-4.57]), 6.2%, (HR [95% CI]: 4.11 [1.33-12.8]) and 10.2% (HR [95% CI]: 6.71 [2.24-20.1]), respectively, and it was 1.6% in the Stratum 1 placebo group. In Stratum 2, the incidence rates of treatment-emergent clinically significant bleeding events for rivaroxaban 5 mg, 10 mg, 15 mg, and 20 mg TDD groups were 9.8% (HR [95% CI]: 2.78 [1.5-5.13]), 11.4% (HR [95% CI]: 3.33 [2.24-4.97]), 12.2% (HR [95% CI]: 3.55 [2.25-5.61]), and 16.4% (HR [95% CI]: 4.90 [3.24-7.43]), respectively, compared with 3.6% in the Stratum 2 placebo group (Table 8).

The results of the pre-specified Net Clinical Benefit endpoint, the composite of death, MI, stroke, severe recurrent ischemia requiring revascularization and Thrombolysis In Myocardial Infarction (TIMI) major or minor bleeding, showed that across strata, rivaroxaban treatment resulted in a favorable net clinical outcome at the 2 lowest dose levels and a loss of this favorable balance at the 2 highest doses due to increased bleeding events. The Net Clinical Benefit endpoint HR (95% CI) for the pooled rivaroxaban 5 mg, 10 mg, 15 mg, and 20 mg TDDs groups compared with the pooled placebo group were 0.80 (0.5-1.28), 0.92 (0.67-1.26), 1.74 (1.13-2.67), and 1.00 (0.7-1.43), respectively (Table 9).

Taken together, the 2 lowest TDDs, rivaroxaban 5 mg and 10 mg, had acceptable safety profiles and less bleeding than the higher doses. Within the 5 mg and 10 mg TDD groups, twice-daily dosing had numerically better efficacy, compared with once-daily dosing. Therefore, b.i.d. doses of 2.5 mg and 5 mg were chosen for the Phase 3 ATLAS ACS 2 TIMI 51 trial. The rationale for studying 2 doses of rivaroxaban was to develop a better understanding of the efficacy and safety profile of rivaroxaban in a dose range.

Table 6: Treatment Effect of Primary and Key Secondary Efficacy Endpoints by Dose Level Against Pooled Placebo Group as Adjudicated by Clinical Events Committee (Study ATLAS ACS TIMI 46: Intent-to-Treat Analysis Set)

Stratum	Parameter	Pooled Placebo K/N (%)	----- Rivaroxaban 5 mg ----- K/N (%)	HR (95% CI)	----- Rivaroxaban 10 mg ----- K/N (%)	HR (95% CI)	----- Rivaroxaban 15 mg --- K/N (%)	HR (95% CI)	----- Rivaroxaban 20 mg ----- K/N (%)	HR (95% CI)
All Strata	Primary	83/1160 (7.2)	23/308 (7.5)	0.85 (0.53,1.36)	55/1056 (5.2)	0.75 (0.53,1.05)	27/356 (7.6)	1.28 (0.82,2)	36/611 (5.9)	0.78 (0.53,1.16)
	Dth/MI/St	66/1160 (5.7)	18/308 (5.8)	0.77 (0.45,1.31)	40/1056 (3.8)	0.69 (0.47,1.03)	21/356 (5.9)	1.38 (0.83,2.3)	22/611 (3.6)	0.59 (0.36,0.96)
Stratum 1	Primary	34/253 (13.4)	14/154 (9.1)	0.65 (0.35,1.22)	17/196 (8.7)	0.64 (0.36,1.15)			9/158 (5.7)	0.40 (0.19,0.84)
	Dth/MI/St	29/253 (11.5)	14/154 (9.1)	0.78 (0.41,1.47)	14/196 (7.1)	0.62 (0.33,1.18)			7/158 (4.4)	0.37 (0.16,0.84)
Stratum 2	Primary	49/907 (5.4)	9/154 (5.8)	1.07 (0.53,2.19)	38/860 (4.4)	0.82 (0.54,1.26)	27/356 (7.6)	1.43 (0.89,2.29)	27/453 (6.0)	1.10 (0.69,1.76)
	Dth/MI/St	37/907 (4.1)	4/154 (2.6)	0.62 (0.22,1.73)	26/860 (3.0)	0.75 (0.45,1.23)	21/356 (5.9)	1.47 (0.86,2.51)	15/453 (3.3)	0.80 (0.44,1.47)

Primary: composite of all cause death, myocardial infarction, stroke or severe recurrent ischemia requiring revascularization (SRI_Rev); Dth/MI/St: composite of all cause death, myocardial infarction or stroke. CV-D/MI/St: composite of cardiovascular death, myocardial infarction, or stroke.

Note: a subject could have more than one component event, only the first event is counted;

Stratum= Aspirin, Stratum 2=Aspirin +Thienopyridine

K/N: Number of subjects having events / number of subjects at risk; HR (95% CI): Hazard ratio (95% confidence interval) as compared with pooled placebo groups;

For each stratum, perform a Cox model with dose level (0/5/10/15/20) as class variable, and for all strata, also adding strata (Aspirin vs. Aspirin+ Thienopyridine); For subjects who didn't have events, the minimum of the last visit date or death date was used as the censoring day.

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Table 7: Treatment Effect of Primary Efficacy and Key Secondary Endpoints by Each Dose-Level Panel(s) as Adjudicated by Clinical Events Committee (Study ATLAS ACS TIMI 46: Intent-to-Treat Analysis Set)

		Dose	Pooled Placebo	----- Rivaroxaban: OD -----	----- Rivaroxaban: BID -----	--Combined Rivaroxaban (OD+BID) --			
Stratum	Parameter	(mg)	K/N (%)	K/N (%)	HR (95% CI)	K/N (%)	HR (95% CI)	K/N (%)	HR (95% CI)
All Strata	Primary	5	83/1160 (7.2)	14/155 (9.0)	1.00 (0.56,1.78)	9/153 (5.9)	0.61 (0.3,1.22)	23/308 (7.5)	0.80 (0.49,1.29)
		10	83/1160 (7.2)	29/529 (5.5)	0.80 (0.52,1.21)	26/527 (4.9)	0.71 (0.46,1.11)	55/1056 (5.2)	0.75 (0.54,1.06)
		15	83/1160 (7.2)	16/178 (9.0)	1.67 (0.95,2.94)	11/178 (6.2)	1.20 (0.62,2.31)	27/356 (7.6)	1.44 (0.9,2.31)
		20	83/1160 (7.2)	16/304 (5.3)	0.70 (0.41,1.19)	20/307 (6.5)	0.86 (0.53,1.41)	36/611 (5.9)	0.78 (0.53,1.15)
	Dth/MI/St	5	66/1160 (5.7)	11/155 (7.1)	0.92 (0.48,1.76)	7/153 (4.6)	0.54 (0.25,1.2)	18/308 (5.8)	0.72 (0.42,1.24)
		10	66/1160 (5.7)	22/529 (4.2)	0.76 (0.47,1.24)	18/527 (3.4)	0.63 (0.37,1.05)	40/1056 (3.8)	0.69 (0.47,1.03)
		15	66/1160 (5.7)	12/178 (6.7)	1.65 (0.86,3.17)	9/178 (5.1)	1.30 (0.63,2.7)	21/356 (5.9)	1.48 (0.87,2.54)
		20	66/1160 (5.7)	9/304 (3.0)	0.48 (0.24,0.97)	13/307 (4.2)	0.69 (0.38,1.26)	22/611 (3.6)	0.59 (0.36,0.95)
Stratum 1	Primary	5	34/253 (13.4)	8/77 (10.4)	0.77 (0.35,1.66)	6/77 (7.8)	0.55 (0.23,1.3)	14/154 (9.1)	0.65 (0.35,1.22)
		10	34/253 (13.4)	8/99 (8.1)	0.60 (0.28,1.29)	9/97 (9.3)	0.69 (0.33,1.43)	17/196 (8.7)	0.64 (0.36,1.15)
		20	34/253 (13.4)	3/78 (3.8)	0.27 (0.08,0.88)	6/80 (7.5)	0.54 (0.22,1.27)	9/158 (5.7)	0.40 (0.19,0.84)
	Dth/MI/St	5	29/253 (11.5)	8/77 (10.4)	0.91 (0.42,1.99)	6/77 (7.8)	0.65 (0.27,1.56)	14/154 (9.1)	0.78 (0.41,1.47)
		10	29/253 (11.5)	7/99 (7.1)	0.61 (0.27,1.4)	7/97 (7.2)	0.63 (0.27,1.43)	14/196 (7.1)	0.62 (0.33,1.17)
		20	29/253 (11.5)	2/78 (2.6)	0.21 (0.05,0.88)	5/80 (6.3)	0.52 (0.2,1.35)	7/158 (4.4)	0.37 (0.16,0.84)
Stratum 2	Primary	5	49/907(5.4)	6/78 (7.7)	1.48 (0.63,3.47)	3/76 (3.9)	0.69 (0.22,2.23)	9/154 (5.8)	1.08(0.53,2.19)
		10	49/907(5.4)	21/430 (4.9)	0.92 (0.55,1.53)	17/430 (4.0)	0.73 (0.42,1.28)	38/860 (4.4)	0.82(0.54,1.26)
		15	49/907(5.4)	16/178 (9.0)	1.67 (0.95,2.94)	11/178 (6.2)	1.20 (0.62,2.31)	27/356 (7.6)	1.44(0.9,2.31)
		20	49/907(5.4)	13/226 (5.8)	1.06 (0.57,1.95)	14/227 (6.2)	1.13 (0.63,2.05)	27/453 (6.0)	1.10(0.68,1.75)
	Dth/MI/St	5	37/907 (4.1)	3/78 (3.8)	0.98 (0.3,3.18)	1/76 (1.3)	0.29 (0.04,2.09)	4/154 (2.6)	0.61 (0.22,1.71)
		10	37/907 (4.1)	15/430 (3.5)	0.86 (0.47,1.57)	11/430 (2.6)	0.63 (0.32,1.23)	26/860 (3.0)	0.75 (0.45,1.23)
		15	37/907 (4.1)	12/178 (6.7)	1.65 (0.86,3.17)	9/178 (5.1)	1.30 (0.63,2.7)	21/356 (5.9)	1.48 (0.87,2.54)
		20	37/907 (4.1)	7/226 (3.1)	0.75 (0.33,1.68)	8/227 (3.5)	0.85 (0.39,1.82)	15/453 (3.3)	0.80 (0.44,1.45)

Primary: composite of all cause death, myocardial infarction, stroke or severe recurrent ischemia requiring revascularization; Dth/MI/St: composite of all cause death, myocardial infarction or stroke. Note: a subject could have more than 1 component events, only the first event is counted;

Stratum= Aspirin, Stratum 2=Aspirin +Thienopyridine OD= once-daily; BID= twice-daily.

K/N: Number of subjects having events / number of subjects at risk; HR (95% CI): Hazard ratio (95% confidence interval) as compared with pooled placebo groups; For each dose-level, perform a Cox model with (pooled placebo from all dose levels) vs. (Rivaroxaban OD/Riva BID in that dose level) by stratum (Aspirin), and for all strata, also adding strata (Aspirin vs. Aspirin+ Thienopyridine) in the model; For combined rivaroxaban, perform another Cox model with dose regimen replaced by treatment group (combined rivaroxaban vs. pooled placebo) by dose level.

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**Table 8: Treatment Effect of Treatment-Emergent Primary Bleeding Endpoints by Dose Level Against Pooled Placebo Group as Adjudicated by CEC
(Study ATLAS ACS TIMI 46: Safety Analysis Set)**

Stratum	Parameter	Pooled Placebo K/N (%)	-----Rivaroxaban 5 mg ----- K/N (%)	HR (95% CI)	----- Rivaroxaban 10 mg ----- K/N (%)	HR (95% CI)	-----Rivaroxaban 15 mg ----- K/N (%)	HR (95% CI)	-----Rivaroxaban 20 mg ----- K/N (%)	HR (95% CI)
All Strata	Clinical sig	36/1153(3.1)	17/307(5.5)	2.14(1.2,3.83)	109/1046(10.4)	3.41(2.34,4.97)	43/353(12.2)	3.59(2.3,5.6)	89/603(14.8)	5.14(3.49,7.57)
	TIMI	3/1153(0.3)	2/307(0.7)	2.99(0.5,18.1)	22/1046(2.1)	8.13(2.43,27.2)	9/353(2.5)	8.86(2.39,32.9)	14/603(2.3)	9.46(2.72,32.9)
	TIMI Major	1/1153(<0.1)	1/307(0.3)	4.24(0.26,68.5)	16/1046(1.5)	17.80(2.36,134)	6/353(1.7)	18.35(2.2,153)	9/603(1.5)	18.11(2.29,143)
	TIMI Minor	2/1153(0.2)	1/307(0.3)	2.49(0.22,27.8)	6/1046(0.6)	3.29(0.66,16.3)	3/353(0.8)	4.17(0.69,25)	5/603(0.8)	5.11(0.99,26.4)
	Med. attent	33/1153(2.9)	17/307(5.5)	2.35(1.3,4.23)	88/1046(8.4)	3.00(2.01,4.47)	35/353(9.9)	3.16(1.96,5.1)	76/603(12.6)	4.76(3.16,7.17)
Stratum 1	Clinical sig	4/252(1.6)	2/154(1.3)	0.84(0.15,4.57)	12/195(6.2)	4.11(1.33,12.8)			16/157(10.2)	6.71(2.24,20.1)
	TIMI	0/252	0/154		4/195(2.1)				1/157(0.6)	
	TIMI Major	0/252	0/154		4/195(2.1)				0/157	
	TIMI Minor	0/252	0/154		0/195				1/157(0.6)	
	Med. attent	4/252(1.6)	2/154(1.3)	0.84(0.15,4.57)	8/195(4.1)	2.74(0.83,9.11)			15/157(9.6)	6.29(2.09,18.9)
Stratum 2	Clinical sig	32/901(3.6)	15/153(9.8)	2.78(1.5,5.13)	97/851(11.4)	3.33(2.24,4.97)	43/353(12.2)	3.55(2.25,5.61)	73/446(16.4)	4.90(3.24,7.43)
	TIMI	3/901(0.3)	2/153(1.3)	3.81(0.64,22.8)	18/851(2.1)	6.50(1.91,22.1)	9/353(2.5)	7.85(2.12,29)	13/446(2.9)	9.06(2.58,31.8)
	TIMI Major	1/901(0.1)	1/153(0.7)	5.72(0.36,91.4)	12/851(1.4)	12.95(1.68,99.6)	6/353(1.7)	15.69(1.89,130)	9/446(2.0)	18.82(2.38,149)
	TIMI Minor	2/901(0.2)	1/153(0.7)	2.86(0.26,31.5)	6/851(0.7)	3.25(0.66,16.1)	3/353(0.8)	3.91(0.65,23.4)	4/446(0.9)	4.16(0.76,22.7)
	Med. attent	29/901(3.2)	15/153(9.8)	3.06(1.64,5.71)	80/851(9.4)	3.03(1.98,4.63)	35/353(9.9)	3.17(1.94,5.19)	61/446(13.7)	4.49(2.88,6.98)

Clinical sig: composite of TIMI major, TIMI minor or bleed requiring medical attention. Note: one subject could have more than one component event, only the first event is counted; TIMI: composite of TIMI major or TIMI minor; Med. attent: Bleed requiring medical attention;

Stratum 1: Aspirin, Stratum 2: Aspirin+ Thienopyridine

K/N: Number of subjects having events / number of subjects at risk;

HR (95% CI): Hazard ratio (95% confidence interval) as compared with pooled placebo;

For each stratum, perform a Cox model with dose level (0/5/10/15/20) as class variable, and for all strata, also adding strata (Aspirin vs. Aspirin+ Thienopyridine);

For subjects with no such events, the minimum of the last dose date plus 2 days and the last contact date was used as censoring day.

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**Table 9: Treatment Effect of Net Clinical Benefit Endpoints by Each Dose-Level Panel(s) as Adjudicated by Clinical Events Committee
(Study ATLAS ACS TIMI 46: Intent-to-Treat Analysis Set)**

Stratum	Parameter	Dose (mg)	Pooled Placebo K/N (%)	----- Rivaroxaban: OD -----		----- Rivaroxaban: BID -----		--Combined Rivaroxaban (OD+BID) --	
				K/N (%)	HR (95% CI)	K/N (%)	HR (95% CI)	K/N (%)	HR (95% CI)
All Strata	Net Benefit	5	88/1160 (7.6)	14/155 (9.0)	0.96 (0.54,1.71)	10/153 (6.5)	0.65 (0.33,1.26)	24/308 (7.8)	0.80 (0.5,1.28)
		10	88/1160 (7.6)	38/529 (7.2)	0.98 (0.67,1.44)	33/527 (6.3)	0.86 (0.57,1.28)	71/1056 (6.7)	0.92 (0.67,1.26)
		15	88/1160 (7.6)	20/178 (11.2)	1.95 (1.17,3.27)	15/178 (8.4)	1.52 (0.85,2.69)	35/356 (9.8)	1.74 (1.13,2.67)
		20	88/1160 (7.6)	23/304 (7.6)	0.96 (0.61,1.52)	25/307 (8.1)	1.04 (0.67,1.62)	48/611 (7.9)	1.00 (0.7,1.43)
	Dth/MI/St/T1	5	68/1160 (5.9)	11/155 (7.1)	0.91 (0.48,1.75)	8/153 (5.2)	0.62 (0.29,1.3)	19/308 (6.2)	0.76 (0.45,1.29)
		10	68/1160 (5.9)	29/529 (5.5)	0.98 (0.63,1.51)	24/527 (4.6)	0.81 (0.51,1.29)	53/1056 (5.0)	0.89 (0.62,1.28)
		15	68/1160 (5.9)	14/178 (7.9)	1.84 (1.3,3.9)	12/178 (6.7)	1.65 (0.87,3.16)	26/356 (7.3)	1.75 (1.06,2.87)
		20	68/1160 (5.9)	13/304 (4.3)	0.69 (0.38,1.25)	17/307 (5.5)	0.90 (0.53,1.53)	30/611 (4.9)	0.79 (0.52,1.22)
Stratum 1	Net Benefit	5	35/253 (13.8)	8/77 (10.4)	0.74 (0.35,1.61)	6/77 (7.8)	0.53 (0.22,1.26)	14/154 (9.1)	0.63 (0.34,1.18)
		10	35/253 (13.8)	9/99 (9.1)	0.66 (0.31,1.36)	10/97 (10.3)	0.75 (0.37,1.51)	19/196 (9.7)	0.70 (0.4,1.22)
		20	35/253 (13.8)	3/78 (3.8)	0.26 (0.08,0.85)	6/80 (7.5)	0.52 (0.22,1.25)	9/158 (5.7)	0.39 (0.19,0.82)
	Dth/MI/St/T1	5	29/253 (11.5)	8/77 (10.4)	0.91 (0.42,1.99)	6/77 (7.8)	0.65 (0.27,1.56)	14/154 (9.1)	0.78 (0.41,1.47)
		10	29/253 (11.5)	8/99 (8.1)	0.71 (0.32,1.54)	8/97 (8.2)	0.72 (0.33,1.58)	16/196 (8.2)	0.71 (0.39,1.31)
		20	29/253 (11.5)	2/78 (2.6)	0.21 (0.05,0.88)	5/80 (6.3)	0.52 (0.2,1.35)	7/158 (4.4)	0.37 (0.16,0.84)
Stratum 2	Net Benefit	5	53/907 (5.8)	6/78 (7.7)	1.37 (0.59,3.18)	4/76 (5.3)	0.86 (0.31,2.37)	10/154 (6.5)	1.10 (0.56,2.17)
		10	53/907 (5.8)	29/430 (6.7)	1.18 (0.75,1.85)	23/430 (5.3)	0.92 (0.57,1.51)	52/860 (6.0)	1.05 (0.72,1.54)
		15	53/907 (5.8)	20/178 (11.2)	1.95 (1.17,3.27)	15/178 (8.4)	1.52 (0.85,2.69)	35/356 (9.8)	1.74 (1.13,2.67)
		20	53/907 (5.8)	20/226 (8.8)	1.53 (0.91,2.55)	19/227 (8.4)	1.44 (0.85,2.43)	39/453 (8.6)	1.48 (0.98,2.24)
	Dth/MI/St/T1	5	39/907 (4.3)	3/78 (3.8)	0.92 (0.28,2.99)	2/76 (2.6)	0.55 (0.13,2.29)	5/154 (3.2)	0.73 (0.29,1.85)
		10	39/907 (4.3)	21/430 (4.9)	1.15 (0.68,1.96)	16/430 (3.7)	0.87 (0.49,1.56)	37/860 (4.3)	1.01 (0.65,1.59)
		15	39/907 (4.3)	14/178 (7.9)	1.84 (1.3,3.9)	12/178 (6.7)	1.65 (0.87,3.16)	26/356 (7.3)	1.75 (1.06,2.87)
		20	39/907 (4.3)	11/226 (4.9)	1.13 (0.58,2.2)	12/227 (5.3)	1.22 (0.64,2.33)	23/453 (5.1)	1.17 (0.7,1.97)

OD= once-daily; BID= twice-daily. Net Benefit: composite of death, Myocardial Infarction (MI), stroke, severe recurrent ischemia (SRI) requiring revascularization, TIMI major or minor; Dth/MI/St/T1: composite of death, MI, Stroke, or TIMI Major.

Stratum 1= Aspirin; Stratum 2=Aspirin+ Thienopyridine

Note: a subject could have more than 1 component event, only the first event is counted; K/N: Number of subjects having events / number of subjects at risk; HR (95% CI):

Hazard ratio (95% confidence interval) as compared with pooled placebo groups;

For each dose-level, perform a Cox model with (Pooled Placebo from all dose levels) vs. (Rivaroxaban OD/ Rivaroxaban BID in that dose level) by stratum (Aspirin), and for all strata, also adding strata (Aspirin vs. Aspirin+ Thienopyridine) in the model; For combined rivaroxaban, perform another Cox model with dose regimen replaced by treatment group (combined rivaroxaban vs. pooled placebo) by dose level.

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Clinical Pharmacology Results Supporting the Selected Doses for Phase 3 Study

Both twice-daily regimens (2.5, 5, 7.5, or 10 mg b.i.d.) and once-daily regimens (5, 10, 15, or 20 mg q.d.) were tested in this study. As expected, lower peaks and higher troughs were observed when rivaroxaban was administered twice-daily when compared with once-daily dosing (Table 10), supporting the selected twice-daily dosing for the Phase 3 study.

Table 10: Predicted Rivaroxaban PK Parameters in ACS patients for 2.5 mg bid or 5 mg bid Dosing Regimens Versus Bleeding and Efficacy Results in ATLAS ACS TIMI 46

Dose Regimen	Estimated Rivaroxaban Exposure Data ^a [Median (5 th – 95 th percentiles)]			Clinically Significant Bleeding ^b [Kaplan-Meier Rate (n/N)]	Composite Efficacy Endpoint ^c [Kaplan-Meier Rate (n/N)]
	C _{min} (µg/L)	C _{max} (µg/L)	AUC ₂₄ (µg·h/L)		
2.5 mg bid	17.2 (6.11 – 36.6)	46 (28.3 – 69.9)	752 (427-1280)	4.8% (7/152)	5.3% (8/153)
5 mg qd	6.08 (1.04-19.4)	60.9 (33.9 – 86.1)	639 (363-1090)	7.4% (11/155)	8.7% (13/155)
5 mg bid	29.3 (10.4 – 62.3)	78.1 (48.1-119)	1280 (725-2180)	11.0% (55/519)	4.4% (22/527)
10 mg qd	12.2 (2.09-38.8)	122 (67.8-172)	1280 (725-2180)	10.8 (55/527)	5.3% (27/529)

^a: Predicted rivaroxaban PK parameters in ACS patients based on final PK model and total study population (n=2290).

^b: TIMI major, TIMI minor, or requiring medical attention

^c: Composite of: death, myocardial infarction, stroke, or severe recurrent ischemia requiring revascularization.

^{b, c}: Data source: Mega et al, 2009²⁵.

4.1.2. Efficacy and Safety of Rivaroxaban in ATLAS ACS TIMI 46

ATLAS ACS TIMI 46 was a robust Phase 2 study that allowed the effect of rivaroxaban on the risk of bleeding in ACS patients to be assessed. The number of efficacy events was relatively small, particularly at the individual dose level, making it difficult to accurately estimate effect size. However, overall, treatment with rivaroxaban demonstrated a trend to reduce the risk of subjects experiencing the primary efficacy endpoint events (death, myocardial infarction, stroke or severe recurrent ischemia requiring revascularization) by 16% (HR: 0.84; 95% CI: 0.64-1.10) for combined doses. Rivaroxaban treatment also resulted in an observed 24% (HR: 0.76; 95% CI: 0.55-1.03) RRR in the risk of the composite endpoint of death, MI or stroke for combine doses. Rivaroxaban demonstrated efficacy at higher (15 mg and 20 mg) as well as at lower (5 mg and 10 mg) TDD groups. The effect of rivaroxaban on the clinical efficacy endpoints appeared to be preserved in most major subgroups. Of note, outcome tended to favor placebo treatment in those subjects with a prior event of stroke or transient ischemic attack (TIA).

Treatment with rivaroxaban resulted in a dose dependent increase in the risk of bleeding in ACS subjects. The majority (84%) of these events were classified as “bleeding requiring medical attention”, rather than the more severe TIMI major or minor types of bleeding events. Overall, subjects receiving ASA alone as their standard antiplatelet therapy, (Stratum 1), tended to bleed less than those subjects prescribed ASA plus a thienopyridine (Stratum 2); however, the relative effect of rivaroxaban on bleeding risk was similar in both strata. No dose panel was stopped for safety reasons. The rates of serious and non-serious adverse events other than bleeding events

were similar between the placebo and rivaroxaban treated groups. The rates of bleeding events in the 15 mg and 20 mg TDD groups were considered sufficiently high as to make them undesirable for inclusion in a definitive Phase 3 study.

4.2. Phase 3 Study ATLAS ACS 2 TIMI 51

ATLAS ACS 2 TIMI 51 (the second trial of Anti-Xa Therapy to Lower Cardiovascular Events in Addition to Aspirin with or without Thienopyridine Therapy in Subjects with Acute Coronary Syndrome) is the single pivotal Phase 3 study for the ACS program (Study number RIVAROXACS3001 or BAY-59-7939/13194).

The single pivotal study concept and key elements of the design of the ATLAS ACS 2 TIMI 51 study, including the sample size, the design (including stratification by the intention to use a thienopyridine) and the statistical analysis strategy, were discussed with the FDA and other worldwide regulatory authorities. The study tested 2 dose regimens of rivaroxaban, 2.5 mg twice daily and 5 mg twice daily, allowing for a robust assessment of efficacy and safety of the drug in this patient population. The double-blind design added rigor to the study, limiting the introduction of bias that can confound the ascertainment and reporting of clinical events, and thus the interpretation of study results. The efficacy and safety results from this study are the focus of this briefing document.

4.2.1. Key Aspects of Study Design

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 acute coronary event (STEMI, NSTEMI, or UA) who were receiving standard care. Two oral doses of rivaroxaban (2.5 mg twice daily and 5 mg twice daily) were studied in comparison with placebo. Randomization was stratified by the intention to use thienopyridine as standard care (Stratum 1 = no, Stratum 2 = yes) in addition to low-dose ASA.

The primary objective of this study was to demonstrate that treatment with rivaroxaban in addition to standard care is superior to treatment with placebo in addition to standard care in reducing the risk of CV death, MI, or stroke in subjects with a recent ACS.

The safety objectives of this study were:

- To assess TIMI major bleeding events not associated with CABG surgery as the primary safety endpoint
- To assess overall safety by examining all bleeding events, serious adverse events, adverse events leading to discontinuation of study drug, and adverse events of special interest.

Study Population

The ATLAS ACS 2 TIMI 51 study enrolled adult subjects who had symptoms suggestive of ACS or developed ACS while being hospitalized, and who were receiving ASA therapy (75 to 100 mg/day) alone or in combination with a thienopyridine (clopidogrel or ticlopidine, per the national or locally indicated dosage) at the time of randomization. The administration of study drug was to be started as soon as possible after stabilization of the index ACS event, including

revascularization procedures, when parenteral anticoagulant therapy would normally be discontinued. Subjects who were 18 to 54 years of age inclusive must also have had either diabetes mellitus or a prior MI in addition to the presenting ACS event to be eligible for the study.

This population was chosen as it represents those patients with a recent ACS who were at a moderate to high risk for thromboembolic CV complications. The decision to require subjects 18 to 54 years of age, inclusive, to also have either diabetes mellitus or a previous MI was based on an analysis of results from the Phase 2 study, ATLAS ACS TIMI 46, demonstrating that this subject group is at increased risk and likely to derive benefit from anticoagulant therapy. Eligible subjects were required to have been hospitalized for symptoms suggestive of ACS. Subjects with NSTEMI were required to have elevated biomarkers of myocardial necrosis plus either transient electrocardiogram (ECG) changes consistent with myocardial ischemia or demonstration of active intracoronary atherothrombosis on coronary angiography. Subjects with UA were required to have ECG changes of myocardial ischemia or a TIMI rescore of 4 or higher.

Key exclusion criteria included:

- **Bleeding risk such as:**
 - Active internal bleeding, clinically significant bleeding, bleeding at a noncompressible site, or bleeding diathesis within 30 days of randomization
 - Platelet count <90,000/μL at screening
 - History of intracranial hemorrhage (ICH)
- **Severe concomitant diseases such as:**
 - Calculated creatinine clearance <30 mL/min at screening
 - Known significant liver disease (e.g., acute hepatitis, chronic active hepatitis, cirrhosis), or liver function test (LFT) abnormalities (confirmed with repeat testing) which would require study drug discontinuation, i.e., alanine aminotransferase (ALT) >5x upper limit of normal (ULN) or ALT >3x ULN plus total bilirubin >2x ULN
 - A prior ischemic stroke or TIA in subjects who the investigator planned to include in Stratum 2 (ASA plus thienopyridine). Subjects with a prior hemorrhagic stroke were excluded completely from the study.
- Atrial fibrillation except for subjects younger than 60 years of age who had no clinical or echocardiographic evidence of cardiopulmonary disease and who had only a single episode of atrial fibrillation that occurred more than 2 years ago
- Other conditions requiring long-term anticoagulation

The decision to exclude subjects with a prior ischemic stroke or TIA from participating in Stratum 2 of the study was based on published findings from a prior study in which it was apparent that subjects with a prior stroke did not benefit from prasugrel⁴⁶. In addition, the data from ATLAS ACS TIMI 46 also suggested that subjects with a prior ischemic stroke did not benefit from rivaroxaban treatment, which is in line with the recommendation from the American Stroke Association, to not routinely use aspirin and clopidogrel in ischemic stroke/TIA patients,.

The original protocol excluded subjects with a prior stroke from participation in Stratum 2. Early in the study, the protocol was amended and additionally subjects with a prior TIA were also excluded from participation in Stratum 2 of the study, and patients with a prior hemorrhagic stroke were completely excluded from the study.

Choice of Standard Care Therapy

The choice of standard care therapy was based on relevant guidelines. The current American College of Cardiology Foundation (ACCF)/American Heart Association (AHA) Guidelines for the Management of Patients with UA/NSTEMI states that “ASA should be administered to UA/NSTEMI patients as soon as possible after hospital presentation and continued indefinitely in patients who tolerate it (Level of Evidence: A)” and that “For UA/NSTEMI patients... clopidogrel (75 mg per day) should be prescribed for at least 1 month (Level of Evidence: B) and ideally up to 1 year (Level of Evidence: B)”⁴⁷. The current ACC/AHA practice guideline for secondary prevention after STEMI states that “Long-term maintenance therapy (e.g., 1 year) with clopidogrel (75 mg per day orally) is reasonable in STEMI patients regardless of whether they undergo reperfusion with fibrinolytic therapy or do not receive reperfusion therapy”³.

ACS patients are at increased risk of bleeding, particularly for those receiving dual antiplatelet therapy. As such the protocol required that the ASA dose should not exceed 100 mg. Although the current guidelines suggest ASA doses of 325mg in patients post-stent insertion, the number of clinical studies employing this dose was small and the evidence suggests that outcomes in patients receiving lower ASA doses is similar to that in patients receiving higher doses^{35,50,37,17,24}.

When the ATLAS ACS 2 TIMI 51 study was initiated neither prasugrel nor ticagrelor was approved, hence the standard care thienopyridine agents in this study were limited to clopidogrel (accounted for 99.4% [14502/14594] of the subjects administered thienopyridine therapy in the study) or ticlopidine (accounted for 0.85% [124/14594] of the subjects administered thienopyridine therapy in the study) only.

Rivaroxaban Dose Selection

The rivaroxaban dose selection in the Phase 3 ATLAS ACS 2 TIMI 51 study was based on results of the Phase 2 ATLAS ACS TIMI 46 study. Refer to Section 4.1.1 for details.

Rationale for Duration of Therapy

The ATLAS ACS 2 TIMI 51 study was an event driven study and as such the duration of therapy was dependent upon reaching a pre-specified number of adjudicated primary efficacy endpoint events in the mITT analysis set (see Section 4.2.2 for details on sample size determination and choice of primary efficacy analysis set). The study was to be stopped when at least 983 adjudicated primary efficacy endpoints accrued across both strata, and at least 728 adjudicated primary efficacy endpoints accrued in Stratum 2 to ensure meaningful conclusions could be reached overall and in Stratum 2. The duration of the treatment period for a given subject was variable. The duration of study treatment was expected to be 33 months to 34 months, but up to a maximum of 36 months depending upon the rate of subject recruitment and endpoint event rates.

The event-driven design ensured that an adequate number of events were obtained in order to perform the primary analysis and draw definitive conclusions relating to the primary hypothesis, while preventing unnecessary exposure of subjects to study drug.

Choice of Primary Efficacy Endpoints

The primary efficacy endpoint was the composite of CV death, MI, or stroke. The primary efficacy endpoint components, i.e., CV death, MI, or stroke, are accepted clinical endpoints for the evaluation of treatments for ACS. A composite primary efficacy endpoint is valuable since it allows the effect of a medicinal product to be assessed across a broad panel of important patient-related outcomes that are mediated by the same underlying pathophysiology. Other recent landmark clinical trials for CV conditions, such as the CURE trial³⁹, the TRITON-TIMI 38⁴⁶ trial, the ACUITY trial³⁸, and the PLATO trial⁴², also used composite efficacy endpoints.

Bleeding Events Assessment

Three bleeding event scales were used to assess bleeding events in the ATLAS ACS 2 TIMI 51 study. The TIMI scale was the primary bleeding scale for this study; it has categories of major, minor, requiring medical attention, and insignificant bleeding events. Two other bleeding scales were also used to provide additional information on bleeding. The rivaroxaban program uses the International Society on Thrombosis and Haemostasis (ISTH) major bleeding event classification³³, which has categories of major bleeding events, clinically relevant non-major bleeding events, and minimal bleeding events. Bleeding events associated with CABG were evaluated separately for the ISTH scale. Finally, the Global Strategies for Opening Occluded Coronary Arteries (GUSTO) scale was also used to categorize bleeding events. For definitions of bleeding scales refer to [Appendix 1](#).

The predefined primary safety endpoint was the occurrence of TIMI major bleeding events not associated with CABG surgery (non-CABG TIMI major bleeding). Time from first dose to the first occurrence of the primary safety endpoint was analyzed and tested in the primary Treatment-Emergent Safety analysis set. All TIMI major bleeding events, including CABG-related bleeding events as defined in [Appendix 1](#), were also accessed.

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

Clinical Events Committee

As defined in the charter, the Clinical Events Committee (CEC) Members was comprised of board-eligible or board-certified cardiologists, and other specialist physicians as appropriate and necessary. Committee members did not directly enroll subjects in the study, were not involved in the study monitoring, nor did they have direct operational responsibilities for the conduct of the study. Members reviewed events that occurred post-randomization as they become available and adjudicated and classified the following events in a consistent and unbiased manner according to definitions in the CEC charter while blinded to treatment assignment:

- Death
- MI
- Stroke
- Severe recurrent ischemia
- Stent thrombosis
- Bleeding events

A total of 9,086 events were adjudicated in the study. A database sweep, using coded terms, was performed periodically to ensure all possible events were reported for adjudication.

Adverse Events Assessment

Given the extensive background of existing safety data from the previously completed Phase 3 rivaroxaban trials, along with the safety data from 3462 subjects in the Phase 2 ATLAS ACS TIMI 46 clinical trial, agreement was reached with the FDA, prior to study initiation, that only serious adverse events, adverse events leading to discontinuation of study drug, and adverse events of special interest were collected in ATLAS ACS 2 TIMI 51 study, with the exception of sites in Japan, where data on all adverse events were collected. Although not required, any nonserious adverse events of particular concern to the investigator could have been recorded on the case report form (CRF) to bring them to the attention of the Sponsor. Adverse events of special interest were defined in the study protocol as:

- Any bleeding event that did not meet the criteria for a serious adverse event
- Any liver-related adverse event, including ALT >3 times the ULN (and normal baseline) with confirmation by retesting (within 5 days)
- Any event that occurred within 30 days before a permanent discontinuation of study medication.

4.2.2. Statistical Methods

ATLAS ACS 2 TIMI 51 was a clinical outcomes study. Endpoint events were adjudicated by the independent blinded Clinical Endpoint Committee (CEC). The efficacy population included all randomized subjects, analyzed as randomized, regardless of whether subjects received treatment or not.

Sample Size Determination

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 risk reduction (RRR, i.e., hazard ratio=0.775) between combined doses of rivaroxaban and placebo arms pooled across Stratum 1 and 2, with a 2-sided type I error rate of 0.05. In Stratum 2, a total of 728 primary efficacy endpoint events were estimated to have approximately 90% power for combined doses, and 486 events at approximately 80% power for each individual dose, to detect a 22.5% RRR.

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 to compare the combined rivaroxaban (2.5 mg b.i.d. and 5 mg b.i.d.) arms with the placebo arm in order to reach the targeted study power. Due to changes in standard of care, fewer subjects were enrolled into Stratum 1 than originally estimated. Since a higher event rate was predicted for subjects in Stratum 1 than those in Stratum 2, as indicated in the protocol, the final sample size was increased to approximately 15,570, in order to allow for accrual of a total of 983 clinical endpoint events, maintaining the originally planned power of the study.

Analysis Datasets

As prospectively defined in the Statistical Analysis Plan (SAP), the efficacy population was all randomized subjects, regardless of treatment exposure. Prior to database lock, Amendment 2 to the SAP specified that subjects from 3 sites (i.e., 091001, 091019, and 091026) were to be excluded from the efficacy population due to potential trial misconduct. The safety population was defined as all randomized subjects who received at least one dose of study drug.

For the time-to-event analyses of efficacy and safety data, there were 6 analysis sets defined in the SAP. As summarized in [Table 11](#) and [Table 12](#), these analysis sets were defined both by a subject population and those events considered countable under the censoring rules for that analysis set. The events considered countable under the censoring rules for an analysis set are called ‘evaluable events’ for that analysis set.

Three of the 6 analysis sets [i.e., Modified Intent-to-Treat (mITT), Intent-to-Treat (ITT), and Intent-to-Treat Total (ITT-Total)] are all based on the efficacy population (i.e., all randomized subjects excluding sites 091001, 091019 and 091026) and differ from one another only in the censoring rules for determining evaluable events. The other 3 analysis sets [i.e., Treatment-Emergent Safety, mITT Approach Safety, and Safety-Observational period] are all based on the safety population (i.e., all randomized subjects who received at least one dose of study drug) and differ from one another only in the censoring rules for determining evaluable events.

Additional sensitivity analyses were performed for both the primary efficacy and safety endpoints which excluded subjects with major protocol deviations (i.e., Per Protocol analysis set: Subject received the incorrect medication kit, Subject was randomized but did not receive study drug and Subject did not withdraw as per protocol). For efficacy, the Per Protocol sensitivity analysis excluded subjects with major protocol deviations from the mITT analysis set. For safety,

the Per Protocol sensitivity analysis excluded subjects with major protocol deviations from the Treatment Emergent Safety analysis set.

Table 11 summarizes the analysis sets used for the primary and sensitivity analyses of the efficacy data. The primary efficacy analysis was based on the mITT analysis set. The ITT, ITT-Total, Treatment-Emergent Safety and Per Protocol analysis sets served as sensitivity analyses to the primary mITT analysis set.

**Table 11: Description of Analysis Sets Used to Analyze Efficacy Data
(Study RIVAROXACS3001)**

Analysis Set	Population	Event Censoring Rule
Primary Efficacy Analysis Set		
mITT	All randomized subjects excluding sites 091001, 091019 and 091026	Endpoint events that occurred from randomization up to the earlier date of 12:01 a.m. local time on 3 June 2011 [i.e., 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).
Efficacy Sensitivity Analysis Sets		
ITT	All randomized subjects excluding sites 091001, 091019 and 091026	Endpoint events from randomization up to 12:01 a.m. local time on 3 June 2011 [i.e., the global treatment end date].
ITT-Total	All randomized subjects excluding sites 091001, 091019 and 091026	Endpoint events from randomization up to the last contact date for each subject
Treatment-Emergent Safety	Safety population (i.e., all randomized subjects who received at least one dose of study drug excluding sites 091001, 091019 and 091026)	Endpoint events from first dose up to the date of last dose of study drug plus 2 days (or 7 days, or 30 days) for each subject
Per Protocol (mITT)	All randomized subjects excluding sites 091001, 091019 and 091026, and excluding subjects with any of the following major protocol deviations: <ul style="list-style-type: none"> – Subject received the incorrect medication kit. – Subject was randomized but did not receive study drug. – Subject did not withdraw as per protocol. 	Same censoring rules as those described above for the mITT analysis set

Note: Prior to database lock, Amendment 2 to the Statistical Analysis Plan specified that 184 subjects from 3 sites (i.e., 091001, 091019, and 091026) were to be excluded from the efficacy population due to potential trial misconduct.

Table 12 summarizes the study populations and censoring rules for the analysis sets used to analyze the safety data. The primary safety analysis set was the Treatment-Emergent Safety analysis set (note that this was also one of the sensitivity analysis sets for efficacy). This analysis

set was used for the primary safety analysis on non-CABG TIMI major bleeding, key AE summaries, and the benefit-risk analyses. The mITT Approach Safety, Safety-Observational period and Per Protocol (Treatment-Emergent Safety) analysis sets were considered secondary safety analysis sets.

**Table 12: Description of Analysis Sets Used to Analyze Safety Results
(Study RIVAROXACS3001)**

Analysis Set	Population	Event Censoring Rule
Primary Safety Analysis Set		
Treatment-Emergent Safety (2 days)	Safety population (i.e., all randomized subjects who received at least one dose of study drug)	All events from first dose up to the date of last dose of study drug plus 2 days for each subject
Secondary Safety Analysis Sets		
mITT Approach Safety	Safety population (i.e., all randomized subjects who received at least one dose of study drug)	All events that occurred from the date of the first dose up to the earlier date of 12:01 a.m. local time on 3 June 2011 [i.e., the global treatment end date], or 30 days after last dose of study drug (for subjects who discontinued study drug prematurely).
Safety-Observational period	Safety population (i.e., all randomized subjects who received at least one dose of study drug)	All events from first dose up to the last contact date for each subject
Per Protocol (TE-Safety)	Safety population (i.e., all randomized subjects who received at least one dose of study drug), excluding subjects with any of the following major protocol deviations: <ul style="list-style-type: none"> – Subject received the incorrect medication kit. – Subject did not withdraw as per protocol. 	Same censoring rule as described above for the Treatment-Emergent Safety analysis set
Treatment-Emergent Safety (7 days and 30 days)	Safety population (i.e., all randomized subjects who received at least one dose of study drug)	All events from first dose up to the date of last dose of study drug plus 7 days or 30 days for each subject

Interim Analysis

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 had occurred, in order to assess whether the study should be stopped for overwhelming superiority. A Haybittle–Peto boundary (one-sided p-value < 0.0001; z-value>3.719) was used as a stopping boundary for combined rivaroxaban doses and individual rivaroxaban doses vs. placebo primary efficacy analyses, and small adjustments were required only for the final primary efficacy analyses (the final primary efficacy analyses were then evaluated using a two-sided $\alpha=0.0499982$). The data cut-off for the interim analysis was November 29, 2010, based on 704 total primary efficacy events. The Independent Data Monitoring Committee met on January 12, 2011 to review the data. The study continued unaltered following that analysis.

Analyses of the Primary Efficacy Endpoint

As determined prior to study initiation and in concordance with advice from health authorities (including the FDA), the primary efficacy analysis was the analysis of the first occurrence of the composite of CV death, MI, or stroke in the modified Intent-to-Treat (mITT) analysis set. The mITT analysis set includes all randomized subjects and 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 ([Table 11](#))).

The primary efficacy analyses were stratified (by the intention to use a thienopyridine [yes or no]) or unstratified (Stratum 2 alone) log-rank tests between the rivaroxaban dose groups and the placebo group. A 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 (CI) for the treatment effect of the hazard ratio (HR) and the relative risk reduction (RRR) ($RRR = 100 \times [1 - HR]\%$). Kaplan-Meier curves were prepared to display the cumulative incidence of events by treatment group.

The incidence of subjects experiencing endpoint events among all subjects in each group were calculated unless otherwise specified.

Secondary Efficacy Endpoints: Definitions and Analyses

The composite secondary efficacy endpoints were:

- Secondary Efficacy Endpoint 1: composite of all-cause death, MI, or stroke
- Secondary Efficacy Endpoint 2: Net Clinical Outcome (i.e., composite of CV death, MI, ischemic stroke, or TIMI major bleeding event not associated with CABG surgery)
- Secondary Efficacy Endpoint 3: composite of CV death, MI, stroke, or severe recurrent ischemia requiring revascularization
- Secondary Efficacy Endpoint 4: composite of CV death, MI, stroke, or severe recurrent ischemia leading to hospitalization

Time from randomization to the first occurrence of each of the secondary efficacy endpoints was analyzed and tested in the mITT analysis set, as well as in the ITT (endpoint events from randomization up to the global treatment end date), ITT-Total (endpoint events from randomization up to the last contact date for each subject excluding the contact only for survival status), and Treatment-Emergent Safety analysis sets (endpoint events from first dose up to the date of last dose of study drug plus 2 days for each subject), using the same methods as those used for the primary efficacy endpoint. All efficacy analysis sets are defined in [Table 11](#).

Statistical Testing Strategy

Primary Efficacy Endpoint

During the pre-NDA meeting with the FDA (dated 10 May 2011), the Agency recommended that the initial analysis be the comparison of the combined rivaroxaban doses versus placebo; if this analysis reached statistical significance across Stratum 1 and Stratum 2 (i.e., in All Strata) then the study would be declared a success. After that, the SAP-specified hierarchical testing procedure was to be followed in Stratum 2 for the US submission; this was to ensure that any treatment benefit demonstrated in the broader population was also confirmed in stratum 2.

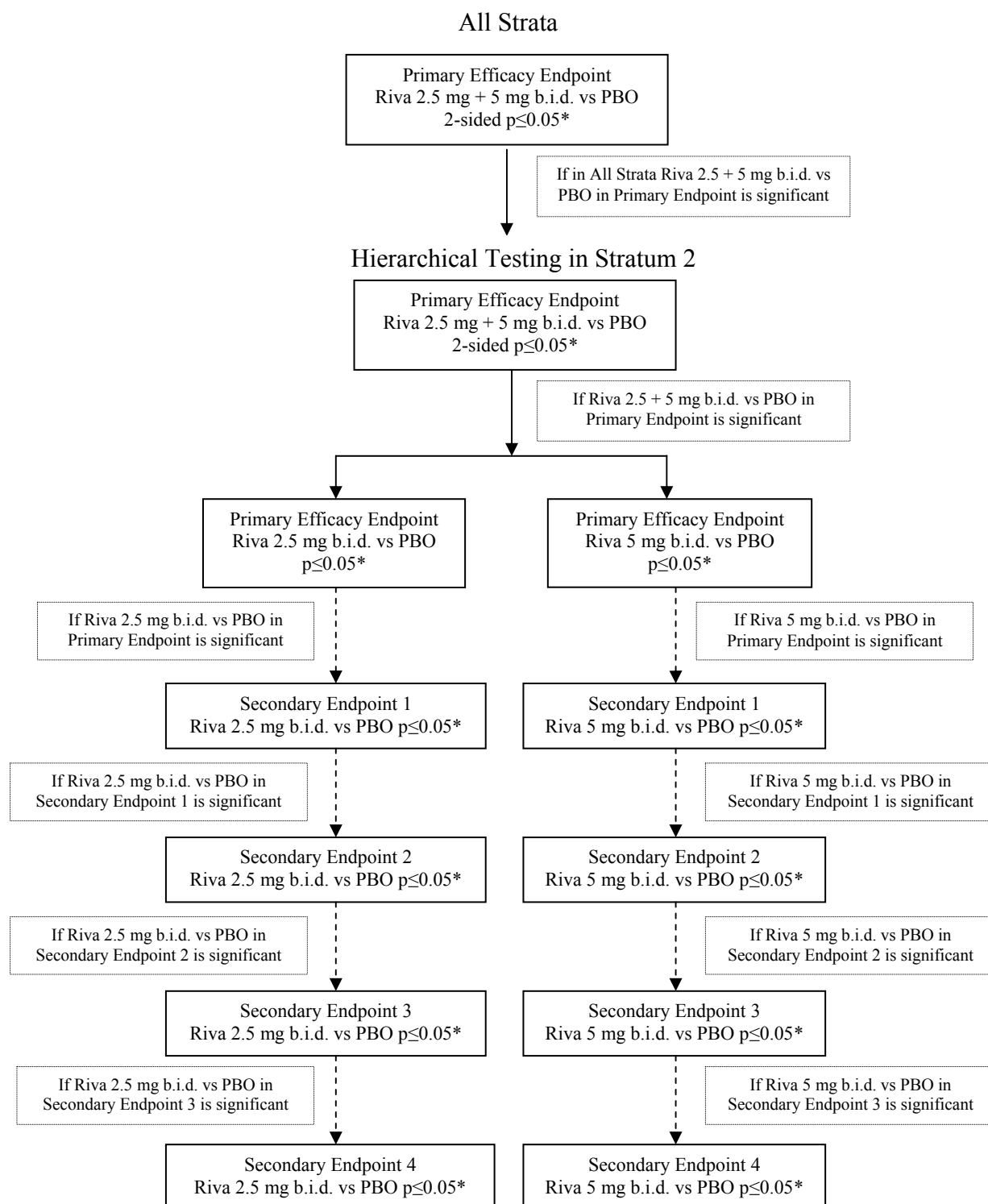
A diagram of the statistical testing procedure is shown in [Figure 5](#). In the hierarchical testing in Stratum 2, if the pooled rivaroxaban groups were found to be superior to placebo, then each of the individual rivaroxaban doses was to be tested separately at a 2-sided significance level of 0.050. This testing procedure for the primary efficacy endpoint controls the family-wise error rate in the strong sense²³.

Secondary Efficacy Endpoints

If the superiority of a dose group was declared for the primary efficacy endpoint, the secondary efficacy endpoints were tested for that dose group, at the same 2-sided significance level of 0.050, in sequential order (i.e., in the order of Secondary Efficacy Endpoint 1, 2, 3 and 4). With each dose group, a secondary endpoint could be declared statistically significant only if both the previous and the current endpoints are statistically significant. If an individual test during any step was not statistically significant, further testing could continue but significance could not be claimed. The testing procedure for the secondary efficacy endpoints does not control the family-wise error rate in the strong sense.

With the exception of the tests in [Figure 5](#), all other statistical tests performed for this study were not adjusted for multiple comparison.

**Figure 5: Diagram of Statistical Testing Procedure
(Study RIVAROXACS3001)**



* Due to a small adjustment necessitated by the interim efficacy analysis, a 2-sided $\alpha=0.0499982$ was used for the primary efficacy analysis

Note: Riva = rivaroxaban, PBO = placebo

Note: Solid line arrows indicate testing with a strong sense of control.

Analyses of Components of Composite Efficacy Endpoints

The components 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 to understand which components were primarily impacting results.

Analyses of Primary Safety Endpoint

The predefined primary safety endpoint was the occurrence of non-CABG TIMI major bleeding events. Time from first dose to the first occurrence of the primary safety endpoint was analyzed in the primary Treatment-Emergent Safety analysis set. All study sites were included in the safety analyses.

Similar to the primary efficacy endpoint analyses, a stratified (by the intention to use a thienopyridine [yes or no]) or unstratified (Stratum 2 alone) log-rank test was the primary analysis. A 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) ($RRR=100 \times [1 - \text{hazard ratio}]$) with treatment group as a class covariate with placebo as reference.

Kaplan-Meier curves were provided for the cumulative incidence of events by treatment group.

Table 12 summarizes the study populations and censoring rules for the analysis sets used to analyze the safety data. The primary safety analysis set was the Treatment-Emergent Safety analysis set (note that this was also one of the sensitivity analysis sets for efficacy). This analysis set was used for the primary safety analysis on non-CABG TIMI major bleeding, and key AE summaries. The mITT Approach Safety, Safety-Observational period and Per Protocol (Treatment-Emergent Safety) analysis sets were considered secondary safety analysis sets.

5. DEMOGRAPHICS AND DISPOSITION – ATLAS ACS 2 TIMI 51

5.1. Population Studied

ATLAS ACS 2 TIMI 51 studied 15,526 randomized subjects with ACS at 766 centers in 44 countries. Approximately 50% of all randomized subjects had STEMI, and NSTEMI and UA each comprised about 25% of the ACS index events for admitting diagnosis. Subjects received standard care for ACS. For the majority of subjects (93%) this consisted of ASA plus a thienopyridine (Stratum 2); however, investigators had discretion to enroll subjects who they intended to treat with ASA alone (Stratum 1). Initially it was estimated that approximately 15% of subjects were to be enrolled into Stratum 1; during the course of the study, it became apparent that the usage of thienopyridine was more prevalent than expected and ultimately only 7% of all randomized subjects were enrolled in Stratum 1.

The demographic and baseline characteristics were representative of a moderate-to-high-risk population of subjects with ACS. The majority of all randomized subjects had CV risk factors, such as hypertension (67.4%), diabetes mellitus (32.0%), history of MI (26.9%), or

hypercholesterolemia (48.6%). There were 60.5% subjects who had a revascularization procedure for the index event; the vast majority of these procedures were percutaneous coronary intervention (PCI). The overall low incidence of subjects with prior ischemic stroke (1.8%) and prior TIA (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 Stratum 1, 15.1% of subjects had prior stroke and 4.5% had prior TIA ([Appendix DSUB04A](#)). These patient baseline characteristics were generally similar to those described for a population of over 13,000 non-ST elevation ACS patients seen in a registry or non-registry real world setting¹⁹.

Of all randomized subjects, 74.7% were men, and the mean age was 61.8 years (range 22 to 98 years). This is consistent with the population in other contemporary ACS trials^{16,42,46}. The majority of subjects were white (73.5%). The highest enrolling region was Eastern Europe (6074 [39.1%]), followed by Asia (3195 [20.6%]) and Western Europe (2241 [14.4%]); and 874 subjects enrolled in the North America region (5.6%) ([Appendix DSUB04A](#)).

Comparing Stratum 1 with Stratum 2, there were some notable differences. Compared with Stratum 2, subjects in Stratum 1 were older (mean age 64.1 years) and there were proportionally more women (478 [45.4%]). The majority of the 1,053 subjects in Stratum 1 had an index event of unstable angina (621 [59.0%]), while 250 (23.7%) subjects had NSTEMI and 182 (17.3%) subjects had STEMI. Substantially fewer subjects (70 [6.6%]) had revascularization procedures for the index event, and higher percentages of subjects underwent CABG as part of their revascularization ([Table 13](#)). The percentage of subjects with prior histories of MI (395 [37.5%]), diabetes (418 [39.7%]) and hypertension (898 [85.3%]) in Stratum 1 were all higher than those reported in Stratum 2. As would be expected based on the protocol exclusion criteria, very few subjects in Stratum 2 had a history of prior ischemic stroke (127 [0.9%]) or TIA (94 [0.6%]) compared with Stratum 1 (159 [15.1%] prior ischemic stroke and 47 [4.5%] prior TIA) ([Appendix DSUB04A](#)).

There were no notable imbalances in baseline demographic, medical history, or index event characteristics between treatment groups in this study.

**Table 13: (TSUB06A) Description of ACS Index Events
(Study RIVAROXACS3001: All Randomized Subjects)**

	-----Total-----		
	Stratum 1 (N=1053)	Stratum 2 (N=14473)	All Strata (N=15526)
	n (%)	n (%)	n (%)
Diagnosis	1053	14473	15526
STEMI	182 (17.3)	7635 (52.8)	7817 (50.3)
NSTEMI	250 (23.7)	3729 (25.8)	3979 (25.6)
Unstable angina	621 (59.0)	3109 (21.5)	3730 (24.0)
Unstable angina	621	3109	3730
TIMI risk score 0-2	18 (2.9)	127 (4.1)	145 (3.9)
TIMI risk score 3-4	478 (77.0)	2457 (79.0)	2935 (78.7)
TIMI risk score ≥ 5	125 (20.1)	525 (16.9)	650 (17.4)
Revascularization procedure for index event*	70	9317	9387
CABG	19 (27.1)	44 (0.5)	63 (0.7)
PCI	51 (72.9)	9273 (99.5)	9324 (99.3)
PTCA/Balloon angioplasty	26 (37.1)	547 (5.9)	573 (6.1)
PCI with bare metal stent	10 (14.3)	3595 (38.6)	3605 (38.4)
PCI with drug eluting stent	5 (7.1)	2240 (24.0)	2245 (23.9)
Combo. of PCI with BM stent/ PTCA/Balloon angioplasty	5 (7.1)	1682 (18.1)	1687 (18.0)
Combo. of PCI with DE stent/ PTCA/Balloon angioplasty	5 (7.1)	1211 (13.0)	1216 (13.0)
Elevation in cardiac biomarkers at index event	1053	14464	15517
Yes	535 (50.8)	12204 (84.4)	12739 (82.1)
Fibrinolytic therapy given in case of STEMI	182	7634	7816
Yes	52 (28.6)	1951 (25.6)	2003 (25.6)
Baseline CABG for index event**	1053	14472	15525
Yes	19 (1.8)	44 (0.3)	63 (0.4)
Baseline PCI for index event**	1053	14472	15525
Yes	51 (4.8)	9273 (64.1)	9324 (60.1)

Note: Percentages calculated with the number of subjects in each category and treatment group as denominator.

Note: BM = Bare metal; DE = Drug eluting.

Note: * This is total number of subjects with any revascularization procedures.

Note: ** This is number of subjects with non-missing data including subjects answered no on having a revascularization procedure associated with index event.

Note: ASA = Acetylsalicylic acid; Thieno = Thienopyridine; CABG = Coronary artery bypass grafting.

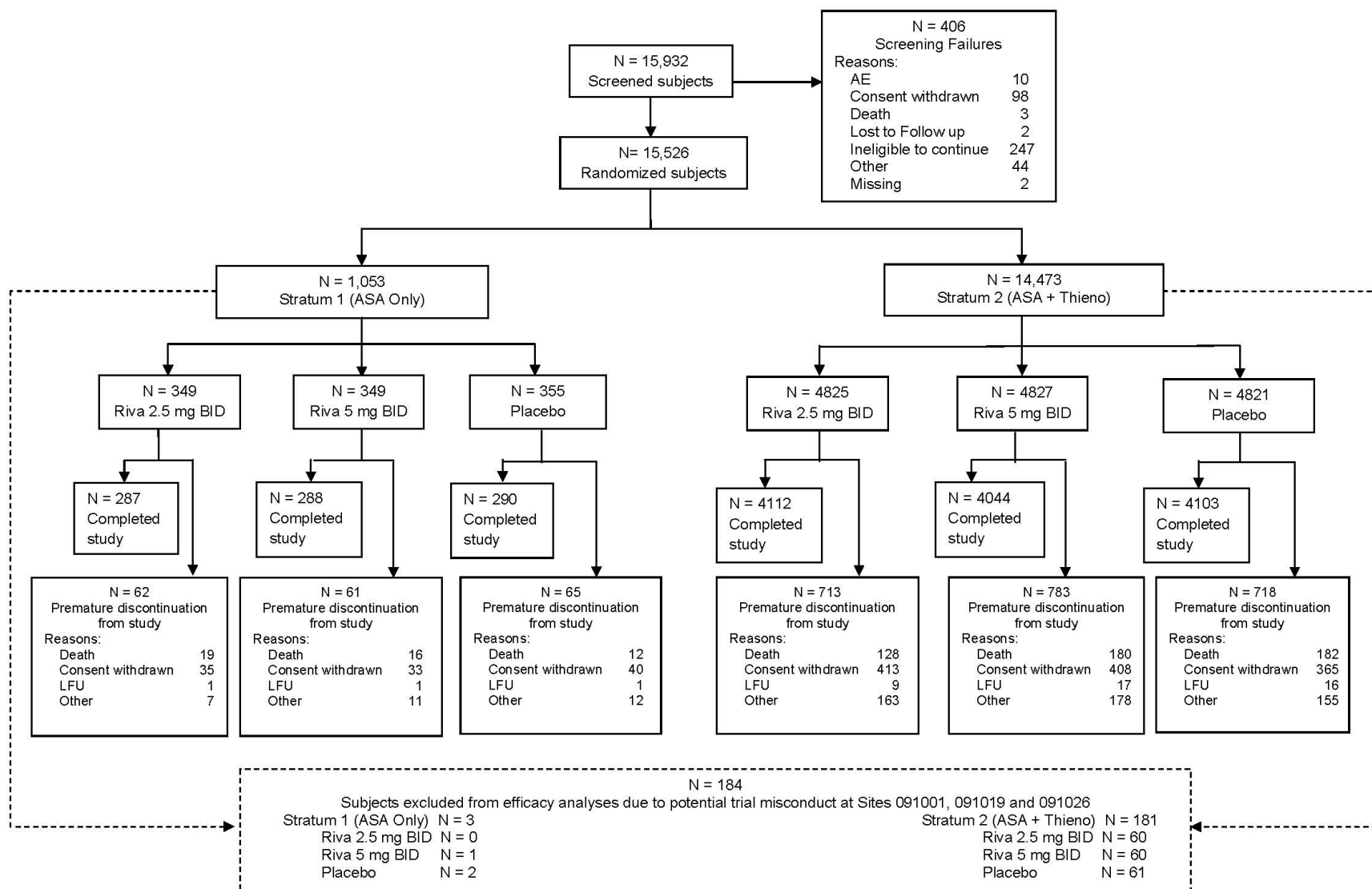
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5.2. Disposition

The study was conducted between 26 November 2008 and 19 September 2011. A total of 15,932 subjects were screened for eligibility; 15,526 (97.5%) subjects were randomized at 766 centers in 44 countries and 406 (2.5%) subjects were screening failures. The most frequent reasons for screening failures were “Subject ineligible to continue” (247 [1.6%]) and “Consent withdrawn” (98 [0.6%]).

The disposition of subjects randomized into the study is summarized in [Figure 6](#). The vast majority of subjects were in Stratum 2 (ASA + thienopyridine). Within each stratum, the randomization to each of 3 treatment groups was well balanced. The percentage of subjects who completed the study, as well as the percentage of subjects who discontinued prematurely from the study, were similar across treatment groups and strata.

**Figure 6: Subject Disposition
(Study RIVAROXACS3001)**



5.2.1. Premature Discontinuation From Study

As shown in [Table 14](#):

- Of the 15,526 subjects randomized, 13,124 (84.5%) subjects completed the study (note that subjects who died during the study [3.5% of all subjects] were not considered to have completed the study). These included:
 - Subjects who completed both the double-blinded treatment period and the follow-up period (11,026 subjects [71.0% of all randomized subjects]);
 - Subjects who discontinued the double-blinded treatment but completed the follow-up period (2,098 subjects [13.5% of all randomized subjects]).
- The percentage of subjects who completed the study was balanced among treatment groups (rivaroxaban 2.5 mg b.i.d.: 85.0%, rivaroxaban 5 mg b.i.d.: 83.7%; placebo: 84.9%). The most common reason overall for not completing the study was consent withdrawn (1294 [8.3%]).
- It should be noted that in some other contemporary trials in ACS, the definition of subjects who completed the study included subjects who completed the double-blind treatment period but did not complete the follow-up period, subjects who died, and subjects who prematurely discontinued from the study but were followed up and for whom vital status information was available at the end of the study. In contrast, subjects with these aforementioned statuses were considered as premature discontinuation in ATLAS ACS 2 TIMI 51.
- The percentage of subjects who withdrew consent was slightly higher in the 2.5 mg b.i.d. (8.7%) and 5 mg b.i.d (8.5%) groups compared with placebo (7.8%).
 - An extensive plan was put in effect to obtain vital status information on consent withdrawn subjects; vital status of subjects who withdrew consent was collected wherever permitted by local regulatory authorities ([Table 15](#)).
 - Vital Status at End of Study - [Table 16](#) summarizes the vital status at end of study for subjects who withdrew consent for participation in the study, as well as the percentage of these subjects who had an endpoint event (i.e., stroke or MI) prior to withdrawing consent. Permission to contact subjects was received from the respective HA/EC/IRBs for 399 (30.8%) of the 1,294 consent withdrawn subjects. Of these 399 subjects, 183 consent withdrawn subjects agreed to be contacted and signed the permission document allowing their vital status information to be collected. The sponsor was not permitted, either by the regional EC/IRB or the subject, to attempt to obtain vital status information on the remaining 1,111 subjects who withdrew consent. Of the 183 consent withdrawn subjects the sponsor had permission to contact, 177 subjects were confirmed to be alive. Six subjects were unable to be contacted after the global treatment end date. Overall, the percentage of subjects with confirmed vital status information was balanced across strata and treatment groups. In All Strata, 55, 58 and 70 subjects signed agreement for vital status in the 2.5 mg b.i.d., 5 mg b.i.d. and placebo groups, respectively, and among them, 54, 57 and 66 were confirmed alive.

It was of interest to explore the extent to which consent withdrawals and other premature discontinuation from study might represent potentially missing data, and how this would impact the efficacy results. A sensitivity analysis addressing this topic is discussed in Section 6.2.1.2.

**Table 14: (TSUB08A) Primary Reasons for Premature Discontinuation from Study
(Study RIVAROXACS3001; All Randomized Subjects)**

Subject Stratum: All Strata					
Status Standardized Disposition Term Reason	----- Rivaroxaban -----				Total (N=15526) n (%)
	2.5 mg BID (N=5174) n (%)	5 mg BID (N=5176) n (%)	Combined (N=10350) n (%)	Placebo (N=5176) n (%)	
Completed study	4399 (85.0)	4332 (83.7)	8731 (84.4)	4393 (84.9)	13124 (84.5)
Completed double blind treatment period	3711 (71.7)	3570 (69.0)	7281 (70.3)	3745 (72.4)	11026 (71.0)
Not completed treatment period	688 (13.3)	762 (14.7)	1450 (14.0)	648 (12.5)	2098 (13.5)
Prematurely discontinued from study	775 (15.0)	844 (16.3)	1619 (15.6)	783 (15.1)	2402 (15.5)
Death	147 (2.8)	196 (3.8)	343 (3.3)	194 (3.7)	537 (3.5)
Consent withdrawn	448 (8.7)	441 (8.5)	889 (8.6)	405 (7.8)	1294 (8.3)
Lost to follow-up	10 (0.2)	18 (0.3)	28 (0.3)	17 (0.3)	45 (0.3)
Other	170 (3.3)	189 (3.7)	359 (3.5)	167 (3.2)	526 (3.4)
Closed/retired sites	37 (0.7)	38 (0.7)	75 (0.7)	42 (0.8)	117 (0.8)
Long travel/relocation/welfare	12 (0.2)	15 (0.3)	27 (0.3)	15 (0.3)	42 (0.3)
Medical reasons/unblinded/prohibited meds	25 (0.5)	26 (0.5)	51 (0.5)	16 (0.3)	67 (0.4)
Never received study medication	2 (<0.1)	3 (0.1)	5 (<0.1)	4 (0.1)	9 (0.1)
Not meeting inclusion/exclusion	25 (0.5)	21 (0.4)	46 (0.4)	16 (0.3)	62 (0.4)
Subject choice/ Non compliance	69 (1.3)	86 (1.7)	155 (1.5)	74 (1.4)	229 (1.5)

Note: Percentages calculated with the number of subjects in each treatment group as denominator.

Note: Discontinued subjects include subjects who were not followed-up till the end of study (global treatment end date +30 days).

Note: ASA = Acetylsalicylic acid; Thieno = Thienopyridine.

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**Table 15: (TSUB10) Consent Withdrawal Effort
(Study RIVAROXACS3001; All Randomized Subjects)**

Subject Stratum Parameter	----- Rivaroxaban -----				Total (N=15526) n (%)
	2.5 mg BID (N=5174) n (%)	5 mg BID (N=5176) n (%)	Combined (N=10350) n (%)	Placebo (N=5176) n (%)	
All Strata	5174	5176	10350	5176	15526
Consent withdrawn subjects	448	441	889	405	1294
Subjects received approval from HA/EC/IRB for vital status collection	128 (28.6)	127 (28.8)	255 (28.7)	144 (35.6)	399 (30.8)
Subjects signed agreement for vital status	55 (12.3)	58 (13.2)	113 (12.7)	70 (17.3)	183 (14.1)
ASA	349	349	698	355	1053
Consent withdrawn subjects	35	33	68	40	108
Subjects received approval from HA/EC/IRB for vital status collection	11 (31.4)	12 (36.4)	23 (33.8)	16 (40.0)	39 (36.1)
Subjects signed agreement for vital status	2 (5.7)	3 (9.1)	5 (7.4)	5 (12.5)	10 (9.3)
ASA + Thieno	4825	4827	9652	4821	14473
Consent withdrawn subjects	413	408	821	365	1186
Subjects received approval from HA/EC/IRB for vital status collection	117 (28.3)	115 (28.2)	232 (28.3)	128 (35.1)	360 (30.4)
Subjects signed agreement for vital status	53 (12.8)	55 (13.5)	108 (13.2)	65 (17.8)	173 (14.6)

Note: Percentages calculated with the number of consent withdrawal subjects in each subject stratum and treatment group as denominator.

Note: ASA = Acetylsalicylic acid; Thieno = Thienopyridine.

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**Table 16: (TSUB28A) Status for Consent Withdrawn Subjects at End of Study
(Study RIVAROXACS3001; All Randomized Subjects)**

Subject Stratum Standardized Disposition Term Reason	----- Rivaroxaban -----			Placebo (N=5176) n (%)	Total (N=15526) n (%)
	2.5 mg BID (N=5174) n (%)	5 mg BID (N=5176) n (%)	Combined (N=10350) n (%)		
All Strata	5174	5176	10350	5176	15526
Consent withdrawn	448	441	889	405	1294
Vital status: Alive	54 (12.1)	57 (12.9)	111 (12.5)	66 (16.3)	177 (13.7)
Vital status: Unknown	394 (87.9)	384 (87.1)	778 (87.5)	339 (83.7)	1117 (86.3)
With CV events before discontinuation	23 (5.1)	16 (3.6)	39 (4.4)	22 (5.4)	61 (4.7)
Without CV events before discontinuation	425 (94.9)	425 (96.4)	850 (95.6)	383 (94.6)	1233 (95.3)
ASA	349	349	698	355	1053
Consent withdrawn	35	33	68	40	108
Vital status: Alive	2 (5.7)	2 (6.1)	4 (5.9)	5 (12.5)	9 (8.3)
Vital status: Unknown	33 (94.3)	31 (93.9)	64 (94.1)	35 (87.5)	99 (91.7)
With CV events before discontinuation	2 (5.7)	3 (9.1)	5 (7.4)	5 (12.5)	10 (9.3)
Without CV events before discontinuation	33 (94.3)	30 (90.9)	63 (92.6)	35 (87.5)	98 (90.7)
ASA + Thieno	4825	4827	9652	4821	14473
Consent withdrawn	413	408	821	365	1186
Vital status: Alive	52 (12.6)	55 (13.5)	107 (13.0)	61 (16.7)	168 (14.2)
Vital status: Unknown	361 (87.4)	353 (86.5)	714 (87.0)	304 (83.3)	1018 (85.8)
With CV events before discontinuation	21 (5.1)	13 (3.2)	34 (4.1)	17 (4.7)	51 (4.3)
Without CV events before discontinuation	392 (94.9)	395 (96.8)	787 (95.9)	348 (95.3)	1135 (95.7)

Note: Percentages calculated with the number of consent withdrawn subjects in each subject stratum and treatment group as denominator.

Note: CV (Cardiovascular) events are myocardial infarction or stroke before consent withdrawal.

Note: The vital status is subject's survival status at the global treatment end date.

Note: ASA = Acetylsalicylic acid; Thieno = Thienopyridine; CW = Consent withdrawn.

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5.2.2. Premature Discontinuation From Study Treatment

The double-blind treatment period started at randomization and ended at the global treatment end date (the projected date of accrual of at least 983 primary efficacy endpoint events anticipated to be adjudicated as mITT events). Subjects who permanently discontinued study drug before the end of treatment visit were considered to have prematurely discontinued during the double-blind treatment period. It should be noted that:

- The protocol defined death as one of the reasons for premature discontinuation of study drug, and thus, subjects who died prior to the global treatment end date (3.5% of all subjects) were counted as having prematurely discontinued treatment.

In All Strata, 11,119 (72.4%) of the 15,350 subjects in the safety analysis set completed the double-blind treatment period (3739 [73.1%] rivaroxaban 2.5 mg b.i.d., 3606 [70.6%] rivaroxaban 5 mg b.i.d. and 3774 [73.6%] placebo). The percentage of subjects who discontinued treatment due to subject consent withdrawn, lost to follow-up and other reasons was balanced between rivaroxaban and placebo treatment groups. Fewer subjects discontinued prematurely due to death in the 2.5 mg b.i.d. group compared with the 5 mg b.i.d. or placebo groups; this

corresponds to a lower incidence of both CV deaths and all-cause mortality in the 2.5 mg b.i.d. rivaroxaban group.

In All Strata, more rivaroxaban-treated subjects (1007 [9.8%]) prematurely discontinued study drug due to an adverse event from the double-blind treatment period than placebo subjects (374 [7.3%], and the percentage was higher in the 5 mg b.i.d. group (559 [10.9%]) than in the 2.5 mg b.i.d. group (448 [8.8%]). This is due, at least in part, to a higher percentage of bleeding-related treatment-emergent adverse events leading to discontinuation observed in the 5 mg b.i.d. group (255 [5.0%]) compared with the 2.5 mg b.i.d. (183 [3.6%]) and placebo (92 [1.8%]) groups ([Table 17](#)).

**Table 17: (TSUB07B) Primary Reasons for Premature Discontinuation From Double-Blind Treatment Period
(Study RIVAROXACS3001: Safety Analysis Set)**

Status Standardized Disposition Term Reason	----- Rivaroxaban -----			Placebo (N=5125) n (%)	Total (N=15350) n (%)
	2.5 mg BID (N=5115) n (%)	5 mg BID (N=5110) n (%)	Combined (N=10225) n (%)		
Subject Stratum: All Strata	5115	5110	10225	5125	15350
Completed double-blind treatment period	3739 (73.1)	3606 (70.6)	7345 (71.8)	3774 (73.6)	11119 (72.4)
Prematurely discontinued treatment	1376 (26.9)	1504 (29.4)	2880 (28.2)	1351 (26.4)	4231 (27.6)
Adverse event	448 (8.8)	559 (10.9)	1007 (9.8)	374 (7.3)	1381 (9.0)
Death	90 (1.8)	132 (2.6)	222 (2.2)	138 (2.7)	360 (2.3)
Consent withdrawn	241 (4.7)	222 (4.3)	463 (4.5)	220 (4.3)	683 (4.4)
Lost to follow-up	8 (0.2)	16 (0.3)	24 (0.2)	16 (0.3)	40 (0.3)
Other	589 (11.5)	575 (11.3)	1164 (11.4)	603 (11.8)	1767 (11.5)
Subject Stratum: ASA	343	342	685	352	1037
Completed double-blind treatment period	247 (72.0)	255 (74.6)	502 (73.3)	254 (72.2)	756 (72.9)
Prematurely discontinued treatment	96 (28.0)	87 (25.4)	183 (26.7)	98 (27.8)	281 (27.1)
Adverse event	24 (7.0)	27 (7.9)	51 (7.4)	24 (6.8)	75 (7.2)
Death	9 (2.6)	8 (2.3)	17 (2.5)	8 (2.3)	25 (2.4)
Consent withdrawn	22 (6.4)	13 (3.8)	35 (5.1)	24 (6.8)	59 (5.7)
Lost to follow-up	1 (0.3)	1 (0.3)	2 (0.3)	1 (0.3)	3 (0.3)
Other	40 (11.7)	38 (11.1)	78 (11.4)	41 (11.6)	119 (11.5)
Subject Stratum: ASA + Thieno	4772	4768	9540	4773	14313
Completed double-blind treatment period	3492 (73.2)	3351 (70.3)	6843 (71.7)	3520 (73.7)	10363 (72.4)
Prematurely discontinued treatment	1280 (26.8)	1417 (29.7)	2697 (28.3)	1253 (26.3)	3950 (27.6)
Adverse event	424 (8.9)	532 (11.2)	956 (10.0)	350 (7.3)	1306 (9.1)
Death	81 (1.7)	124 (2.6)	205 (2.1)	130 (2.7)	335 (2.3)
Consent withdrawn	219 (4.6)	209 (4.4)	428 (4.5)	196 (4.1)	624 (4.4)
Lost to follow-up	7 (0.1)	15 (0.3)	22 (0.2)	15 (0.3)	37 (0.3)
Other	549 (11.5)	537 (11.3)	1086 (11.4)	562 (11.8)	1648 (11.5)

Note: Percentages calculated with the number of subjects in each treatment group as denominator.

Note: ASA = Acetylsalicylic acid; Thieno = Thienopyridine.

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6. CLINICAL EFFICACY – ATLAS ACS 2 TIMI 51

The number of subjects included in the mITT analysis set for efficacy analyses are 15,342 (rivaroxaban 2.5 mg b.i.d: 5114, rivaroxaban 5 mg b.i.d: 5,115, placebo: 5113). A total of 184 subjects from 3 sites (091001, 091019, and 091026) were excluded from the efficacy analyses due to potential trial misconduct. Sensitivity analysis with the 3 sites included in the mITT analysis set provided similar results and did not change the conclusions drawn from the analysis excluding these sites.

In this document, the incidence of subjects experiencing endpoint events among all subjects in each group are generally provided unless otherwise specified. Since the median exposure to study treatment was slightly more than a year (390.5 days for all treated subjects, see [Table 34](#)), the event rate calculated as per 100 patient-year is in general slightly lower than the incidence.

As mentioned earlier, presentation of efficacy data is focused on the rivaroxaban 2.5 mg b.i.d. treatment group, compared with placebo, in All Strata and Stratum 2. Results in Stratum 1 are summarized separately in Section [6.7](#).

6.1. Statistical Testing Results

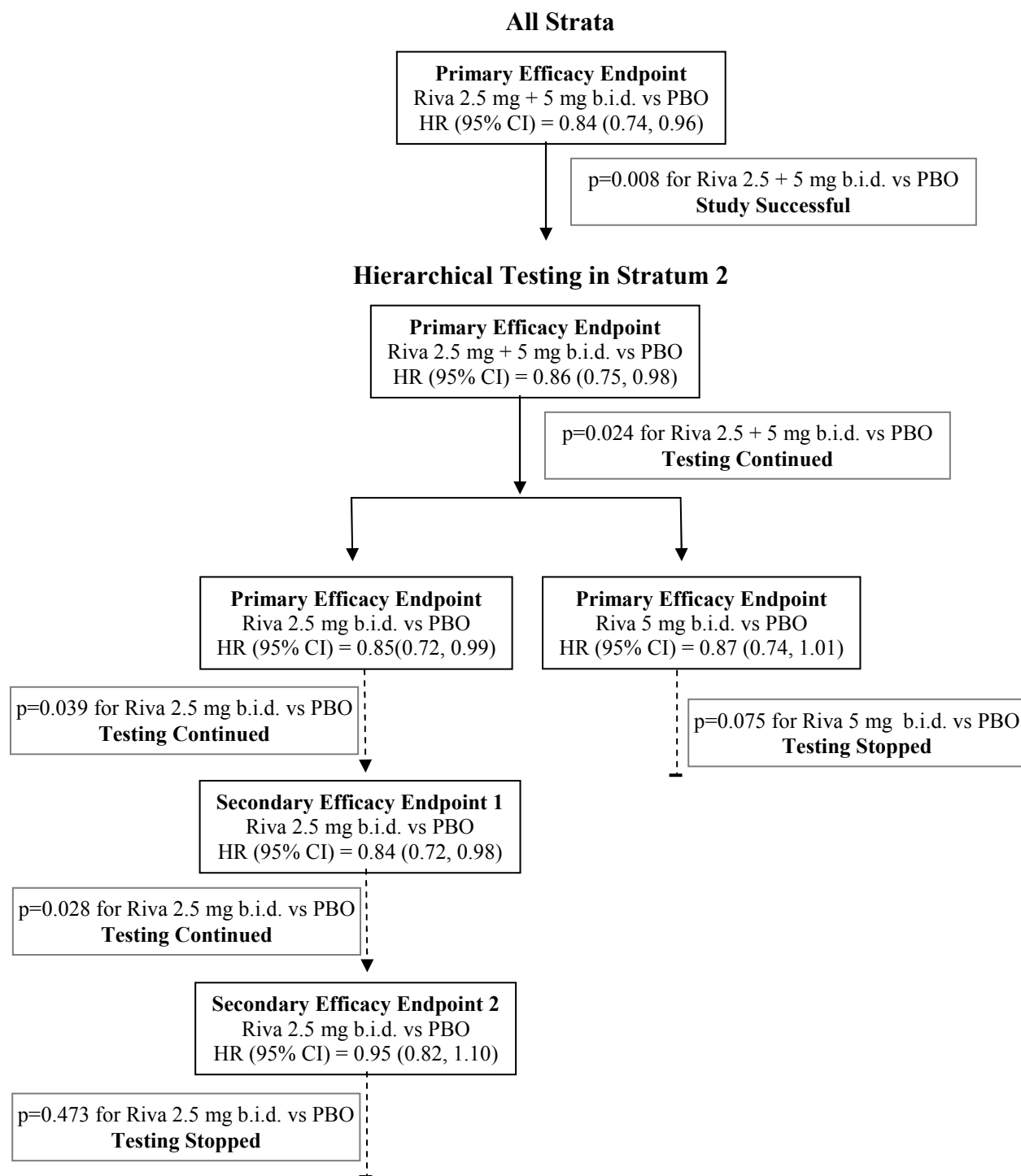
The statistical testing strategy was described in Section [4.2.2.](#), and illustrated in [Figure 5](#). After the pre-NDA meeting with the FDA (dated 10 May 2011), the Agency suggested that the study was to be determined a success if the initial analysis of the combined rivaroxaban doses reached statistical significance compared with placebo for the primary efficacy endpoint in All Strata. After that, the sequential testing procedure was to be followed in Stratum 2. If the combined rivaroxaban doses were found to be superior to placebo for primary efficacy endpoint, then each of the individual rivaroxaban doses was to be tested. If the superiority of a dose group was declared for the primary efficacy endpoint, the secondary efficacy endpoints were to be tested for that dose group, in sequential order. Testing on the secondary efficacy endpoints would continue until statistical significance failed to be met, at which point formal hierarchical testing would stop within the dose group.

The combined rivaroxaban doses showed superiority to placebo for primary efficacy endpoint in All Strata (6.1% rivaroxaban vs. 7.4% placebo; HR: 0.84, 95% CI: 0.74, 0.96; p=0.008), demonstrating the success of ATLAS ACS 2 TIMI 51 study.

[Figure 7](#) shows the results of the hierarchical testing in Stratum 2. The combined rivaroxaban doses met statistical significance. Further, the 2.5 mg b.i.d. dose met statistical significance for the primary efficacy and the Secondary Efficacy Endpoint 1, and testing stopped at Secondary Efficacy Endpoint 2. The 5 mg b.i.d. dose did not meet statistical significance for the primary efficacy endpoint, and the statistical testing was therefore stopped.

Even though they are not all part of the formal statistical testing, the results for analyses of all secondary efficacy endpoints were performed and they are described in Section [6.3](#).

Figure 7: Results of Statistical Testing Procedure
(Study RIVAROXACS3001; mITT (Excluding Sites 091001, 091019 and 091026) Analysis Set)



Note: The primary efficacy endpoint was the composite of cardiovascular death, myocardial infarction, or stroke.

The Secondary Efficacy Endpoint 1 was the composite of all-cause death, myocardial infarction, or stroke.

The Secondary Efficacy Endpoint 2 was the composite of cardiovascular death, myocardial infarction, ischemic stroke or non-CABG TIMI major bleeding events.

Note: HR= hazard ratio, Riva = rivaroxaban, PBO = placebo

Source: TEFF02A, TEFF05A.

6.2. Primary Efficacy Endpoint Analyses

The primary objective of this study was to demonstrate that treatment with rivaroxaban is superior to treatment with placebo in addition to standard care in reducing the risk of the primary efficacy endpoint (i.e., the composite of CV death, MI, or stroke) in subjects with a recent ACS. This objective was met for the combined rivaroxaban doses in All Strata and Stratum 2. For individual doses, in All Strata, both the 2.5 mg b.i.d. dose and the 5 mg b.i.d dose met the objective, and the 2.5 mg b.i.d. dose also met the objective in Stratum 2.

In All Strata, the occurrence of primary efficacy endpoint events was significantly reduced in the combined rivaroxaban groups compared with placebo (6.1% rivaroxaban vs. 7.4% placebo; HR: 0.84, 95% CI: 0.74, 0.96; $p=0.008$), in the 2.5 mg b.i.d. group (HR: 0.84, 95% CI: 0.72, 0.97; $p=0.020$), as well as the 5 mg b.i.d. group (HR: 0.85, 95% CI: 0.73, 0.98; $p=0.028$) compared with the placebo group. In All Strata, the effect of rivaroxaban 2.5 mg b.i.d. on the primary efficacy endpoint was largely driven by the reduction in CV deaths (HR: 0.66, 95% CI: 0.51, 0.86), whereas the effect in the 5 mg b.i.d. group was largely driven by the reduction in MIs (HR: 0.79, 95% CI: 0.65, 0.97) ([Table 18](#)).

In Stratum 2, the results for the combined rivaroxaban groups mirrored those observed for All Strata. Rivaroxaban was significantly superior to placebo in reducing the occurrence of the composite endpoint of CV death, MI, or stroke for the combined doses (6.0% rivaroxaban vs. 7.1% placebo; HR: 0.86, 95% CI: 0.75, 0.98; $p=0.024$) and in the 2.5 mg b.i.d. group (6.0% rivaroxaban vs. 7.1% placebo; HR: 0.85, 95% CI: 0.72, 0.99; $p=0.039$). The 5 mg b.i.d. group had numerically fewer events than the placebo group (6.1% rivaroxaban vs. 7.1% placebo), but did not reach statistical significance (HR: 0.87, 95% CI: 0.74, 1.01; $p=0.075$). In Stratum 2, the effect of rivaroxaban 2.5 mg b.i.d. on the primary efficacy endpoint was largely driven by the reduction in CV deaths (HR: 0.62, 95% CI: 0.47, 0.82) ([Table 18](#)).

[Figure 8](#) shows the Kaplan-Meier estimates of the primary efficacy endpoint by treatment group. The separation between the curves for rivaroxaban 2.5 mg b.i.d. and placebo group started as early as Day 30 and maintained through the course of the study.

A log-log plot of survival function regarding the primary efficacy endpoint for All Strata in the mITT analysis set is provided in [Figure 9](#). Overall, the plotted lines are relatively parallel across treatment group, which confirms the proportional hazard assumption, and suggests a relatively constant hazard ratio over time, which supports the use of the Cox model for the primary efficacy time-to-first-event analysis.

**Table 18: (TEFF02A) Effect of Rivaroxaban Compared with Placebo on the Primary Efficacy Endpoint as Adjudicated by the CEC (First Occurrence of Cardiovascular Death, MI, Stroke)
(Study RIVAROXACS3001; mITT (Excluding Sites 091001, 091019 and 091026) Analysis Set)**

Subject Stratum Parameter	----- Rivaroxaban -----				-- 2.5 mg BID vs. Placebo --		-- 5 mg BID vs. Placebo --		-- Combined vs. Placebo --	
	2.5 mg BID (N=5114) n(%)	5 mg BID (N=5115) n(%)	Combined (N=10229) n(%)	Placebo (N=5113) n(%)	HR (95% CI)	Log-Rank P-value	HR (95% CI)	Log-Rank P-value	HR (95% CI)	Log-Rank P-value
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)	0.020	0.85 (0.73,0.98)	0.028	0.84 (0.74,0.96)	0.008
CV_Dth	94(1.8)	132(2.6)	226(2.2)	143(2.8)	0.66 (0.51,0.86)	0.002	0.94 (0.75,1.20)	0.633	0.80 (0.65,0.99)	0.038
MI	205(4.0)	179(3.5)	384(3.8)	229(4.5)	0.90 (0.75,1.09)	0.270	0.79 (0.65,0.97)	0.020	0.85 (0.72,1.00)	0.047
Stroke	46(0.9)	54(1.1)	100(1.0)	41(0.8)	1.13 (0.74,1.73)	0.562	1.34 (0.90,2.02)	0.151	1.24 (0.86,1.78)	0.246
ASA	349	348	697	353						
Primary	27(7.7)	24(6.9)	51(7.3)	36(10.2)	0.74 (0.45,1.22)	0.234	0.64 (0.38,1.07)	0.089	0.69 (0.45,1.05)	0.084
CV_Dth	12(3.4)	9(2.6)	21(3.0)	10(2.8)	1.20 (0.52,2.77)	0.673	0.89 (0.36,2.20)	0.805	1.04 (0.49,2.21)	0.913
MI	16(4.6)	10(2.9)	26(3.7)	22(6.2)	0.72 (0.38,1.37)	0.310	0.44 (0.21,0.93)	0.026	0.58 (0.33,1.02)	0.053
Stroke	2(0.6)	8(2.3)	10(1.4)	7(2.0)	0.28 (0.06,1.37)	0.095	1.13 (0.41,3.12)	0.812	0.71 (0.27,1.86)	0.483
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)	0.039	0.87 (0.74,1.01)	0.075	0.86 (0.75,0.98)	0.024
CV_Dth	82(1.7)	123(2.6)	205(2.2)	133(2.8)	0.62 (0.47,0.82)	0.0006	0.95 (0.74,1.21)	0.669	0.78 (0.63,0.97)	0.028
MI	189(4.0)	169(3.5)	358(3.8)	207(4.3)	0.92 (0.75,1.12)	0.401	0.83 (0.68,1.02)	0.077	0.88 (0.74,1.04)	0.131
Stroke	44(0.9)	46(1.0)	90(0.9)	34(0.7)	1.31 (0.84,2.05)	0.238	1.39 (0.89,2.16)	0.144	1.35 (0.91,2.00)	0.135

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: CV_Dth: Cardiovascular death including unknown death; MI: Myocardial infarction.

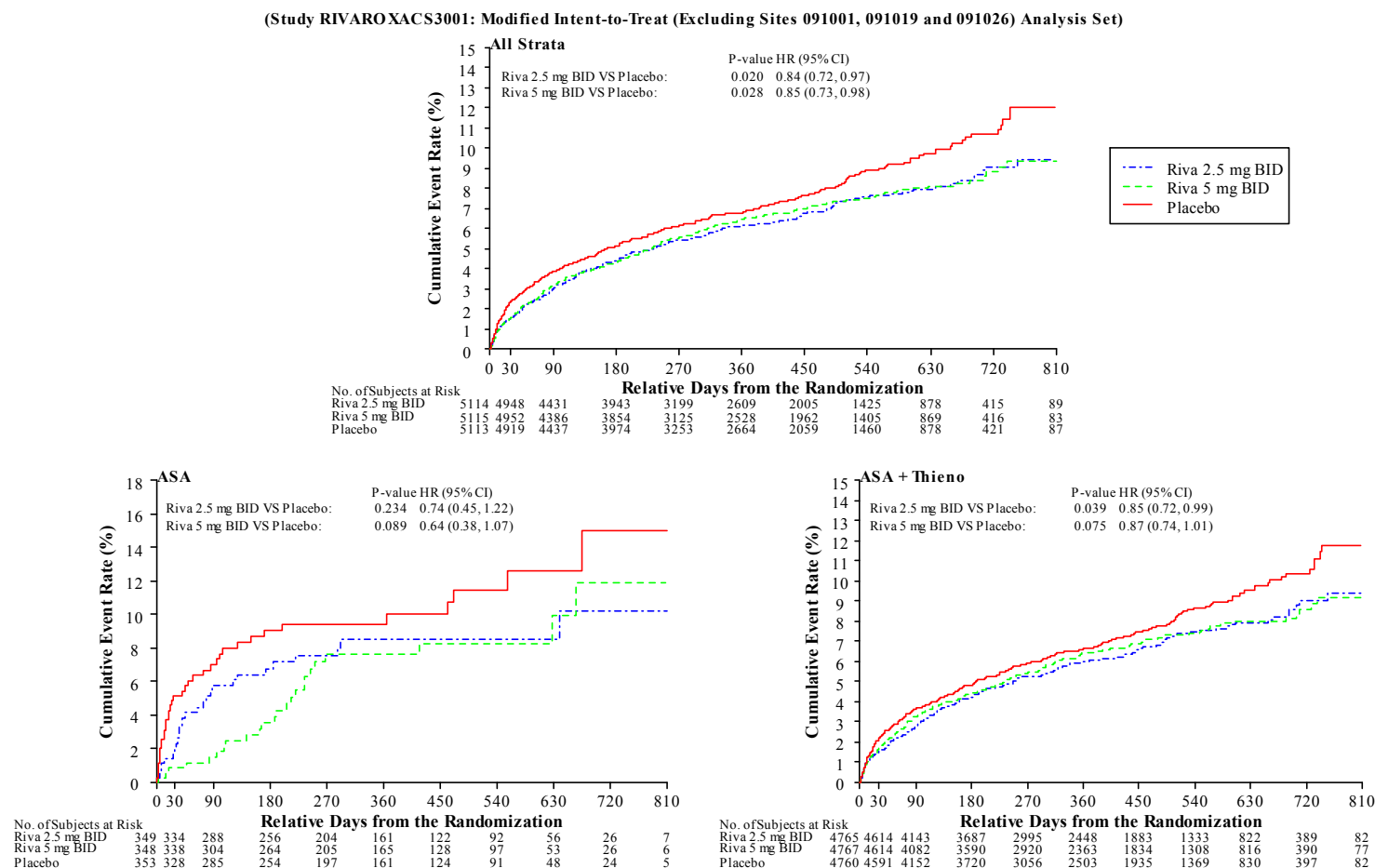
Note: HR (95% CI): Hazard ratios (95% confidence interval) as compared with placebo arm are based on the (stratified, only for all strata) Cox proportional hazards model.

Note: Log-Rank P-value: P-values (two-sided) as compared with placebo arm are based on the (stratified, only for all strata) log rank test.

Note: ASA = Acetylsalicylic acid; Thieno = Thienopyridine.

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Figure 8: (Feff01a) Kaplan-Meier Estimates of The Primary Efficacy Endpoint (Cardiovascular Death, MI, Stroke) by Stratum as Adjudicated by the CEC (Study Rivaroxacs3001: mITT[Excluding Sites 091001, 091019 And 091026] Analysis Set)

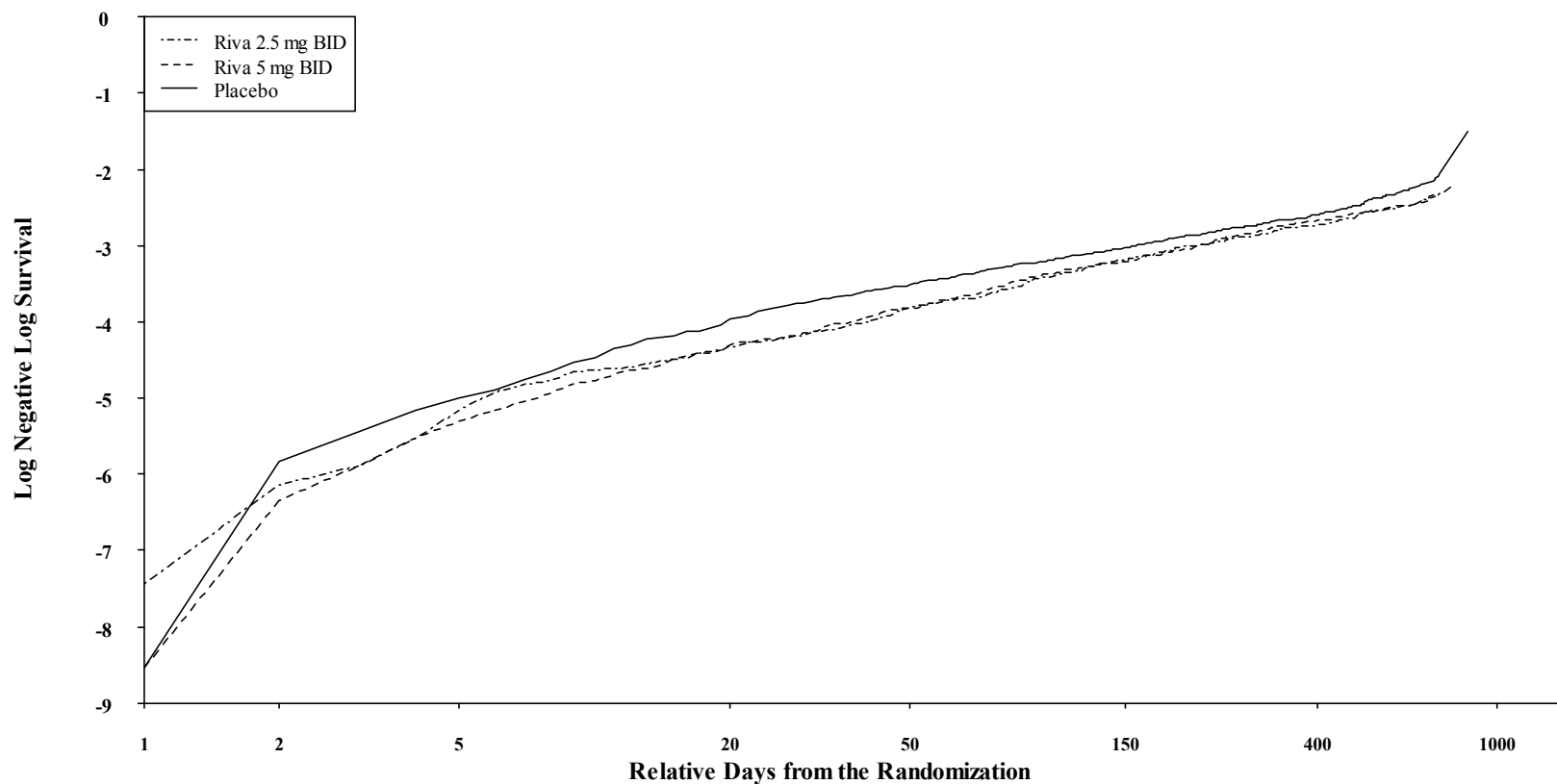


Note: The data shown are for all randomized subjects and the endpoint events occurring at or after randomization and the earliest date of the global treatment end date, 30 days after study drug was prematurely discontinued and 30 days after randomization for those subjects who were randomized but not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

Note: P-value is based on (stratified, only for all strata) log-rank test and HR (95% CI) is based on (stratified, only for all strata) Cox proportional hazards model.

Note: KM curves for all treatment groups are not displayed when number of subjects at risk in any treatment group reaches less than 50 or 1 percent of that at the starting time point whichever is less.

**Figure 9: (FEFF00A) Log (-log) Plots of Survival Function Regarding the Primary Efficacy Endpoint (First Occurrence of Cardiovascular Death, MI, Stroke) as Adjudicated by the CEC in All Strata
(Study: JNJ39039039C-ACS3001: Modified Intent-to-Treat (Excluding Sites 091001, 091019 and 091026) Analysis Set)**



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: The x-axis is on a logarithmic scale of relative days from the randomization.

6.2.1. Sensitivity Analysis of the Primary Efficacy Endpoint

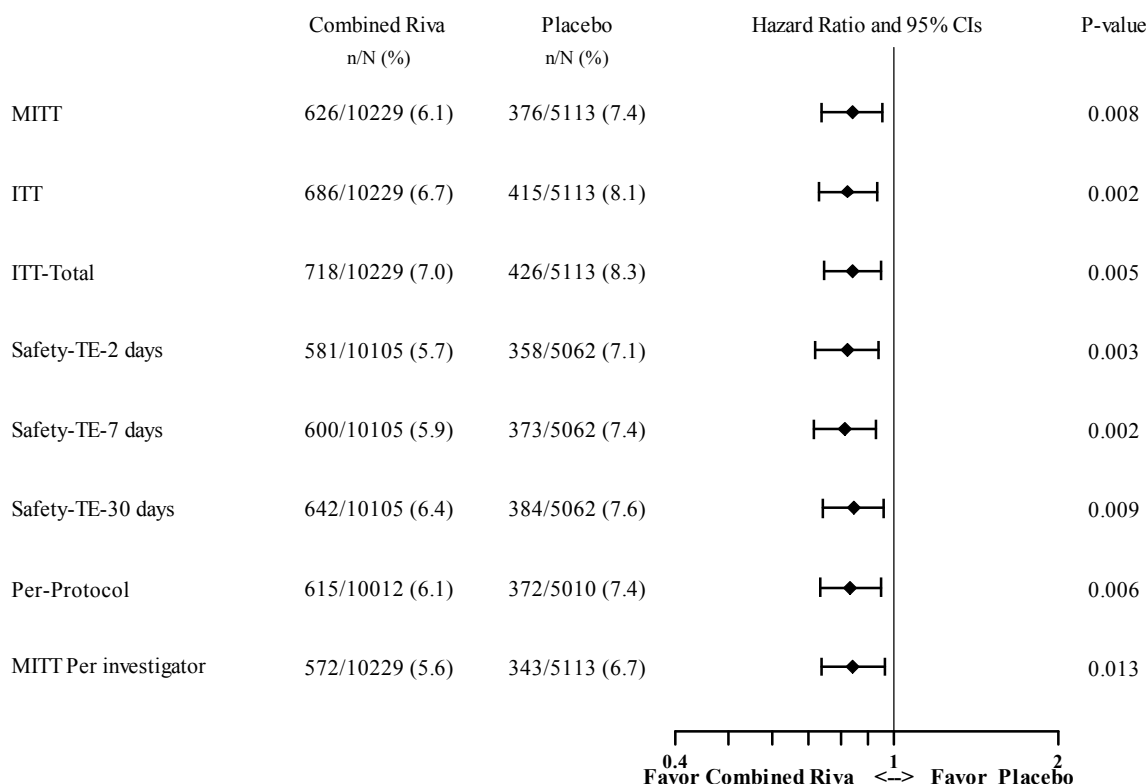
6.2.1.1. Sensitivity Analysis in Different Analysis Sets

To confirm the robustness of the primary efficacy analysis results, the primary efficacy endpoint was analyzed, using the same methods as those used for the primary efficacy analysis in the mITT analysis set, in an array of additional analysis sets. Figure 10 and Figure 11 are forest plots showing the results of sensitivity analyses for the combined rivaroxaban doses in All Strata, and for the rivaroxaban 2.5 mg b.i.d group in Stratum 2, respectively.

Results of the sensitivity analyses were consistent with the results of the primary efficacy analysis in showing significant results favoring rivaroxaban across analysis sets, including the ITT and ITT-Total analysis sets.

There was a high rate of concordance in the assessments between the investigators and the CEC on each component of the composite primary efficacy endpoint [i.e., CV deaths (98%), MIs (85%) and strokes (85%)] and the sensitivity analysis using investigator-reported events in the primary efficacy analysis was consistent with the analysis using CEC-adjudicated events.

Figure 10: (FEFF19A) Effect of Combined Rivaroxaban Compared with Placebo on the Primary Efficacy Endpoint (First Occurrence of Cardiovascular Death, MI, Stroke) in All Strata (Study RIVAROXACS3001; Excluding Sites 091001, 091019 and 091026 Analysis Set)



Note: Sites 091001, 091019 and 091026 were excluded for the analyses

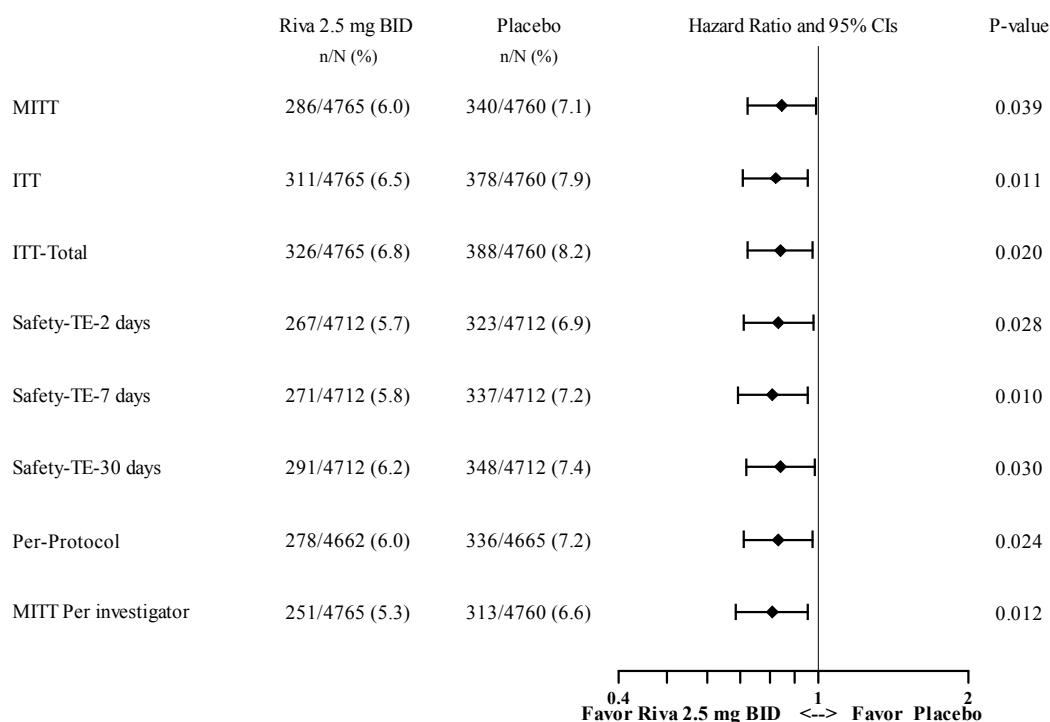
Note: Other than 'MITT per investigator', the analysis is based on data as adjudicated by CEC.

Note: P-value is based on stratified log-rank test and HR (95% confidence interval) is based on stratified Cox proportional hazards model.

Note: Scale of X axis was based on log transformation of the ratio. Tick labels of X axis are in the original ratio scale.

Page 1 of 1 for figure FEFF19A

Figure 11: (FEFF19E) Effect of Rivaroxaban 2.5 mg BID Compared with Placebo on the Primary Efficacy Endpoint (First Occurrence of Cardiovascular Death, MI, Stroke) in Stratum 2 (Study RIVAROXACS3001; Excluding Sites 091001, 091019 and 091026 Analysis Set)



Note: Sites 091001, 091019 and 091026 were excluded for the analyses

Note: Other than 'MITT' per investigator, the analysis is based on data as adjudicated by CEC.

Note: P-value is based on unstratified log-rank test and HR (95% confidence interval) is based on unstratified Cox proportional hazards model.

Note: Scale of X axis was based on log transformation of the ratio. Tick labels of X axis are in the original ratio scale.

Page 1 of 1 for figure FEFF19E

6.2.1.2. Sensitivity Analysis Using Imputed Events for Missing Data

In ATLAS ACS 2 TIMI 51, the rate of premature discontinuation from the study was 15.5% for all randomized subjects (it should be noted that this rate included those subjects who died during the study [3.5%]), and the rate of discontinuation from the study treatment was 27.6% for all treated subjects (also including those subjects who died [2.3%]). To further explore the impact of the missing data due to premature discontinuation on the efficacy endpoint analyses, some post hoc sensitivity analyses were performed (Table 19 and Table 22).

As shown in Section 5.2.1, although the rate of discontinuation from the study was balanced among treatment groups, the rates of death were not (2.8%, 3.8%, and 3.7% for the 2.5 mg b.i.d., the 5 mg b.i.d., and placebo, respectively), and the incidence of consent withdrawn was higher in the rivaroxaban groups than in placebo (8.7%, 8.5%, and 7.8% for the 2.5 mg b.i.d., the 5 mg b.i.d., and placebo, respectively) (Table 14).

Table 19 shows that the missing follow-up years due to premature discontinuation from the study for reasons other than death accounted for 5.9% and 5.3% of the expected total follow-up years, in the rivaroxaban group and the placebo group, respectively.

**Table 19: (TSUBPH01a) Summary of Missing Follow-up Duration As a Proportion of Total Study Duration, to the Global Treatment End Date
(Study RIVAROXACS3001; All Randomized Subjects Analysis Set)**

	----- Rivaroxaban -----									
	2.5 mg BID (N=5174)		5 mg BID (N=5176)		Combined (N=10350)		Placebo (N=5176)		Total (N=15526)	
	n	Follow Up (%)	n	Follow Up (%)	n	Follow Up (%)	n	Follow Up (%)	n	Follow Up (%)
Subject Stratification: All Strata										
Total follow-up (years)	5174	6680.4	5176	6637.6	10350	13317.9	5176	6654.2	15526	19972.1
Total missing follow-up	441	391.1 (5.9)	456	391.8 (5.9)	897	782.9 (5.9)	401	353.7 (5.3)	1298	1136.6 (5.7)
Subject Stratification: ASA										
Total follow-up (years)	349	421.4	349	430.4	698	851.7	355	434.3	1053	1286.0
Total missing follow-up	34	23.1 (5.5)	34	22.5 (5.2)	68	45.6 (5.4)	38	32.6 (7.5)	106	78.2 (6.1)
Subject Stratification: ASA + Thieno										
Total follow-up (years)	4825	6259.0	4827	6207.2	9652	12466.2	4821	6219.9	14473	18686.1
Total missing follow-up	407	367.9 (5.9)	422	369.4 (6.0)	829	737.3 (5.9)	363	321.1 (5.2)	1192	1058.4 (5.7)

Note: Total follow-up is calculated by sum of (minimum (global treatment end date, death date) - randomization date +1)/365.25.

Note: Missing FU is calculated for subjects whose last known survival date is prior to global end date by sum of (global treatment end date - last known survival date)/365.25. Missing FU is not calculated for subjects who died.

Note: Percentages calculated with total follow-up (years) in each subject stratum and treatment group as denominator.

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Table 20 provides the baseline characteristics of the subjects whose vital status was missing at the global treatment end date, and allows for a comparison of those subjects to subjects who were alive on the global treatment end date, as well as to subjects who died by the global treatment end date. The results show that the subjects with missing vital status more closely resemble subjects who were alive at the global treatment end date. Importantly, in terms of age, prior MI, baseline PCI for index event, creatinine clearance (all of which are well established predictors for adverse outcome in ACS patients), subjects with missing vital status were similar in these characteristics to those subjects who were alive at the global treatment end date.

The incidences of important clinical events (MI, stroke, non-CABG major bleeding events or non-bleeding adverse events) occurring 30 days prior to the last contact for those subjects with missing vital status were shown in **Table 21**. There was no unexpected imbalance between treatment groups.

Taken together these analyses provide reassurance that the subjects with incomplete follow-up and whose vital status was later unknown were comparable to subjects who were alive for a variety of important clinical predictive features. Specifically, no clinically important imbalances in the occurrence of MI, stroke, non-CABG major bleeding or non-bleeding adverse events were observed in the 30-day period before their last contact in those who were receiving rivaroxaban treatment vs. placebo.

**Table 20: Comparison of Baseline Characteristics of Subjects with Unknown Vital Status vs Subjects Who Died or Who were Alive at the Global Treatment End Date
(Study: JNJ39039039C-ACS3001: All Randomized Subjects)**

Subject Stratum: All Strata			
	Subjects with Missing Follow Up (n=1298)	Subjects who Died before Global Treatment End Date (n=500)	Subjects who Survived on or after Global Treatment End Date (n=13728)
Age (years)	1298	500	13728
Mean (SD)	62.2 (10.36)	65.1 (10.24)	61.6 (9.04)
Prior MI	1298	500	13728
Yes n (%)	373 (28.7)	212 (42.4)	3596 (26.2)
Baseline PCI for index event*	1298	500	13727
Yes n (%)	692 (53.3)	178 (35.6)	8454 (61.6)
Baseline Creatinine Clearance (ml/min)	1189	492	13654
Mean (SD)	83.77 (30.368)	76.82 (30.429)	89.35 (29.441)

Note: Percentages calculated with the number of subjects in each group as denominator.

Note: * This is number of subjects with non-missing data including subjects answered no on having a revascularization procedure associated with index event.

MI = Myocardial infarction.

Source: DSUB1324, DSUB1325, DSUB1400, DSUB1401, DSUB1402, DSUB1403, DSUB1404.

**Table 21: (TEFF1855 and TAE0072) Incidence of Efficacy and Safety Events as Adjudicated by the CEC in the 30 Days Prior to the Last Contact date for Subjects who had Unknown Vital Status at Global Treatment End Date
(Study RIVAROXACS3001: All Randomized Subjects)**

Subject Stratum: All Strata				
	----- Rivaroxaban -----			
	2.5 mg BID (N=441) n (%)	5 mg BID (N=456) n (%)	Combined (N=897) n (%)	Placebo (N=401) n (%)
MI	0	2 (0.44)	2 (0.22)	1 (0.25)
Stroke	4 (0.91)	3 (0.66)	7 (0.78)	2 (0.50)
Non-CABG TIMI major bleeding event	1 (0.23)	2 (0.44)	3 (0.33)	0
Non-bleeding adverse event	42 (9.5)	32 (7.0)	74 (8.2)	32 (8.0)

Note: Percentages calculated with the number of subjects in each group as denominator.

Note: AE coding is based on MedDRA version 14.0.

MI = Myocardial infarction.

Source: teff1855.rtf generated by ref1855.sas, 13APR2012 18:22; tae0072.rtf generated by raeph0072.sas, 13APR2012 17:58

To further investigate the impact of the missing data in the missing follow-up period on the primary efficacy endpoint, subjects were considered to have missing follow-up status if their last contact date was on or before the global treatment end date, and they did not have a primary efficacy event prior to global treatment end date, and the reasons for discontinuation was “lost to follow-up”, “consent withdrawn”, or category of “other”. In All Strata, there were 466 subjects in the rivaroxaban 2.5 mg group, 481 subjects in the rivaroxaban 5 mg group, and 420 subjects in the placebo group that were considered to have missing data. In Stratum 2, there were 431, 444 and 381 subjects in the rivaroxaban 2.5 mg group, 5 mg group, and placebo group, respectively.

Table 22 provides results of a post hoc sensitivity analysis examining the maximum event rate in the rivaroxaban treatment groups that would maintain nominal statistical significance compared

with placebo (or an upper bound of the 95% CI < 1). For the placebo group, it was assumed that the event rate for the missing follow-up period was the same as the observed event rate. For the combined rivaroxaban group in the All Strata analysis, the event rate needed to just maintain statistical significance was 11.39 events/100 patient-years. This would represent an approximate doubling of the observed event rate (5.80 events/100 pt yrs), which provides strong evidence that the efficacy results of the study were robust to potential issues with the missing data. The corresponding results for individual doses and for Stratum 2 alone are generally consistent with the results of the combined rivaroxaban in All Strata.

Table 22: (TEFFPHCO01) Hazard Ratio of the Primary Efficacy Endpoint (Adjudicated by the CEC) after Imputing Event Rates for Missing Data (Study: JNJ39039039C-ACS3001: Intent-to-Treat (Excluding Sites 091001, 091019 and 091026) Analysis Set)

Planned Treatment Subject Stratum	N	Rivaroxaban			N	Placebo			HR (95% CI) *
		Observed	Missing	Combined *		Observed	Missing	Combined *	
		Follow-up	Follow-up			Follow-up	Follow-up		
		Period	Period			Period	Period		
		(Hypothetical)	(Hypothetical)	(Hypothetical)		(Hypothetical)			
n	n	n	n	n	n	n	n	n	
(Event Rate	(Event Rate	(Event Rate	(Event Rate	(Event Rate	(Event Rate	(Event Rate	(Event Rate	(Event Rate	
/100 pt-yr)	/100 pt-yr)	/100 pt-yr)	/100 pt-yr)	/100 pt-yr)	/100 pt-yr)	/100 pt-yr)	/100 pt-yr)	/100 pt-yr)	
Combined Riva									
All Strata	10229	686(5.80)	99(11.39)	785(6.24)	5113	415(7.02)	28(7.11)	443(7.02)	0.89(0.79, <1.00)
ASA + Thieno	9532	627(5.66)	81(9.88)	708(6.00)	4760	378(6.81)	24(6.71)	402(6.81)	0.88(0.78, <1.00)
Riva 2.5 mg BID									
All Strata	5114	341(5.76)	43(9.80)	384(6.09)	5113	415(7.02)	28(7.11)	443(7.02)	0.87(0.76, <1.00)
ASA + Thieno	4765	311(5.61)	36(8.67)	347(5.87)	4760	378(6.81)	24(6.71)	402(6.81)	0.86(0.75, <1.00)
Riva 5 mg BID									
All Strata	5115	345(5.83)	39(9.06)	384(6.10)	5113	415(7.02)	28(7.11)	443(7.02)	0.87(0.76, <1.00)
ASA + Thieno	4767	316(5.72)	30(7.41)	346(5.87)	4760	378(6.81)	24(6.71)	402(6.81)	0.87(0.75, <1.00)

Note: Subjects are considered to have missing follow-up status if their reference end dates are on or before the global treatment end date, they don't have a primary efficacy event prior to global treatment end date and the reasons for discontinuation are 'lost to follow-up', 'consent withdrawn', or 'other'.

Note: Rivaroxaban n at Missing Follow-up Period = imputed maximum events to reach upper confidence interval <1.

Note: Placebo n at Missing Follow-up Period = imputed events to keep the event rate at missing follow-up period the same as the observed rate.

Note: Event Rate at Missing Follow-up Period = 100*imputed events/missing follow-up time.

Note: Combined Rate = 100*(observed + imputed events)/(observed and missing follow-up time).

Note: HR (95% CI): Hazard ratios (95% confidence interval) as compared with placebo arm are based on the (stratified, only for all strata) Cox proportional hazards model.

Note: * Based on the least favorable time allocation for imputed rivaroxavan events and most favorable time for imputed placebo events and censored cases with missing follow-up status.

Note: ASA = Acetylsalicylic acid; Thieno = Thienopyridine.

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6.2.1.3. Sensitivity Analysis by Actual Antiplatelet Agent Use

As described in Section 7.1.2, over 99% of subjects in Stratum 2 received a thienopyridine, while in Stratum 1, even though 13.6% of subjects received a thienopyridine, it was generally transient in nature.

For subjects who had at least 1 dose of thienopyridine, the event rates (provided as events per 100 patient-years) of the primary efficacy endpoint and its components, are shown in Table 23. Note that this analysis included only events that occurred up to the last dose of thienopyridine. These results are consistent with the primary efficacy analyses. In particular, in Stratum 2, which included subjects stratified to receive a thienopyridine, the HR (95% CI) for the combined doses was 0.86 (0.74, 0.99) compared with placebo, and for the 2.5 mg b.i.d group it was 0.85 (0.72, 1.01), with a relative risk reduction similar to the primary efficacy analysis. The event rates of the primary efficacy endpoint and its components that occurred after the last dose of thienopyridine are shown in Table 24, and they were consistent with the findings in subjects while receiving a thienopyridine.

Figure 12 shows the Kaplan-Meier estimates of the primary efficacy endpoint by treatment group up to the last dose of thienopyridine for subjects who had at least 1 dose of thienopyridine in Stratum 2.

Table 25 summarizes the extent of exposure to concomitant thienopyridine for the subjects who used thienopyridine at or after randomization. The median duration of exposure to thienopyridine during the double-blind treatment period in All Strata was slightly lower in the 5 mg b.i.d. (323 days) group compared with the 2.5 mg b.i.d. (333 days) and placebo (341 days) groups. Figure 13 presents the cumulative incidence of thienopyridine termination during the study in All Strata. Subjects still using a thienopyridine at their last study visit were censored at the last contact date. The during-study thienopyridine termination rate increased more rapidly after one-year treatment, which was 18.2%, 18.9% and 16.9% at 12 months, and became 40.9%, 43.9% and 39.8% at 24 months for the 2.5 mg b.i.d., the 5 mg b.i.d., and placebo, respectively.

In conclusion, it appears that the occurrence of the composite of CV death, MI, and stroke was consistently reduced regardless of the discontinuation of thienopyridine therapy. In particular, the reduction was significant while subjects were on thienopyridine therapy when comparing combined rivaroxaban doses versus placebo in All Strata and Stratum 2 (Table 23), confirming the positive outcome of the study.

**Table 23: (TEFFUS26A) Effect of Rivaroxaban Compared with Placebo on the Primary Efficacy Endpoint (First Occurrence of Cardiovascular Death, MI, Stroke) and its Components Occurring Up to the Last Dose of Thienopyridine as Adjudicated by the CEC
(Study RIVAROXACS3001: Modified Intent-to-Treat (Excluding Sites 091001, 091019 and 091026) Analysis Set)**

Subject Stratum Parameter	----- Rivaroxaban -----								-- 2.5 mg BID --	--- 5 mg BID ---	--- Combined ---
	----- 2.5 mg BID -----		----- 5 mg BID -----		----- Combined -----		----- Placebo -----		----- vs. -----	----- vs. -----	----- vs. -----
	(N=4810)	Event Rate n(%) (100 pt-yr)	(N=4798)	Event Rate n(%) (100 pt-yr)	(N=9608)	Event Rate n(%) (100 pt-yr)	(N=4805)	Event Rate n(%) (100 pt-yr)	---- Placebo --- HR (95% CI)	---- Placebo --- HR (95% CI)	---- Placebo --- HR (95% CI)
All Strata	4810		4798		9608		4805				
Primary	251(5.2)	5.92	250(5.2)	6.03	501(5.2)	5.98	306(6.4)	7.04	0.84 (0.71,0.99)	0.84 (0.71,1.00)	0.84 (0.73,0.97)
CV_Dth	48(1.0)	1.10	76(1.6)	1.79	124(1.3)	1.44	84(1.7)	1.88	0.58 (0.41,0.83)	0.94 (0.69,1.28)	0.76 (0.58,1.00)
MI	188(3.9)	4.43	164(3.4)	3.95	352(3.7)	4.19	211(4.4)	4.85	0.91 (0.74,1.10)	0.80 (0.65,0.99)	0.86 (0.72,1.01)
Stroke	35(0.7)	0.80	40(0.8)	0.95	75(0.8)	0.87	29(0.6)	0.65	1.24 (0.76,2.02)	1.45 (0.90,2.33)	1.34 (0.87,2.06)
ASA + Thieno	4744		4748		9492		4733				
Primary	244(5.1)	5.82	243(5.1)	5.92	487(5.1)	5.87	291(6.1)	6.77	0.85 (0.72,1.01)	0.86 (0.72,1.02)	0.86 (0.74,0.99)
CV_Dth	48(1.0)	1.11	74(1.6)	1.77	122(1.3)	1.44	84(1.8)	1.90	0.58 (0.41,0.83)	0.92 (0.67,1.25)	0.75 (0.57,0.99)
MI	182(3.8)	4.33	160(3.4)	3.89	342(3.6)	4.11	197(4.2)	4.58	0.94 (0.77,1.15)	0.83 (0.68,1.03)	0.89 (0.74,1.06)
Stroke	34(0.7)	0.79	38(0.8)	0.91	72(0.8)	0.85	27(0.6)	0.61	1.29 (0.78,2.13)	1.46 (0.89,2.39)	1.37 (0.88,2.14)

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: Event Rate (100 pt-yr): number of events per 100 patient years of follow up.

Note: Primary: first occurrence of cardiovascular death including unknown death, MI, or stroke; CV_Dth: Cardiovascular death including unknown death;

Note: Only subjects with at least one dose of the concomitant medication will be included in the table.

Note: HR (95% CI): Hazard ratios (95% confidence interval) as compared with 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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Table 24: (TEFFUS27) Incidence of the Primary Efficacy Endpoint and its Components Occurring after the Last Dose of Thienopyridine as Adjudicated by the CEC (Study RIVAROXACS3001: : Modified Intent-to-Treat (Excluding Sites 091001, 091019 and 091026) Analysis Set)

Subject Stratum Parameter	----- Rivaroxaban -----							
	----- 2.5 mg BID ----		----- 5 mg BID -----		----- Combined -----		----- Placebo -----	
	n/N (%)	Event Rate (100 pt-yr)	(N=4798) n/N (%)	Event Rate (100 pt-yr)	(N=9608) n/N (%)	Event Rate (100 pt-yr)	(N=4805) n/N (%)	Event Rate (100 pt-yr)
All Strata								
Primary	40/1106(3.6)	5.28	48/1113(4.3)	6.55	88/2219(4.0)	5.91	48/1057(4.5)	6.81
CV_Dth	33/1143(2.9)	4.23	49/1153(4.2)	6.47	82/2296(3.6)	5.33	48/1100(4.4)	6.62
MI	7/1113(0.6)	0.92	9/1125(0.8)	1.21	16/2238(0.7)	1.06	10/1065(0.9)	1.41
Stroke	9/1134(0.8)	1.16	11/1140(1.0)	1.47	20/2274(0.9)	1.31	7/1092(0.6)	0.97
ASA + Thieno								
Primary	40/1088(3.7)	5.41	45/1102(4.1)	6.18	85/2190(3.9)	5.79	46/1037(4.4)	6.64
CV_Dth	33/1125(2.9)	4.33	48/1140(4.2)	6.39	81/2265(3.6)	5.35	46/1078(4.3)	6.47
MI	7/1095(0.6)	0.94	9/1113(0.8)	1.22	16/2208(0.7)	1.08	10/1045(1.0)	1.44
Stroke	9/1116(0.8)	1.19	8/1128(0.7)	1.08	17/2244(0.8)	1.13	7/1070(0.7)	0.99

Note: <a> Analysis sets excluding sites: 091001, 091019 and 091026.

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

Note: n = number of subjects with events;

Note: N = number of subjects who were at risk for the endpoint at the beginning of the reported time interval;

Note: % = 100 * n / N.

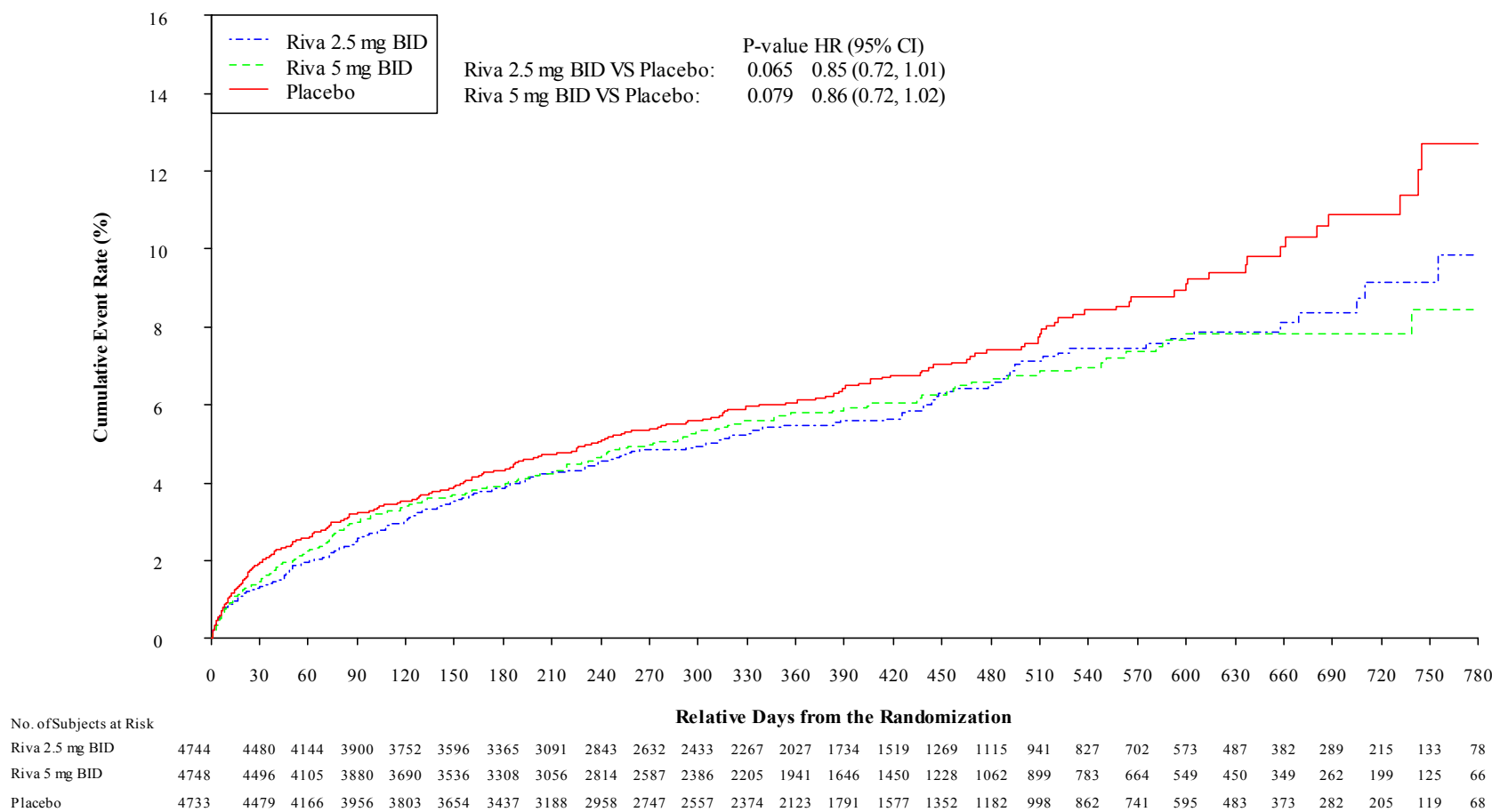
Note: Cardiovascular death including unknown death; MI: Myocardial infarction.

Note: Only subjects who used at least one dose of the concomitant medication, had at least one day follow up after discontinuation, and did not have events before the discontinuation dates of the medication are included in the table.

Note: ASA = Acetylsalicylic acid; Thieno = Thienopyridine.

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Figure 12: (FEFF1020) Kaplan-Meier Estimates of the Primary Efficacy Endpoint (First Occurrence of Cardiovascular Death, MI, Stroke) Up to the Last Dose of Thienopyridine as Adjudicated by the CEC in Stratum 2 (Study RIVAROXACS3001: Modified Intent-to-Treat (Excluding Sites 091001, 091019 and 091026) Analysis Set)



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: P-value is based on (stratified, only for all strata) log-rank test and HR (95% CI) is based on (stratified, only for all strata) Cox proportional hazards model.

Note: KM curves for all treatment groups are not displayed when number of subjects at risk in any treatment group reaches less than 50 or 1 percent of that at the starting

**Table 25: (TSUB25B) Extent of Exposure to Concomitant Thienopyridine Between the First Dose of Study Drug and the Last Dose of Study Drug
(Study RIVAROXACS3001: Safety Analysis Set)**

	----- Rivaroxaban -----				
	-- 2.5 mg BID -- (N=5115)	--- 5 mg BID --- (N=5110)	--- Combined --- (N=10225)	---- Placebo --- (N=5125)	----- Total ---- (N=15350)
All Strata					
N	4795	4788	9583	4791	14374
Mean	335.4	326.1	330.7	345.4	335.6
SD	217.57	216.21	216.93	215.64	216.60
Median	333.0	323.0	330.0	341.0	334.0
Minimum	1	1	1	1	1
Maximum	913	911	913	900	913
Total Exposure (patient years)	4403.4	4274.3	8677.7	4530.8	13208.6
<u>Cumulative duration, n (%)</u>					
N	4795	4788	9583	4791	14374
>= 3 months	3948 (82.3)	3875 (80.9)	7823 (81.6)	4005 (83.6)	11828 (82.3)
>= 6 months	3474 (72.5)	3407 (71.2)	6881 (71.8)	3579 (74.7)	10460 (72.8)
>= 12 months	2179 (45.4)	2067 (43.2)	4246 (44.3)	2266 (47.3)	6512 (45.3)
>= 18 months	919 (19.2)	876 (18.3)	1795 (18.7)	985 (20.6)	2780 (19.3)
>= 24 months	266 (5.5)	241 (5.0)	507 (5.3)	257 (5.4)	764 (5.3)
ASA					
N	48	40	88	53	141
Mean	238.7	282.0	258.4	287.5	269.3
SD	223.66	246.91	234.14	246.56	238.43
Median	206.5	251.5	228.5	252.0	244.0
Minimum	1	1	1	1	1
Maximum	720	777	777	833	833
Total Exposure (patient years)	31.4	30.9	62.3	41.7	104.0
<u>Cumulative duration, n (%)</u>					
N	48	40	88	53	141
>= 3 months	30 (62.5)	28 (70.0)	58 (65.9)	36 (67.9)	94 (66.7)
>= 6 months	25 (52.1)	22 (55.0)	47 (53.4)	32 (60.4)	79 (56.0)
>= 12 months	13 (27.1)	16 (40.0)	29 (33.0)	20 (37.7)	49 (34.8)
>= 18 months	7 (14.6)	7 (17.5)	14 (15.9)	10 (18.9)	24 (17.0)
>= 24 months	1 (2.1)	2 (5.0)	3 (3.4)	3 (5.7)	6 (4.3)

Note: Total duration (including days off thienopyridine) = date of the last thienopyridine administration - date of the first thienopyridine administration + 1.

Note: Percentages calculated with the number of subjects in each subject stratum and treatment group as denominator.

Note: The unit for duration is days.

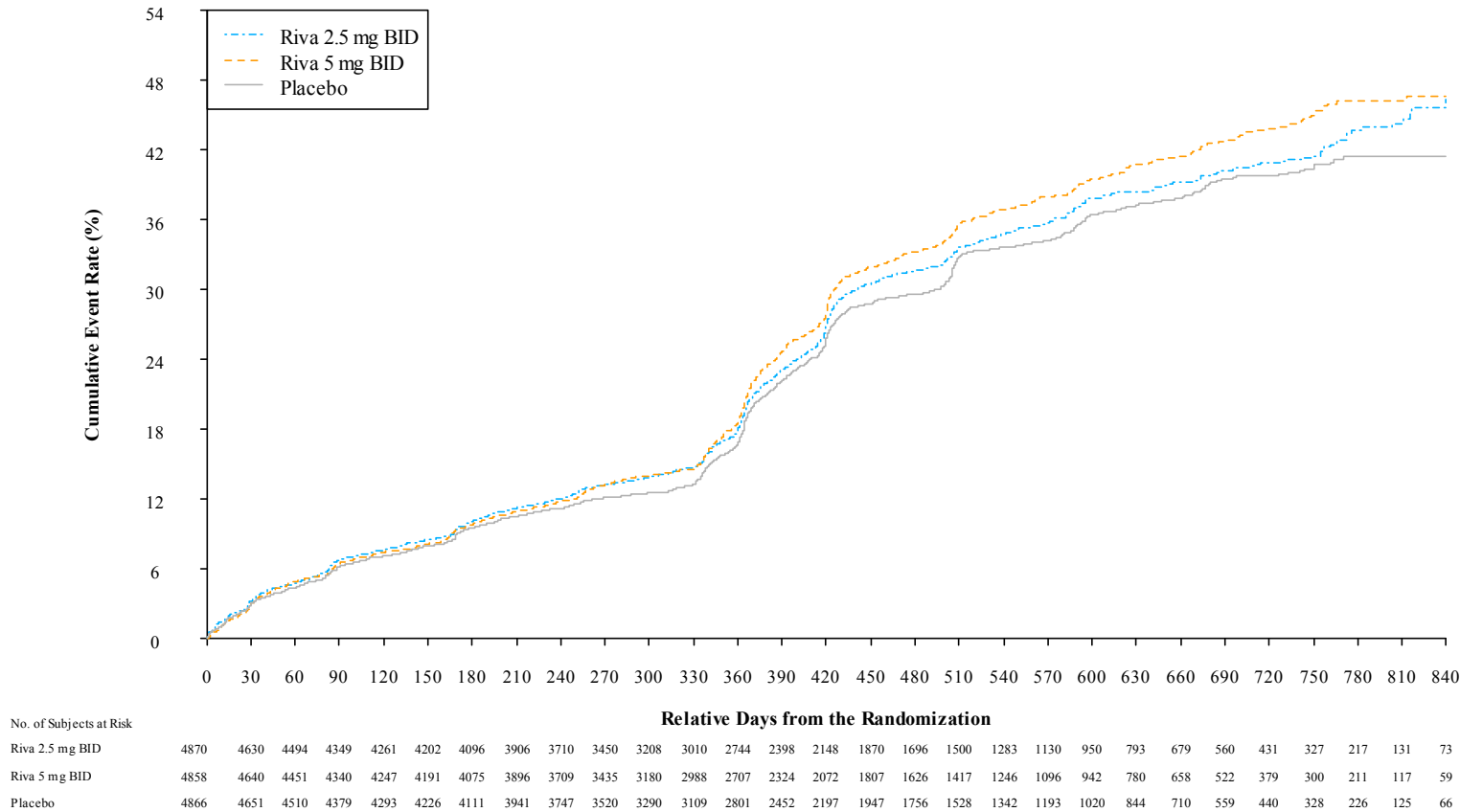
Note: ASA = Acetylsalicylic acid; Thieno = Thienopyridine.

Table 25 Continued (TSUB25B): Extent of Exposure to Concomitant Thienopyridine between the First Dose of Study Drug and the Last Dose of Study Drug
(Study RIVAROXACS3001: Safety Analysis Set)

	Rivaroxaban				
	-- 2.5 mg BID -- (N=5115)	--- 5 mg BID --- (N=5110)	--- Combined --- (N=10225)	---- Placebo --- (N=5125)	----- Total ---- (N=15350)
ASA + Thieno					
N	4747	4748	9495	4738	14233
Mean	336.4	326.4	331.4	346.1	336.3
SD	217.31	215.93	216.67	215.21	216.28
Median	334.0	323.5	330.0	341.0	335.0
Minimum	1	1	1	1	1
Maximum	913	911	913	900	913
Total Exposure (patient years)	4372.0	4243.4	8615.5	4489.1	13104.6
Cumulative duration, n (%)					
N	4747	4748	9495	4738	14233
>= 3 months	3918 (82.5)	3847 (81.0)	7765 (81.8)	3969 (83.8)	11734 (82.4)
>= 6 months	3449 (72.7)	3385 (71.3)	6834 (72.0)	3547 (74.9)	10381 (72.9)
>= 12 months	2166 (45.6)	2051 (43.2)	4217 (44.4)	2246 (47.4)	6463 (45.4)
>= 18 months	912 (19.2)	869 (18.3)	1781 (18.8)	975 (20.6)	2756 (19.4)
>= 24 months	265 (5.6)	239 (5.0)	504 (5.3)	254 (5.4)	758 (5.3)

See footnotes on the first page of the table.
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**Figure 13: (FBSUBPH04): Kaplan-Meier Estimates of Thienopyridine Discontinuation During Study for All Strata
(Study RIVAROXACS3001: All Randomized Subjects with Actual Thienopyridine Use)**



Note: only including subjects who used at least one dose of Thienopyridine after randomization.
Note: Subjects who were still on thienopyridine at the end of study are censored at last contact date.
Note: KM curves for all treatment groups are not displayed when number of subjects at risk in any treatment group reaches less than 50 or 1 percent of that at the starting time point whichever is less.

6.3. Secondary Efficacy Endpoints

6.3.1. Secondary Efficacy Endpoint 1: Composite of All-Cause Death, MI, or Stroke

The composite Secondary Efficacy Endpoint 1 differs from the primary efficacy endpoint only by replacing the CV death component with all cause death. Since 92% of all-cause deaths were adjudicated to having CV causes, the results of Secondary Efficacy Endpoint 1 in the mITT analysis set were generally consistent with those of primary efficacy endpoint, for both rivaroxaban doses.

Rivaroxaban 2.5 mg b.i.d. significantly reduced the occurrence of death, MI or stroke compared with placebo, in addition to standard care, both in All Strata (HR: 0.83; 95%CI: 0.72, 0.97) and in Stratum 2 (HR: 0.84; 95%CI: 0.72, 0.98). The results were primarily driven by the nominally significant reduction in all-cause deaths in the 2.5 mg b.i.d. group in both All Strata (HR: 0.68; 95%CI: 0.53, 0.87), and Stratum 2 (HR: 0.64; 95% CI: 0.49, 0.83) ([Table 26](#)).

6.3.2. Secondary Efficacy Endpoint 2: Net Clinical Outcome

Secondary Efficacy Endpoint 2, also referred to as Net Clinical Outcome (NCO), was defined as the composite of CV death, MI, ischemic stroke or non-CABG TIMI major bleeding events. Although the HR numerically favored rivaroxaban across strata, rivaroxaban 2.5 mg b.i.d. did not show a statistically significant reduction compared with placebo in the risk of this composite endpoint for All Strata (HR: 0.93; 95%CI: 0.81, 1.07) or Stratum 2 (HR: 0.95; 95%CI: 0.82, 1.10), neither did the 5 mg b.i.d. dose ([Table 26](#)).

The NCO endpoint was intended to assess the efficacy and bleeding risk of rivaroxaban in one composite endpoint that included components of CV death, MI, ischemic stroke and non-CABG TIMI major bleeding. Further discussions on this endpoint and additional benefit-risk analyses are presented in [Section 8.1](#).

6.3.3. Other Composite Secondary Efficacy Endpoints

Results of Secondary Efficacy Endpoint 3 (the composite of CV death, MI, stroke, or severe recurrent ischemia requiring revascularization [SRIR]) and Secondary Efficacy Endpoint 4 (the composite of CV death, MI, stroke, or severe recurrent ischemia leading to hospitalization [SRIH]) are presented [Table 26](#).

Table 26: (TEFF05A) Effect of Rivaroxaban Compared With Placebo on Secondary Efficacy Endpoints as Adjudicated by the CEC (Study RIVAROXACS3001; mITT (Excluding Sites 091001, 091019 and 091026) Analysis Set)

Subject Stratum Parameter	----- Rivaroxaban -----				-- 2.5 mg BID vs. Placebo --		-- 5 mg BID vs. Placebo --		-- Combined vs. Placebo --	
	2.5 mg BID (N=5114) n(%)	5 mg BID (N=5115) n(%)	Combined (N=10229) n(%)	Placebo (N=5113) n(%)	HR (95% CI)	Log-Rank P-value	HR (95% CI)	Log-Rank P-value	HR (95% CI)	Log-Rank P-value
All Strata	5114	5115	10229	5113						
Dth/MI/St	320(6.3)	321(6.3)	641(6.3)	386(7.5)	0.83 (0.72,0.97)	0.016	0.84 (0.73,0.98)	0.025	0.84 (0.74,0.95)	0.006
Net Clin. Outcome	361(7.1)	366(7.2)	727(7.1)	391(7.6)	0.93 (0.81,1.07)	0.320	0.95 (0.83,1.10)	0.508	0.94 (0.83,1.06)	0.337
CV_Dth/MI/St/SRIR	437(8.5)	421(8.2)	858(8.4)	481(9.4)	0.92 (0.80,1.04)	0.185	0.89 (0.78,1.01)	0.081	0.90 (0.81,1.01)	0.074
CV_Dth/MI/St/SRIH	372(7.3)	388(7.6)	760(7.4)	447(8.7)	0.84 (0.73,0.96)	0.011	0.88 (0.77,1.01)	0.070	0.86 (0.76,0.97)	0.011
Death	103(2.0)	142(2.8)	245(2.4)	153(3.0)	0.68 (0.53,0.87)	0.002	0.95 (0.76,1.19)	0.662	0.81 (0.66,1.00)	0.044
Ischemic Stroke	30(0.6)	35(0.7)	65(0.6)	34(0.7)	0.89 (0.55,1.45)	0.643	1.05 (0.65,1.68)	0.844	0.97 (0.64,1.47)	0.886
NonCABG TIMI Maj.	68(1.3)	85(1.7)	153(1.5)	23(0.4)	2.99 (1.86,4.80)	<0.001	3.81 (2.40,6.04)	<0.001	3.40 (2.19,5.26)	<0.001
SRI_Revas	132(2.6)	122(2.4)	254(2.5)	121(2.4)	1.10 (0.86,1.41)	0.445	1.03 (0.80,1.33)	0.798	1.07 (0.86,1.32)	0.557
SRI_Hosp	74(1.4)	93(1.8)	167(1.6)	99(1.9)	0.75 (0.56,1.02)	0.063	0.96 (0.73,1.28)	0.798	0.86 (0.67,1.10)	0.223
ASA	349	348	697	353						
Dth/MI/St	28(8.0)	24(6.9)	52(7.5)	36(10.2)	0.77 (0.47,1.26)	0.291	0.64 (0.38,1.07)	0.089	0.70 (0.46,1.07)	0.101
Net Clin. Outcome	28(8.0)	25(7.2)	53(7.6)	36(10.2)	0.77 (0.47,1.26)	0.290	0.67 (0.40,1.11)	0.120	0.72 (0.47,1.09)	0.120
CV_Dth/MI/St/SRIR	31(8.9)	28(8.0)	59(8.5)	39(11.0)	0.78 (0.49,1.26)	0.313	0.69 (0.43,1.13)	0.136	0.74 (0.49,1.10)	0.138
CV_Dth/MI/St/SRIH	32(9.2)	30(8.6)	62(8.9)	42(11.9)	0.75 (0.47,1.19)	0.219	0.69 (0.43,1.09)	0.112	0.72 (0.48,1.06)	0.093
Death	13(3.7)	9(2.6)	22(3.2)	10(2.8)	1.30 (0.57,2.96)	0.533	0.89 (0.36,2.20)	0.805	1.09 (0.52,2.31)	0.814
Ischemic Stroke	1(0.3)	5(1.4)	6(0.9)	6(1.7)	0.17 (0.02,1.38)	0.059	0.82 (0.25,2.70)	0.749	0.50 (0.16,1.54)	0.216
NonCABG TIMI Maj.	2(0.6)	4(1.1)	6(0.9)	0		0.160		0.046		0.085
SRI_Revas	4(1.1)	4(1.1)	8(1.1)	4(1.1)	1.00 (0.25,4.01)	0.995	1.00 (0.25,3.99)	0.997	1.00 (0.30,3.32)	0.999
SRI_Hosp	6(1.7)	7(2.0)	13(1.9)	8(2.3)	0.74 (0.26,2.13)	0.574	0.87 (0.31,2.39)	0.779	0.80 (0.33,1.94)	0.627

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: Dth/MI/St: first occurrence of all cause death, MI or stroke;

Net Clin. Outcome: first occurrence of cardiovascular death including unknown death, MI, ischemic stroke or TIMI major bleeding not associated with CABG surgery;

CV_Dth/MI/St/SRIR: first occurrence of cardiovascular death including unknown death, MI, stroke or severe recurrent ischemia requiring revascularization;

CV_Dth/MI/St/SRIH: first occurrence of cardiovascular death including unknown death, MI, stroke or severe recurrent ischemia leading to hospitalization;

NonCABG TIMI Maj.: TIMI major bleeding event not associated with CABG surgery;

SRI_Revas: severe recurrent ischemia requiring revascularization; SRI_Hosp: severe recurrent ischemia leading to hospitalization.

Note: HR (95% CI): Hazard ratios (95% confidence interval) as compared with placebo arm are based on the (stratified, only for all strata) Cox proportional hazards model.

Note: Log-Rank P-value: P-values (two-sided) as compared with placebo arm are based on the (stratified, only for all strata) log rank test.

Note: ASA = Acetylsalicylic acid; Thieno = Thienopyridine; CABG = Coronary artery bypass grafting; MI = Myocardial infarction.

Table 26 Continued (TEFF05A): Effect of Rivaroxaban Compared with Placebo on the Secondary Efficacy Endpoints and Components as Adjudicated by the CEC
(Study RIVAROXACS3001: Modified Intent-to-Treat (Excluding Sites 091001, 091019 and 091026) Analysis Set)

Subject Stratum Parameter	----- Rivaroxaban -----				-- 2.5 mg BID vs. Placebo --		-- 5 mg BID vs. Placebo --		-- Combined vs. Placebo --	
	2.5 mg BID (N=5114) n(%)	5 mg BID (N=5115) n(%)	Combined (N=10229) n(%)	Placebo (N=5113) n(%)	HR (95% CI)	Log-Rank P-value	HR (95% CI)	Log-Rank P-value	HR (95% CI)	Log-Rank P-value
ASA + Thieno	4765	4767	9532	4760						
Dth/MI/St	292(6.1)	297(6.2)	589(6.2)	350(7.4)	0.84 (0.72,0.98)	0.028	0.87 (0.74,1.01)	0.068	0.85 (0.75,0.97)	0.019
Net Clin. Outcome	333(7.0)	341(7.2)	674(7.1)	355(7.5)	0.95 (0.82,1.10)	0.473	0.98 (0.85,1.14)	0.818	0.96 (0.85,1.10)	0.585
CV_Dth/MI/St/SRIR	406(8.5)	393(8.2)	799(8.4)	442(9.3)	0.93 (0.81,1.06)	0.276	0.91 (0.79,1.04)	0.164	0.92 (0.82,1.03)	0.149
CV_Dth/MI/St/SRIH	340(7.1)	358(7.5)	698(7.3)	405(8.5)	0.85 (0.73,0.98)	0.022	0.90 (0.78,1.04)	0.159	0.87 (0.77,0.99)	0.031
Death	90(1.9)	133(2.8)	223(2.3)	143(3.0)	0.64 (0.49,0.83)	<0.001	0.95 (0.75,1.21)	0.698	0.79 (0.64,0.98)	0.030
Ischemic Stroke	29(0.6)	30(0.6)	59(0.6)	28(0.6)	1.05 (0.62,1.76)	0.864	1.10 (0.66,1.84)	0.723	1.07 (0.68,1.68)	0.760
NonCABG TIMI Maj.	66(1.4)	81(1.7)	147(1.5)	23(0.5)	2.90 (1.81,4.67)	<0.001	3.64 (2.29,5.78)	<0.001	3.27 (2.10,5.07)	<0.001
SRI_Revas	128(2.7)	118(2.5)	246(2.6)	117(2.5)	1.10 (0.86,1.42)	0.438	1.03 (0.80,1.34)	0.794	1.07 (0.86,1.33)	0.551
SRI_Hosp	68(1.4)	86(1.8)	154(1.6)	91(1.9)	0.75 (0.55,1.03)	0.077	0.97 (0.72,1.31)	0.853	0.86 (0.66,1.12)	0.259

See footnotes on the first page of the table.

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6.4. Components of Composite Efficacy Endpoints

The significant effects of each dose of rivaroxaban on reducing the occurrence of the primary efficacy endpoint was driven by differing effects on individual components of the composite endpoints. These effects are further discussed below.

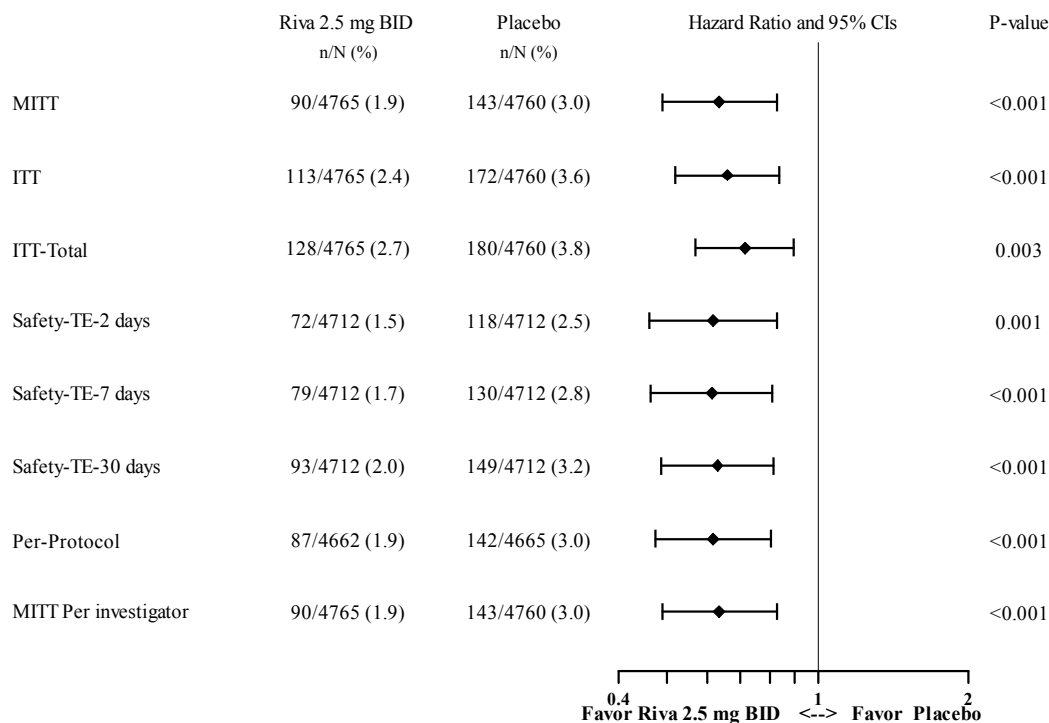
6.4.1. Cardiovascular Death and All Cause Death

In All Strata, the 2.5 mg b.i.d. dose of rivaroxaban was superior to placebo in reducing CV deaths (HR: 0.66, 95% CI: 0.51, 0.86; nominal p-value=0.002), a statistically significant reduction in CV deaths was not observed in the 5 mg b.i.d. group (HR: 0.94; 95% CI 0.75-1.20; nominal p-value=0.633). In Stratum 2, the results were consistent with those in All Strata ([Table 18](#)).

The results for all-cause death parallel those for CV death, as 92% of all-cause deaths were adjudicated to having CV causes. The impact of rivaroxaban on all-cause mortality mirrored that seen for cardiovascular mortality, while deaths from non-cardiovascular causes were balanced between treatment groups.

[Figure 14](#) presents forest plots of sensitivity analyses of all cause death in ITT, ITT-Total, Treatment-Emergent Safety, and other analysis sets for rivaroxaban 2.5 mg b.i.d. compared with placebo in Stratum 2. These results confirmed the robustness of the effect of 2.5 mg b.i.d. rivaroxaban on reducing all cause deaths; in all analysis sets tested, including the all inclusive ITT-Total analysis set, 2.5 mg b.i.d. rivaroxaban nominally significantly reduced the incidence of all cause death compared with placebo.

Figure 14: (FEFF1060e) Effect of Rivaroxaban 2.5 mg BID Compared with Placebo on All Cause Death as Adjudicated by the CEC in Stratum 2 (Study RIVAROXACS3001)



Note: Sites 091001, 091019 and 091026 were excluded for the analyses
 Note: Other than 'MITT per investigator', the analysis is based on data as adjudicated by CEC.
 Note: P-value is based on unstratified log-rank test and HR (95% confidence interval) is based on unstratified Cox proportional hazards model.
 Note: Scale of X axis was based on log transformation of the ratio. Tick labels of X axis are in the original ratio scale.

Page 1 of 1 for figure FEFF1060e

In contrast to the consistent results with the 2.5 mg b.i.d. dose, the 5 mg b.i.d. rivaroxaban dose did not appear to confer a CV survival benefit. While the mechanisms underlying this asymmetry are not entirely clear, there was a higher incidence of fatal bleeding in the 5 mg b.i.d. dose group compared with the 2.5 mg b.i.d. dose group, and there was numerically more deaths due to MI and congestive heart failure (CHF)/cardiogenic shock (Table 27), which contributed to the diminished effect of this dose on the reduction of CV death compared with the 2.5 mg b.i.d. dose. Potential explanations for the apparent lack of benefit in the reduction of CV death (as well as all-cause death) with rivaroxaban at a dose of 5 mg b.i.d. despite a nominally statistically significant reduction at a dose of 2.5 mg b.i.d. are further discussed in Section 6.9.1.

Table 27: (TAEPH02) Summary of Cardiovascular Deaths by Primary Cause as Adjudicated by the CEC (Study RIVAROXACS3001: Modified Intent-To-Treat (Excluding Sites 091001, 091019 and 091026) Analysis Set)

Subject Stratum: All Strata	----- Rivaroxaban -----			
	2.5 mg BID (N=5114)	5 mg BID (N=5115)	Combined (N=10229)	Placebo (N=5113)
	n (%)	n (%)	n (%)	n (%)
Cardiovascular Deaths	92 (1.8)	129 (2.5)	221 (2.2)	142 (2.8)
Non-hemorrhagic stroke	1 (<0.1)	3 (0.1)	4 (<0.1)	3 (0.1)
Intracranial hemorrhage	5 (0.1)	6 (0.1)	11 (0.1)	4 (0.1)
Atherosclerotic vascular disease (excluding coronary)	1 (<0.1)	1 (<0.1)	2 (<0.1)	1 (<0.1)
Congestive heart failure / Cardiogenic shock	8 (0.2)	19 (0.4)	27 (0.3)	17 (0.3)
Directly related to revascularization (CABG or PCI)	3 (0.1)	2 (<0.1)	5 (<0.1)	4 (0.1)
Cardiac arrhythmia	1 (<0.1)	4 (0.1)	5 (<0.1)	5 (0.1)
Pulmonary embolism	0	0	0	3 (0.1)
Sudden or unwitnessed death	55 (1.1)	59 (1.2)	114 (1.1)	81 (1.6)
Hemorrhage, not intracranial	0	5 (0.1)	5 (<0.1)	1 (<0.1)
Myocardial infarction	18 (0.4)	30 (0.6)	48 (0.5)	23 (0.4)
Other vascular	0	0	0	0
Unknown	2 (<0.1)	3 (0.1)	5 (<0.1)	1 (<0.1)

Note: Percentages calculated with the number of subjects in each treatment group as denominator.

Note: Death events occur 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: ASA = Acetylsalicylic acid; Thieno = Thienopyridine; CABG = Coronary artery bypass grafting.

6.4.2. Myocardial Infarction

Although the directionality of the reduction in MI was consistent in the 2.5 mg b.i.d and 5 mg b.i.d. dose groups, In All Strata, a nominally statistically significant reduction in MIs was not seen with 2.5 mg b.i.d. treatment group (HR: 0.90; 95% CI: 0.75, 1.09); however a nominally statistically significant reduction in MIs was seen with the 5 mg b.i.d. treatment group (HR: 0.79; 95% CI: 0.65, 0.97) (Table 18). Results in Stratum 2 are directionally consistent with All Strata. It is notable that in both All Strata and Stratum 2, even though the rivaroxaban 5 mg b.i.d. dose group had greater reduction of MIs than the 2.5 mg b.i.d. dose, higher percentage of subjects with MIs had a fatal outcome as reported by the investigators in the 5 mg b.i.d. group (7.8% in 2.5 mg b.i.d. group vs. 16.2% in 5 mg b.i.d. group), which contributed to the higher CV death incidence in the 5 mg b.i.d. group.

6.4.3. Stroke

Stroke of any cause (ischemic, hemorrhagic, and uncertain) was a component of the primary efficacy endpoint and Secondary Efficacy Endpoint 1.

Neither rivaroxaban dose appeared to reduce the risk of 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 0.7% in the placebo group. The HR (95% CI) for the rivaroxaban 2.5 mg b.i.d. and 5 mg b.i.d. doses compared with placebo were 0.89 (0.55,1.45) and 1.05 (0.65,1.68), respectively. The rates of hemorrhagic stroke were higher in the rivaroxaban

groups (0.3% in the 2.5 mg b.i.d. group and 0.4% in the 5 mg b.i.d. group) compared with the placebo group (0.1%), however the number of fatal ICH were similar in the 2.5 mg b.i.d. group and in the placebo group (Section 7.2 and Section 7.2.3).

The subcategories of stroke by dose group are presented in Table 28.

Table 29 summarizes a post hoc analysis of the effect of rivaroxaban compared with placebo on the proportion of strokes classified as causing either no symptom or slight disability (i.e., scores of 0 to 2 on modified Rankin scale) compared with disabling or fatal strokes (i.e., scores of 3 to 6 on modified Rankin scale). Based on investigator reported modified Rankin scale scores, 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 in All Strata and Stratum 2. No significant difference in the percentage of subjects with mild strokes vs. disabling or fatal strokes was seen in the 5 mg b.i.d. group compared with placebo.

**Table 28: (TEFF00A) Stroke by Subcategories as Adjudicated by the CEC
(Study RIVAROXACS3001: Modified Intent-To-Treat (Excluding Sites 091001, 091019 and 091026)
Analysis Set)**

	----- Rivaroxaban -----			
	2.5 mg BID n (%)	5 mg BID n (%)	Combined n (%)	Placebo n (%)
Subject Stratum: All Strata	5114	5115	10229	5113
Stroke	46 (0.9)	54 (1.1)	100 (1.0)	41 (0.8)
Ischemic Stroke	30 (0.6)	35 (0.7)	65 (0.6)	34 (0.7)
Ischemic Infarction	30 (0.6)	35 (0.7)	65 (0.6)	34 (0.7)
Ischemic Infarction with Hemorrhagic Conversion	0	0	0	0
Hemorrhagic Stroke	14 (0.3)	18 (0.4)	32 (0.3)	5 (0.1)
Primary Hemorrhagic Intraparenchymal Hemorrhage (including subarachnoid hemorrhage)	14 (0.3)	14 (0.3)	28 (0.3)	5 (0.1)
Primary Hemorrhagic Subdural Hematoma	0	4 (0.1)	4 (<0.1)	0
Primary Hemorrhagic Epidural Hematoma	0	0	0	0
Uncertain Stroke	2 (<0.1)	1 (<0.1)	3 (<0.1)	2 (<0.1)
Subject Stratum: Stratum ASA	349	348	697	353
Stroke	2 (0.6)	8 (2.3)	10 (1.4)	7 (2.0)
Ischemic Stroke	1 (0.3)	5 (1.4)	6 (0.9)	6 (1.7)
Ischemic Infarction	1 (0.3)	5 (1.4)	6 (0.9)	6 (1.7)
Ischemic Infarction with Hemorrhagic Conversion	0	0	0	0
Hemorrhagic Stroke	1 (0.3)	2 (0.6)	3 (0.4)	0
Primary Hemorrhagic Intraparenchymal Hemorrhage (including subarachnoid hemorrhage)	1 (0.3)	2 (0.6)	3 (0.4)	0
Primary Hemorrhagic Subdural Hematoma	0	0	0	0
Primary Hemorrhagic Epidural Hematoma	0	0	0	0
Uncertain Stroke	0	1 (0.3)	1 (0.1)	1 (0.3)
Subject Stratum: Stratum ASA+Thieno	4765	4767	9532	4760
Stroke	44 (0.9)	46 (1.0)	90 (0.9)	34 (0.7)
Ischemic Stroke	29 (0.6)	30 (0.6)	59 (0.6)	28 (0.6)
Ischemic Infarction	29 (0.6)	30 (0.6)	59 (0.6)	28 (0.6)
Ischemic Infarction with Hemorrhagic Conversion	0	0	0	0
Hemorrhagic Stroke	13 (0.3)	16 (0.3)	29 (0.3)	5 (0.1)
Primary Hemorrhagic Intraparenchymal Hemorrhage (including subarachnoid hemorrhage)	13 (0.3)	12 (0.3)	25 (0.3)	5 (0.1)
Primary Hemorrhagic Subdural Hematoma	0	4 (0.1)	4 (<0.1)	0
Primary Hemorrhagic Epidural Hematoma	0	0	0	0
Uncertain Stroke	2 (<0.1)	0	2 (<0.1)	1 (<0.1)

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: Percentages calculated with the number of subjects in each treatment group as denominator.

Note: Incidences are based on the number of subjects, not the number of events. Although a subject may have had 2 or more events, the subject is counted only once in a category. The same subject may appear in different categories.

ASA = Acetylsalicylic acid; Thieno = Thienopyridine; CABG = Coronary artery bypass grafting; MI = Myocardial infarction.

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Table 29: (TEFF1800) Cochran–Mantel–Haenszel Test by Modified Rankin Scale for Subjects Who Experienced Stroke as Reported by Investigator (Study RIVAROXACS3001; Modified Intent-to-Treat (Excluding Sites 091001, 091019 and 091026) Analysis Set)

Subject Stratum Modified Rankin Scale	----- Rivaroxaban -----				----- P-value -----	
	2.5 mg BID (N=5114) n(%)	5 mg BID (N=5115) n(%)	- Combined - (N=10229) n(%)	- Placebo - (N=5113) n(%)	2.5 mg BID vs. Placebo	5 mg BID vs. Placebo
All Strata	48	65	113	44	0.002	0.971
No Symptom to Slight Disability	36 (75.0)	30 (46.2)	66 (58.4)	21 (47.7)		
Disability or Death	7 (14.6)	29 (44.6)	36 (31.9)	20 (45.5)		
Not Done	5 (10.4)	6 (9.2)	11 (9.7)	3 (6.8)		
ASA	2	8	10	6	0.378	0.411
No Symptom to Slight Disability	1 (50.0)	3 (37.5)	4 (40.0)	1 (16.7)		
Disability or Death	1 (50.0)	5 (62.5)	6 (60.0)	5 (83.3)		
Not Done	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)		
ASA + Thieno	46	57	103	38	0.006	0.702
No Symptom to Slight Disability	35 (76.1)	27 (47.4)	62 (60.2)	20 (52.6)		
Disability or Death	6 (13.0)	24 (42.1)	30 (29.1)	15 (39.5)		
Not Done	5 (10.9)	6 (10.5)	11 (10.7)	3 (7.9)		

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: Percentages calculated with the number of subjects in each subject stratum and treatment group as denominator.

Note: If a subject had more than one Rankin Score, the severest one was selected.

Note: Test was done among subjects who reported Rankin Score.

Note: ASA = Acetylsalicylic acid; Thieno = Thienopyridine.

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6.5. Efficacy in Subgroups

Forest plots of the hazard ratio by subgroup baseline characteristics in the mITT analysis set for the primary efficacy endpoint are presented in [Figure 15](#) for rivaroxaban 2.5 mg b.i.d. vs. placebo in Stratum 2. A forest plot for the combined rivaroxaban doses vs. placebo in All Strata is included in [Appendix FEFF20A](#).

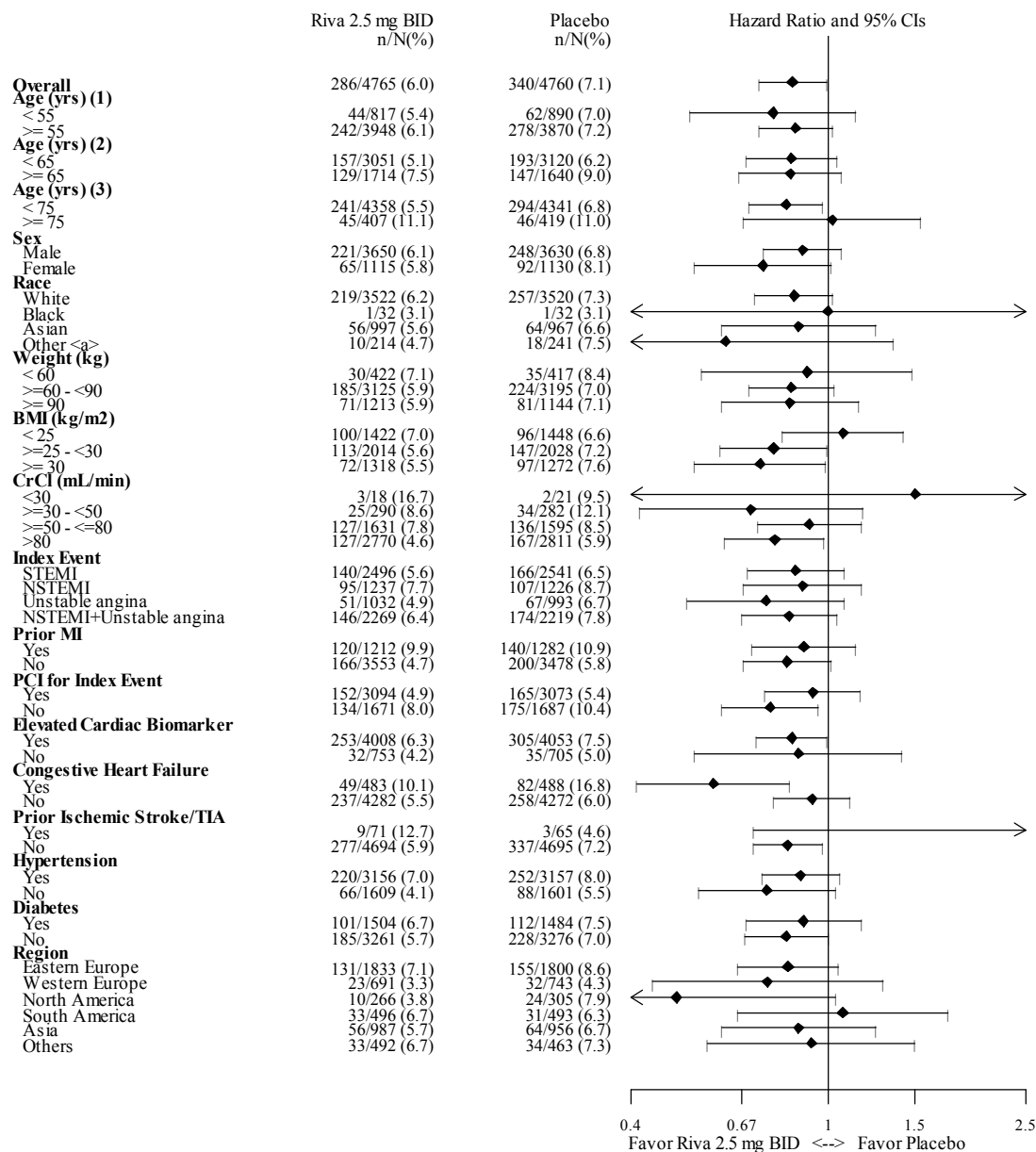
In general, rivaroxaban treatment was consistently associated with improved outcomes on the primary efficacy endpoint across all major subgroups. A favorable HR for rivaroxaban compared with placebo was observed across the majority of subgroups. For the majority of analyses, interaction p-values were >0.05.

- There was no significant interaction in the primary efficacy endpoint results by region; subjects across all regions benefited from treatment with rivaroxaban compared with placebo. Subjects in the North America region had a HR of 0.45 (95% CI: 0.22, 0.93) for rivaroxaban 2.5 mg group and a HR of 0.69 (95% CI: 0.37, 1.26) for rivaroxaban 5 mg group in All Strata, although the number of events was small (10 events in rivaroxaban 2.5 mg b.i.d. group, 17 events in rivaroxaban 5 mg group, and 27 events in placebo).
- The benefit of rivaroxaban was consistently demonstrated whether subjects had STEMI, NSTEMI or UA as their index event.

- The benefit of rivaroxaban was consistently shown in subjects who had PCI for index event and those who did not undergo intervention.
- The benefit of rivaroxaban was consistently shown in the presence or absence of prior diabetes.
- There was a nominally significant interaction for history of CHF. Subjects with a history of CHF appeared to derive a greater benefit from rivaroxaban treatment compared with subjects who did not have prior CHF in All Strata and Stratum 2. For all Strata, the rivaroxaban 2.5 b.i.d. group had a HR of 0.58 (95% CI: 0.42, 0.81) vs. placebo, showing a greater benefit compared with those without prior CHF (HR: 0.92, 95% CI: 0.77, 1.09); the interaction p-value was 0.016. Consistent with this, the rivaroxaban 5 mg b.i.d. group had a HR of 0.61 (95% CI: 0.44, 0.83) for subjects with CHF history, and an interaction p-value was 0.030. This result is further discussed in Section 6.9.4.
- It is important to note that the percentages of subjects with prior ischemic stroke (1.8%) and prior TIA (0.9%) were expectedly low, 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). For All Strata, in the rivaroxaban 2.5 mg b.i.d. group, subjects with a history of ischemic stroke or TIA showed a HR of 1.84 (95% CI: 0.82, 4.01) compared with placebo (although this subgroup was small [rivaroxaban 2.5 mg b.i.d.: 18/139; placebo: 9/131]), whereas subjects who did not have a prior ischemic stroke or TIA showed a HR of 0.81 (95% CI: 0.69, 0.94) compared with placebo; the interaction was nominally significant (p=0.047) favoring subjects without a history of a prior stroke or TIA. Results for the 5 mg b.i.d. group were directionally consistent, however the test for interaction was not significant (p=0.330). Results in Stratum 1 were also directionally consistent in each rivaroxaban dose group.
- Subjects with CrCl values <30 mL/min at screening were excluded from the study and subjects with confirmed post-baseline CrCl values <15 mL/min were permanently discontinued from treatment. The benefit of rivaroxaban was consistently shown in subjects across all creatinine clearance categories.
- Three populations of subjects were identified and defined post hoc as “fragile” using the following criteria: 1) subjects with CrCl values <50 mL/min at screening; 2) subjects ≥ 75 years old at screening; and 3) subjects with weight less than 60 kg. The interaction testing methods and results of the analysis of the primary efficacy endpoint in the “fragile” population in the 2.5 mg b.i.d. group for All Strata and Stratum 2 are shown in Table 30.

In All Strata, the subgroup meeting criterion 1), 2) or 3) had HRs favoring rivaroxaban, subgroups meeting any combination of the 3 criteria had small number of events, but also generally favored rivaroxaban. Results for the 5 mg b.i.d group were consistent.

Figure 15: (FEFF20B) Hazard Ratios and Rates of the Primary Efficacy Endpoint (First Occurrence of Cardiovascular Death, MI, Stroke) by Subgroup for Rivaroxaban 2.5 mg BID Dose Group Compared With Placebo in Stratum 2 (Study RIVAROXACS3001; mITT (Excluding Sites 091001, 091019, and 091026) Analysis Set



Note: Hazard Ratio and 95% confidence interval as compared to placebo arm is based on the unstratified Cox proportional hazards model.
Note: Scale of X axis was based on log transformation of the ratio. Tick labels of X axis are in the original ratio scale.
Note: <a> Including 'American Indian or Alaska Native', 'Native Hawaiian or Other Pacific Islander' and 'Other' per CRF.
Note: Arrow (< or >) of a line indicates that the confidence interval limit exceeds the X-axis range.

Table 30: (TEFF1032B) Effect of Rivaroxaban 2.5 mg Compared with Placebo on First Occurrence of Primary Efficacy Events as Adjudicated by the CEC by Subgroup
(Study RIVAROXACS3001: Modified Intent-to-Treat (Excluding Sites 091001, 091019 and 091026) Analysis Set)

Subject Stratum: All Strata						
Baseline Covariates	Categories	Riva 2.5 mg BID k/N (%)	-- Placebo -- k/N (%)	HR (95% CI)	P-value (a)	P-value (b)
1) Renal Impaired (<50)	Yes	35/357(9.8)	49/368(13.3)	0.73 (0.47,1.12)	0.509	-
	No	274/4695(5.8)	326/4691(6.9)	0.84 (0.72,0.99)		
2) Older (≥ 75)	Yes	51/462(11.0)	62/494(12.6)	0.90 (0.62,1.30)	0.753	-
	No	262/4652(5.6)	314/4619(6.8)	0.83 (0.71,0.98)		
3) Weight <60	Yes	33/458(7.2)	39/462(8.4)	0.91 (0.57,1.44)	0.714	-
	No	280/4651(6.0)	337/4647(7.3)	0.83 (0.71,0.97)		
1) and 2)	Yes	17/157(10.8)	33/178(18.5)	0.55 (0.31,0.99)	0.133	-
	No	292/4895(6.0)	342/4881(7.0)	0.86 (0.73,1.00)		
1) and 3)	Yes	11/121(9.1)	16/129(12.4)	0.73 (0.34,1.58)	0.794	-
	No	298/4927(6.0)	359/4926(7.3)	0.83 (0.71,0.97)		
2) and 3)	Yes	9/73(12.3)	11/83(13.3)	1.00 (0.41,2.41)	0.766	-
	No	304/5036(6.0)	365/5026(7.3)	0.84 (0.72,0.97)		
1) and 2) and 3)	Yes	4/43(9.3)	10/65(15.4)	0.61 (0.19,1.95)	0.549	-
	No	305/5005(6.1)	365/4990(7.3)	0.84 (0.72,0.97)		
Subject Stratum: ASA + Thieno						
Baseline Covariates	Categories	Riva 2.5 mg BID k/N (%)	-- Placebo -- k/N (%)	HR (95% CI)	P-value (a)	P-value (b)
1) Renal Impaired (<50)	Yes	28/308(9.1)	36/303(11.9)	0.74 (0.45,1.22)	0.651	-
	No	254/4401(5.8)	303/4406(6.9)	0.85 (0.72,1.00)		
2) Older (≥ 75)	Yes	45/407(11.1)	46/419(11.0)	1.02 (0.68,1.54)	0.347	-
	No	241/4358(5.5)	294/4341(6.8)	0.82 (0.69,0.98)		
3) Weight <60	Yes	30/422(7.1)	35/417(8.4)	0.91 (0.56,1.48)	0.779	-
	No	256/4338(5.9)	305/4339(7.0)	0.84 (0.71,0.99)		
1) and 2)	Yes	14/132(10.6)	20/142(14.1)	0.70 (0.35,1.39)	0.611	-
	No	268/4577(5.9)	319/4567(7.0)	0.85 (0.72,1.00)		
1) and 3)	Yes	10/100(10.0)	12/104(11.5)	0.89 (0.38,2.06)	0.859	-
	No	272/4605(5.9)	327/4601(7.1)	0.84 (0.71,0.98)		
2) and 3)	Yes	8/62(12.9)	7/68(10.3)	1.43 (0.52,3.94)	0.351	-
	No	278/4698(5.9)	333/4688(7.1)	0.84 (0.72,0.98)		
1) and 2) and 3)	Yes	4/34(11.8)	6/52(11.5)	1.12 (0.32,3.97)	0.690	-
	No	278/4671(6.0)	333/4653(7.2)	0.84 (0.71,0.98)		

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: k/N: Number of subjects having events / number of subjects at risk; % = 100 * k / N.

Note: HR (95% CI): Hazard ratio (95% confidence interval) as compared with placebo arm is based on the (stratified, only for all strata) Cox proportional hazards model.

Note: (a) P-value (two-sided) for the interaction of treatment group and each baseline subgroup based on the Cox proportional hazards model including treatment group, baseline subgroup and their interaction.

(footnote continued on next page)

Table 30 continued

Note: (b) Gail Simon P-value (two-sided) for the interaction of treatment group and the baseline subgroup is provided when proportional hazards model p-value is significant at 0.05 level.

Note: ASA = Acetylsalicylic acid; Thieno = Thienopyridine; CABG = Coronary artery bypass grafting.

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6.6. Off-Treatment Cardiovascular Events

Cardiovascular events that occurred after subjects were off treatment were assessed for all study drug-treated subjects who had at least 1 day follow-up after the last dose of study drug administration and for the endpoint events that occurred after the last dose of study drug administration.

Results of the analysis of CV events that occurred anytime after the last dose of study drug are shown in [Table 31](#).

In general, CV events after the last dose of study drug were well-balanced in the rivaroxaban and placebo treatment groups. There was no evidence of increased risk for off-treatment CV ischemic events following the last dose of rivaroxaban. This was consistently observed for all subjects including those who discontinued study drug at any time of the trial, as well as for those subjects who completed the double-blind treatment period per protocol (completers). Notably the rivaroxaban 2.5 mg b.i.d. group consistently had numerically fewer CV events occurring after the last dose of study drug than placebo, while the rivaroxaban 5 mg b.i.d. group appeared to have numerically more events after the last dose of study drug than placebo, for subject in All Strata and Stratum 2.

**Table 31: (TEFF33) Incidence of the Primary Efficacy Endpoint and Secondary Efficacy Endpoint after the Last Dose as Adjudicated by the CEC
(Study RIVAROXACS3001; Rebound (Excluding Sites 091001, 091019 and 091026) Analysis Set)**

Status	----- Rivaroxaban -----			
	2.5 mg BID (N=4940)	5 mg BID (N=4924)	Combined (N=9864)	Placebo (N=4910)
Parameter	n/N (%)	n/N (%)	n/N (%)	n/N (%)
Subject Stratum: All Strata				
Safety				
Anytime After the Last Dose				
Cardiovascular Death, MI, Stroke	120/4940(2.4)	173/4924(3.5)	293/9864(3.0)	148/4910(3.0)
Death, MI, Stroke	140/4940(2.8)	199/4924(4.0)	339/9864(3.4)	167/4910(3.4)
Death	100/4940(2.0)	137/4924(2.8)	237/9864(2.4)	113/4910(2.3)
Cardiovascular Death	79/4940(1.6)	109/4924(2.2)	188/9864(1.9)	93/4910(1.9)
MI	45/4940(0.9)	64/4924(1.3)	109/9864(1.1)	49/4910(1.0)
Stroke	17/4940(0.3)	30/4924(0.6)	47/9864(0.5)	23/4910(0.5)
Safety Completer				
Anytime After the Last Dose				
Cardiovascular Death, MI, Stroke	13/3718(0.3)	17/3581(0.5)	30/7299(0.4)	12/3748(0.3)
Death, MI, Stroke	15/3718(0.4)	18/3581(0.5)	33/7299(0.5)	15/3748(0.4)
Death	8/3718(0.2)	8/3581(0.2)	16/7299(0.2)	8/3748(0.2)
Cardiovascular Death	6/3718(0.2)	7/3581(0.2)	13/7299(0.2)	5/3748(0.1)
MI	9/3718(0.2)	10/3581(0.3)	19/7299(0.3)	5/3748(0.1)
Stroke	0/3718	1/3581(<0.1)	1/7299(<0.1)	3/3748(0.1)
Subject Stratum: Stratum 2				
Safety				
Anytime After the Last Dose				
Cardiovascular Death, MI, Stroke	105/4610(2.3)	157/4591(3.4)	262/9201(2.8)	135/4570(3.0)
Death, MI, Stroke	123/4610(2.7)	182/4591(4.0)	305/9201(3.3)	153/4570(3.3)
Death	86/4610(1.9)	126/4591(2.7)	212/9201(2.3)	104/4570(2.3)
Cardiovascular Death	67/4610(1.5)	99/4591(2.2)	166/9201(1.8)	85/4570(1.9)
MI	40/4610(0.9)	59/4591(1.3)	99/9201(1.1)	45/4570(1.0)
Stroke	15/4610(0.3)	27/4591(0.6)	42/9201(0.5)	20/4570(0.4)
Safety Completer				
Anytime After the Last Dose				
Cardiovascular Death, MI, Stroke	13/3471(0.4)	13/3327(0.4)	26/6798(0.4)	12/3494(0.3)
Death, MI, Stroke	15/3471(0.4)	14/3327(0.4)	29/6798(0.4)	15/3494(0.4)
Death	8/3471(0.2)	5/3327(0.2)	13/6798(0.2)	8/3494(0.2)
Cardiovascular Death	6/3471(0.2)	4/3327(0.1)	10/6798(0.1)	5/3494(0.1)
MI	9/3471(0.3)	8/3327(0.2)	17/6798(0.3)	5/3494(0.1)
Stroke	0/3471	1/3327(<0.1)	1/6798(<0.1)	3/3494(0.1)

Note: The data shown are for all study drug treated subjects who had at least one day follow up after last dose of study drug administration and the endpoint events occurring after last dose of study drug administration.

Note: Safety Completer: Safety subjects who completed double blind treatment period as per CRF.

Note: n = number of subjects with events;

Note: N = number of subjects who were at risk for the endpoint at the beginning of the reported time interval;

Note: % = 100 * n / N.

Note: Cardiovascular death including unknown death; MI: Myocardial infarction.

Note: ASA = Acetylsalicylic acid; Thieno = Thienopyridine.

6.7. Efficacy in Stratum 1

In ATLAS ACS 2 TIMI 51, there were a total of 1053 randomized subjects in Stratum 1 (i.e., subjects intended to be treated with ASA alone). Overall, efficacy results in Stratum 1 were directionally consistent with those in Stratum 2 and favored rivaroxaban treatment. Results in Stratum 1 were similar between the 2 rivaroxaban dose groups, with the point estimates for treatment effect favoring rivaroxaban, but not reaching statistical significance in either group.

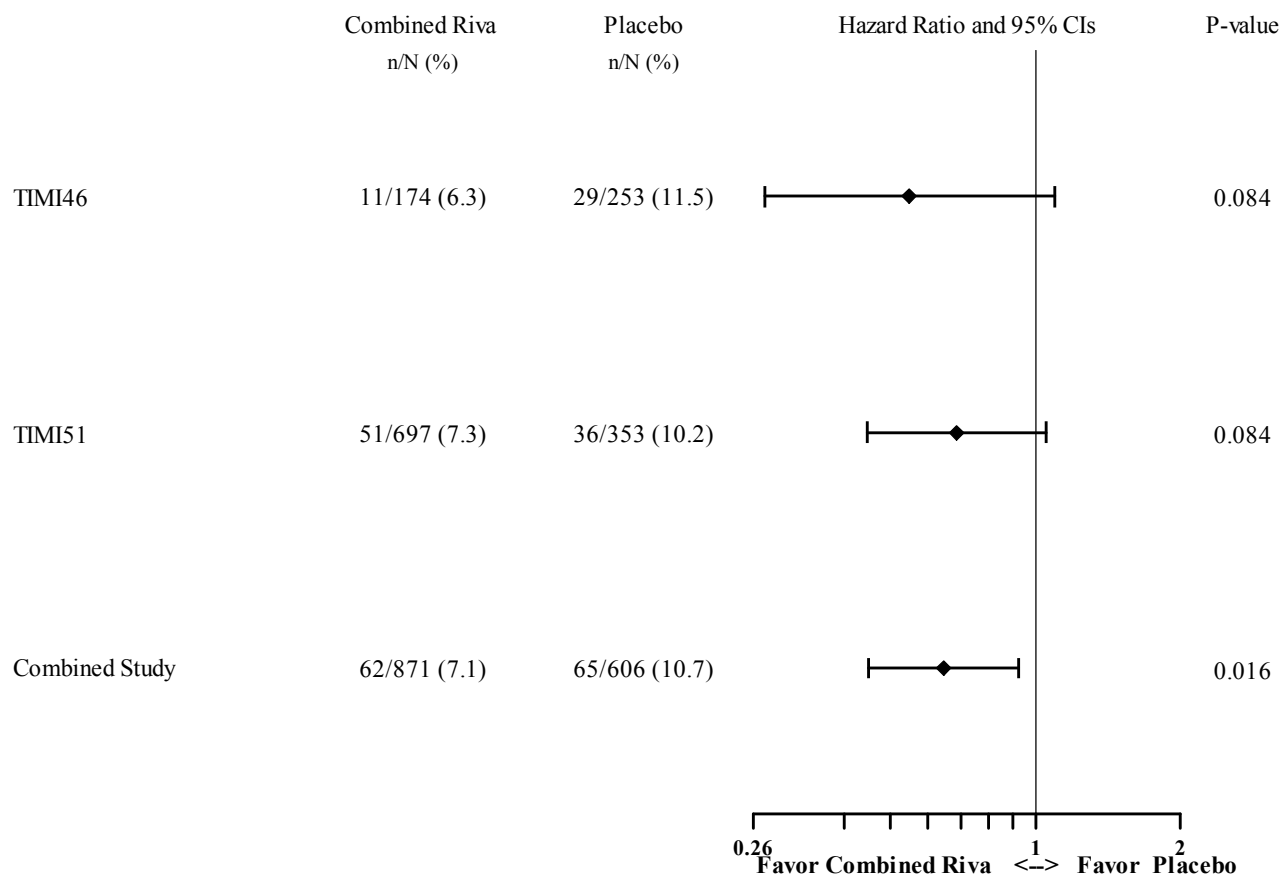
For Stratum 1, the incidence of the primary efficacy endpoint (the composite of CV death, MI or stroke) was numerically lower in the 2.5 mg b.i.d. (27 [7.7%]; HR: 0.74, 95% CI: 0.45, 1.22) and the 5 mg b.i.d. (24 [6.9%]; HR: 0.64, 95% CI: 0.38, 1.07) groups compared with the placebo group (36 [10.2%]). As shown in [Table 18](#), the effect of rivaroxaban in Stratum 1 was primarily driven by a numerical reduction in MIs (HR: 0.72, 95% CI: 0.38, 1.37) and strokes (HR: 0.28, 95% CI: 0.06, 1.37) in the 2.5 mg b.i.d. group and by a reduction in MIs (HR: 0.44; 95% CI: 0.21, 0.93) in the 5 mg b.i.d. group.

The results for Secondary Efficacy Endpoint 1 (the composite of all cause death, MI or stroke) closely mirrored those of the primary efficacy endpoint. For Secondary Efficacy Endpoint 2 (NCO), HRs favored rivaroxaban both for the 2.5 mg b.i.d. dose (HR: 0.77; 95% CI: 0.47, 1.26) and the 5 mg b.i.d. dose (HR: 0.67; 95% CI: 0.40, 1.11) ([Table 26](#)).

Pooled Stratum 1 from the Phase 2 and Phase 3 Studies

Subjects in Stratum 1 who received rivaroxaban 2.5 mg b.i.d., 5 mg b.i.d and placebo in ATLAS ACS TIMI 46 were pooled with subjects in Stratum 1 in ATLAS ACS 2 TMI 51 and analyzed for the primary efficacy endpoint. As shown in [Figure 16](#), the results of primary efficacy endpoint favored the combined rivaroxban doses group compared with the placebo group in each study, and for the pooled data across the 2 studies. The results from the pooled data confirm the efficacy results in Stratum 1 of ATLAS ACS 2 TIMI 51, and show directional consistency with results in Stratum 2 of ATLAS ACS 2 TIMI 51.

Figure 16: (FEFF4001g) Effect of Rivaroxaban Compared with Placebo on the Primary Efficacy Endpoint (First Occurrence of Cardiovascular Death, MI, or Stroke) as Adjudicated by the CEC in ASA Stratum
(Integrated Summary of Efficacy of Study 39039039ACS2001 and Study RIVAROXACS3001: Modified Intent-to-Treat (Excluding Sites 091001, 091019 and 091026) Analysis Set)



Note: Sites 091001, 091019 and 091026 were excluded for the analyses
 Note: P-value is based on unstratified log-rank test and HR (95% confidence interval) is based on unstratified Cox proportional hazards model.
 Note: Analyses are also stratified by Study in Cox proportional hazards model and Log-Rank test for combined study.
 Note: Scale of X axis was based on log transformation of the ratio. Tick labels of X axis are in the original ratio scale.

Page 1 of 1 for figure FEFF4001g

6.8. Summary of Clinical Benefits

The key efficacy results of the ATLAS ACS 2 TIMI 51 study are summarized in [Table 32](#).

Superiority of the combined rivaroxaban doses to placebo in reducing the composite endpoint of CV death, MI, or stroke was achieved across both strata and in Stratum 2 (subjects intended to receive ASA plus a thienopyridine). In Stratum 2, only the 2.5 mg b.i.d. dose achieved superiority; the result was driven by a nominally significant reduction in CV deaths. While the 5 mg b.i.d. dose in Stratum 2 had a HR of 0.87 (CI%: 0.74, 1.01) favoring rivaroxaban, it did not reach statistical significance. Although the overall results of the study were driven by the considerably larger Stratum 2, directionally consistent results favoring rivaroxaban were observed in Stratum 1 (subjects intended to receive ASA only). Within Stratum 2 the benefit of rivaroxaban was consistently demonstrated whether subjects were or were not receiving a thienopyridine.

The survival benefit for CV death observed with the 2.5 mg b.i.d. dose was nominally statistically significant both in All Strata and in Stratum 2. The results for all-cause death parallel those for CV death, as 92% of all-cause deaths were CV deaths (including deaths adjudicated to have CV causes or unknown causes). Across strata, the 2.5 mg b.i.d. dose resulted in an absolute rate reduction of 1.0% in CV deaths (placebo 2.8% vs. rivaroxaban 2.5 mg 1.8%), with a HR of 0.66 (95%: 0.51, 0.86), and an absolute rate reduction of 1.0% in all cause deaths (placebo 3.0% vs. rivaroxaban 2.5 mg 2.0%), with a HR of 0.68 (95%: 0.53, 0.87). The reduction in deaths observed in the 2.5 mg b.i.d. group was primarily due to a reduction in deaths attributed to CHF/cardiogenic shock and sudden or unwitnessed death. The 5 mg b.i.d. rivaroxaban dose, while directionally consistent, did not confer a statistically significant benefit in reducing CV death.

The 5 mg b.i.d. group showed nominal statistical significance compared with placebo in reducing MIs for Stratum 1, and for Stratum 2, the effects were directionally consistent, but the difference compared with placebo was not statistically significant. Although the 5 mg b.i.d. dose of rivaroxaban showed a greater reduction in the incidence of MIs than the 2.5 mg b.i.d. dose, a higher percentage of MIs in the 5 mg b.i.d. group were fatal, both in All Strata and Stratum 2, which contributed to the higher CV death incidence in the 5 mg b.i.d. group.

Neither rivaroxaban dose reduced the risk of ischemic stroke, however, the incidences of stroke were low overall and balanced across treatment groups. Subjects in the 2.5 mg b.i.d. rivaroxaban group experienced less debilitating strokes compared with subjects in the 5 mg b.i.d. and placebo groups, according to the investigator-reported Rankin scale data. Since the absolute number of stroke events occurring in this trial was small, a conclusion cannot be made on the effect of rivaroxaban on ischemic stroke in patients with ACS.

Table 32: Comparison of Key Efficacy Results of the 2.5 mg b.i.d. and 5 mg b.i.d. Treatment Groups in All Strata and Stratum 2
(Study RIVAROXACS3001: mITT (Excluding Sites 091001, 091019 and 091026) Analysis Set)

	Rivaroxaban 2.5 mg b.i.d. (N=5114 for All Strata; N= 4765 for Stratum 2)	Rivaroxaban 5 mg b.i.d. (N=5115 for All Strata; N= 4767 for Stratum 2)	Placebo (N=5113 for All Strata; N= 4760 for Stratum 2)
Primary Efficacy Endpoint (the composite of cardiovascular death, MI or stroke)			
All Strata			
Event Incidence (n [%])	313 (6.1%)	313 (6.1%)	376 (7.4%)
HR (95% CI) vs Placebo	0.84 (0.72,0.97)	0.85 (0.73,0.98)	-
Stratum 2			
Event Incidence (n [%])	286 (6.0%)	289 (6.1%)	340 (7.1%)
HR (95% CI) vs Placebo	0.85 (0.72,0.99)	0.87 (0.74,1.01)	-
Secondary Efficacy Endpoint 1 (the composite of all-cause death, MI or stroke)			
All Strata			
Event Incidence (n [%])	320 (6.3%)	321 (6.3%)	386 (7.5%)
HR (95% CI) vs Placebo	0.83 (0.72,0.97)	0.84 (0.73,0.98)	-
Stratum 2			
Event Incidence	292 (6.1%)	297 (6.2%)	350 (7.4%)
HR (95% CI) vs Placebo	0.84 (0.72,0.98)	0.87 (0.74,1.01)	-
Cardiovascular Death			
All Strata			
Event Incidence (n [%])	94 (1.8%)	132 (2.6%)	143 (2.8%)
HR (95% CI) vs Placebo	0.66 (0.51,0.86)	0.94 (0.75,1.20)	-
Stratum 2			
Event Incidence (n [%])	82 (1.7%)	123 (2.6%)	133 (2.8%)
HR (95% CI) vs Placebo	0.62 (0.47,0.82)	0.95 (0.74,1.21)	-
All-cause Death			
All Strata			
Event Incidence (n [%])	103 (2.0%)	142 (2.8%)	153 (3.0%)
HR (95% CI) vs Placebo	0.68 (0.53,0.87)	0.95 (0.76,1.19)	-
Stratum 2			
Event Incidence (n [%])	90 (1.9%)	133 (2.8%)	143 (3.0%)
HR (95% CI) vs Placebo	0.64 (0.49,0.83)	0.95 (0.75,1.21)	-
Myocardial Infarction			
All Strata			
Event Incidence (n [%])	205 (4.0%)	179 (3.5%)	229 (4.5%)
HR (95% CI) vs Placebo	0.90 (0.75,1.09)	0.79 (0.65,0.97)	-
Stratum 2			
Event Incidence (n [%])	189 (4.0%)	169 (3.5%)	207 (4.3%)
HR (95% CI) vs Placebo	0.92 (0.75,1.12)	0.83 (0.68,1.02)	-
Stroke			
All Strata			
Event Incidence (n [%])	46 (0.9%)	54 (1.1%)	41 (0.8%)
HR (95% CI) vs Placebo	1.13 (0.74,1.73)	1.34 (0.90,2.02)	-
Stratum 2			
Event Incidence (n [%])	44 (0.9%)	46 (1.0%)	34 (0.7%)
HR (95% CI) vs Placebo	1.31 (0.84,2.05)	1.39 (0.89,2.16)	-

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. Endpoint events were adjudicated by the Clinical Endpoint Committee. Source outputs: DEFF02A, DEFF05A.

6.9. Efficacy Discussion

The ATLAS ACS 2 TIMI 51 study met its primary objective, demonstrating the overall superiority of rivaroxaban to placebo in addition to standard of care in reducing risk of the primary efficacy endpoint events (CV death, MI or stroke) in subjects with ACS.

In addition to rivaroxaban, another FXa inhibitor, apixaban, has also been tested in a Phase 3 clinical trial, APPRAISE-2, in ACS patients. In the Phase 2 studies ATLAS ACS TIMI 46 (of rivaroxaban) and APPRAISE-1 (of apixaban), both compounds appeared to reduce the risk of CV death, MI or stroke, with a dose dependent increase in bleeding risk. In ATLAS ACS TIMI 46, rivaroxaban in addition to aspirin alone reduced the risk of cardiovascular death, MI or stroke dose-dependently. In those subjects receiving aspirin plus a thienopyridine as standard care, rivaroxaban was associated with a relatively flat dose response effect, in that higher doses did not appear to further reduce the risk of this composite efficacy endpoint. The Phase 3 APPRAISE-2 trial differed from the APPRAISE-1 trial (and also from the Phase 3 ATLAS ACS 2 TIMI 51 trial) by inclusion of higher risk patients, and enrollment of approximately 10% of subjects with a history of prior stroke. It is uncertain if these patient characteristics, in particular the patients with prior stroke in whom the point estimate of HR for the primary efficacy endpoint was 1.5, in favor of placebo treatment, contributed to the negative outcome, but the APPRAISE-2 study was stopped prematurely by the independent data monitoring committee because of increased bleeding, including a 3-fold increase in intracranial bleeding, not offset by a reduction in cardiovascular events.

6.9.1. The Differential Effect Between the Dose Groups

The survival benefit for CV death observed with the rivaroxaban 2.5 mg b.i.d. dose was nominally statistically significant both across strata and in Stratum 2. The results for all-cause death parallel those for CV death, as 92% of all-cause deaths were adjudicated to have cardiovascular causes. Across strata, the 2.5 mg b.i.d. dose resulted in an absolute rate reduction of 1.0% in CV deaths (placebo 2.8% vs. rivaroxaban 2.5 mg 1.8%), with a HR of 0.66 (95% CI: 0.51, 0.86), and an absolute rate reduction of 1.0% in all cause deaths (placebo 3.0% vs. rivaroxaban 2.5 mg 2.0%), with a HR of 0.68 (95% CI: 0.53, 0.87). The 5 mg b.i.d. rivaroxaban dose, while directionally consistent, did not confer a statistically significant benefit in reducing CV death or all cause death.

The significantly higher risk of fatal bleeding and the numerically higher incidences of death due to CHF/cardiogenic shock and MI in the 5 mg b.i.d. group compared with the 2.5 mg b.i.d. dose contributed to the diminished effect of this dose on the reduction of CV death (Table 27). It is also of interest to note that the large reduction in the risk of CV death in the 2.5mg b.i.d dose group occurred without a nominally significant reduction in the risk of MI. A similar result was observed in the PROVE-IT TIMI 22 trial of pravastatin versus atorvastatin; where atorvastatin treatment resulted in a 1% absolute reduction in mortality, with a somewhat smaller reduction in MI⁴⁵.

Why rivaroxaban at a dose of 2.5 mg b.i.d. was found to exert a reduction in CV death, but the 5 mg b.i.d. dose was not, is uncertain, but a number of hypotheses exist.

It has been demonstrated in a number of independent analyses that the adjusted risk of 30-day mortality was higher in ACS patients with major bleeding events compared with those with no bleeding events^{11,15}. The difference in the reduction of CV death between the 2 rivaroxaban dose groups may be partially explained by the higher dose of rivaroxaban (5 mg b.i.d.) increasing the rate of major bleeding, which while not being immediately fatal, portends a fatal outcome due to medical complications within the following 30 days.

Support for this hypothesis comes from a post hoc analysis that was performed to examine the odds ratio for death in subjects with non-CABG TIMI major bleeding events (note for all except 2 deaths, 1 in 5 mg group and 1 in placebo group, the non-CABG TIMI major bleeding events occurred in the 30 days immediately prior to the event of death), compared with that in subjects without non-CABG TIMI major bleeding in each treatment group. Odds ratio of death anytime after non-CABG TIMI major bleeding event were 5.92 (95% CI 2.64, 13.27) in the 2.5 mg b.i.d group, 9.03 (95% CI 5.09, 15.99) in the 5 mg b.i.d group, and 6.98 (95% CI 2.35, 20.77) for placebo in All Strata (Table 33). These results indicate that subjects who experienced a non-CABG TIMI major bleeding event are at higher risk of death following the bleeding event. Since the rivaroxaban 5 mg b.i.d. dose had significantly more bleeding events (including non-CABG TIMI major bleeding events) than the 2.5 mg b.i.d dose group (see Section 7.5), the lack of a clear mortality reduction at that dose is not unexpected.

Taken together, these data suggest that rivaroxaban reduces the risk of CV death. This is clearly apparent at a dose of 2.5 mg b.i.d., however, at the higher rivaroxaban dose of 5 mg b.i.d., which carries with it a greater liability for bleeding, the positive cardio-protective effect of rivaroxaban is overcome by the increased risk of serious bleeding which carries its own hazard for adverse outcome.

An alternative explanation is chance or variation, i.e., if the efficacy dose response has plateaued at 2.5 mg dose (as supported by ATLAS ACS TIMI 46 Stratum 2 results and also the ATLAS ACS 2 TIMI 51 composite endpoint results) then the best estimate of efficacy for the components of the composite could be the results in the combined rivaroxaban doses (Table 18), which demonstrates a 20% (HR 0.80, 95% CI 0.65-0.99) RRR for CV death and a 15% (HR 0.85, 95% CI 0.72-1.00) RRR for MI events--both of which show nominal significance.

**Table 33: (TEFF1040) Summary of Non-CABG TIMI Major Bleeding Events (adjudicated by CEC) Prior to Death
(Study RIVAROXACS3001: Modified Intent-to-Treat (Excluding Sites 091001, 091019 and 091026) Analysis Set)**

		----- Non-CABG TIMI major bleeding events -----							
		----- Rivaroxaban -----							
Parameter	Category	----- 2.5 mg BID -----		----- 5 mg BID -----		----- Combined -----		----- Placebo -----	
		YES	NO	YES	NO	YES	NO	YES	NO
Subject Stratification: All Strata									
Death	YES	7	96	16	126	23	222	4	149
	NO	61	4950	69	4904	130	9854	19	4941
	Odds Ratio		5.92		9.03		7.85		6.98
	95% CI		(2.64,13.27)		(5.09,15.99)		(4.94,12.48)		(2.35,20.77)
Subject Stratification: ASA + Thieno									
Death	YES	6	84	16	117	22	201	4	139
	NO	60	4615	65	4569	125	9184	19	4598
	Odds Ratio		5.49		9.61		8.04		6.96
	95% CI		(2.31,13.07)		(5.40,17.12)		(5.00,12.92)		(2.34,20.74)

Note: all subjects with death outcome died within 30 days of non-CABG TIMI major bleeding except one in 5 mg BID and one in placebo.

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6.9.2. The Effect of Rivaroxaban on Stroke

While the number of strokes observed in this study were small, that rivaroxaban treatment did not result in a reduction in the risk of stroke is intriguing. The risk of hemorrhagic stroke was increased with rivaroxaban, in particular the 5 mg b.i.d dosing regimen, but when hemorrhagic events were excluded and only ischemic, non-hemorrhagic strokes were considered, rivaroxaban still did not reduce the risk of those events. However, based on investigator reported modified Rankin scale scores, 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 in All Strata and Stratum 2. This finding may be explained by considering the literature relating thrombin generation to neuronal apoptosis^{6,48}. Since rivaroxaban ultimately blocks thrombin generation, and since thrombin is known to be a potent mediator of neuronal apoptosis, the inhibition of the thrombin may ameliorate early brain injury and improve neurological outcome, which can be reflected in the improved Rankin score. While stroke ultimately is the result of neuronal ischemia, the underlying pathophysiology that results in this in ACS patients may not be amenable to treatment with rivaroxaban, unlike thromboembolic stroke prevention in atrial fibrillation. The same study also found that a history of MI was associated with intracranial plaques and a previous stroke was associated with intracranial stenosis.

6.9.3. Time Course of Efficacy Benefit

As described in Section 6.2, the use of rivaroxaban conferred an efficacy benefit that was apparent early, and continued to be present over the duration of the trial. As described in Section 6.2.1.3, there was no apparent differential thienopyridine use or discontinuation between

treatment groups, and the benefit of rivaroxaban treatment was apparent while subjects were using a thienopyridine as well as in subjects who discontinued thienopyridine.

6.9.4. Outcome in Subgroups

Subjects with Prior Stroke/TIA

As noted in Section 6.5, outcomes consistently favored treatment with rivaroxaban across all major subgroups, with the exception of those subjects with a prior stroke or TIA, in whom outcome tended to be better in subjects receiving placebo. It is interesting to note that those subjects with a prior stroke or TIA who received rivaroxaban tended to experience a MI as their first primary efficacy endpoint event, and not a stroke, as might have been expected. During the early conduct of the study, after release of the data from TRITON study, the protocol for ATLAS ACS 2 TIMI 51 was amended to exclude subjects with a prior TIA from participation in Stratum 2, in addition to the already excluded subjects with a prior stroke. At the same time, subjects with a prior ischemic stroke or TIA were allowed to be randomized into Stratum 1 if ASA only was the treatment for the ACS event chosen by a managing physician. The finding in ATLAS ACS 2 TIMI 51 that subjects with a history of stroke or TIA had worse CV outcomes, primarily a higher rate of MI, compared with those without a prior stroke or TIA, is in line with findings from other clinical trials and registries^{1,13,46}. However, it is noteworthy that only 1 out of 139 subjects in the rivaroxaban 2.5 mg b.i.d. and 1 out of 145 subjects in the 5 mg b.i.d. group with a history of stroke or TIA had hemorrhagic stroke. In TRITON-TIMI 38, patients with a history of stroke or TIA derived less benefit (there was a positive interaction indicating harm) from more intensive antiplatelet treatment with prasugrel⁴⁶. In the MATCH study, patients with a history of stroke or TIA on dual antiplatelet therapy (ASA and clopidogrel) had a greater incidence of life-threatening bleeding without any additional CV benefit in reducing major CV events compared with patients with a history of stroke or TIA treated with ASA only⁹. Dual antiplatelet therapy with aspirin plus clopidogrel was associated with no benefit, greater bleeding and higher mortality in the National Institute of Neurological Disorders and Stroke (NINDS) randomized secondary prevention trial of patients with subcortical stroke.

Subjects with CHF

Also of interest is the finding in the group of subjects with a history of CHF. In this group of subjects outcome particularly favored treatment with rivaroxaban: the 2.5 b.i.d. group had a HR of 0.58 (95% CI: 0.42, 0.81) vs. placebo in All Strata. The information of ejection fraction was available in approximately 60% of the subjects. In those subjects where ejection fraction was available, the mean for the group was 47-48% for each treatment group in All Strata and Stratum 2. In subjects without a history of CHF, CV death was still reduced by treatment with rivaroxaban at a dose of 2.5 mg b.i.d. (HR: 0.72; 95% CI: 0.52-1.00 in Stratum 2). Only sparse baseline CHF information was collected in the study, as such, it is difficult to draw definitive conclusions.

7. CLINICAL SAFETY – ATLAS ACS 2 TIMI 51

7.1. Extent of Exposure

7.1.1. Exposure to Study Drug

Since ATLAS ACS 2 TIMI 51 was an event-driven study, subjects were exposed to study drug for varying lengths of time, depending on their time of randomization. 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. Across all treatment groups, 78.9% had cumulative durations of exposure ≥ 6 months, 53.8% for ≥ 12 months, and 30.9% 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. The lower exposure to study drug in the 5 mg b.i.d. group is most likely related to a higher rate of premature discontinuation from double-blind treatment in this group. Similar results were observed both in Stratum 1 and in Stratum 2 ([Table 34](#)).

**Table 34: (TSUB17) Total Duration of Treatment (Including Any Study Drug Interruption)
(Study RIVAROXACS3001; Safety Analysis Set)**

	----- Rivaroxaban -----				
	2.5 mg BID (N=5115)	- 5 mg BID - (N=5110)	- Combined - (N=10225)	-- Placebo - (N=5125)	--- Total --- (N=15350)
All Strata					
N	5115	5110	10225	5125	15350
Mean	395.8	385.6	390.7	399.9	393.8
SD	233.28	237.28	235.33	232.55	234.44
Median	397.0	376.5	386.0	399.0	390.5
Minimum	1	1	1	1	1
Maximum	927	929	929	932	932
Total Exposure (patient years)	5542.4	5394.8	10937.2	5611.2	16548.5
<u>Cumulative duration of treatment, n (%)</u>					
N	5115	5110	10225	5125	15350
≥ 3 months	4449 (87.0)	4342 (85.0)	8791 (86.0)	4465 (87.1)	13256 (86.4)
≥ 6 months	4054 (79.3)	3942 (77.1)	7996 (78.2)	4109 (80.2)	12105 (78.9)
≥ 12 months	2785 (54.4)	2657 (52.0)	5442 (53.2)	2816 (54.9)	8258 (53.8)
≥ 18 months	1574 (30.8)	1547 (30.3)	3121 (30.5)	1624 (31.7)	4745 (30.9)
≥ 24 months	509 (10.0)	498 (9.7)	1007 (9.8)	508 (9.9)	1515 (9.9)
ASA + Thieno					
N	4772	4768	9540	4773	14313
Mean	397.1	385.8	391.4	402.1	395.0
SD	233.08	237.51	235.36	232.13	234.34
Median	399.0	377.5	388.0	401.0	392.0
Minimum	1	1	1	1	1
Maximum	927	929	929	932	932
Total Exposure (patient years)	5187.5	5035.8	10223.3	5254.4	15477.7
<u>Cumulative duration of treatment, n (%)</u>					
N	4772	4768	9540	4773	14313
≥ 3 months	4157 (87.1)	4048 (84.9)	8205 (86.0)	4170 (87.4)	12375 (86.5)
≥ 6 months	3792 (79.5)	3673 (77.0)	7465 (78.2)	3845 (80.6)	11310 (79.0)
≥ 12 months	2615 (54.8)	2486 (52.1)	5101 (53.5)	2643 (55.4)	7744 (54.1)
≥ 18 months	1472 (30.8)	1442 (30.2)	2914 (30.5)	1520 (31.8)	4434 (31.0)
≥ 24 months	477 (10.0)	469 (9.8)	946 (9.9)	480 (10.1)	1426 (10.0)

Note: Total duration of treatment (including days on/off study drug) = date of the last study medication administration - date of the first study medication administration + 1.

Note: Percentages calculated with the number of subjects who received study drug in each subject stratum and group as denominator.

Note: The unit for duration is days.

Note: ASA = Acetylsalicylic acid; Thieno = Thienopyridine.

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7.1.2. Exposure to Concomitant Standard Care

All subjects were to receive oral antiplatelet therapy of low-dose ASA (75 to 100 mg/day) and a thienopyridine (clopidogrel or ticlopidine only, per the national or locally indicated dosage) as standard care for subjects with ACS, unless the subject was not considered an appropriate

candidate for thienopyridine therapy. Subjects were stratified by the intention of the investigator to use dual anti-platelet therapy (Stratum 2) or ASA only (Stratum 1).

Of the 15,350 subjects in the safety population, only 10 subjects (all in Stratum 2) did not receive ASA therapy during the double-blind treatment period. Exposure to ASA therapy was similar to exposure to study drug. In All Strata, across all treatment groups, 78.8% of subjects in the safety population were exposed to concomitant ASA for ≥ 6 months, 53.8% for ≥ 12 months, and 30.9% for ≥ 18 months. In Stratum 2, 99.4% of subjects in the safety population received a thienopyridine and the majority received clopidogrel (98.8%); the use of ticlopidine (122 [0.9%]) and other thienopyridines (60 [0.4%]) in Stratum 2 was minimal. In Stratum 2, across all treatment groups, 72.9%, 45.4%, and 19.4% subjects were exposed to thienopyridine for ≥ 6 months, ≥ 12 months, and ≥ 18 months, respectively. Thienopyridine use in Stratum 1 overall was expectedly lower (141 [13.6%]) than in Stratum 2 and transient in nature, based on median exposure; use of a concomitant thienopyridine in Stratum 1 was lowest in the 5 mg b.i.d. group (40 [11.7%]), followed by 2.5 mg b.i.d. (48 [14.0%]) and placebo (53 [15.1%]). ([Table 25](#), [Appendix DSUB24B](#)).

7.2. Bleeding Events

In ATLAS ACS 2 TIMI 51, only TIMI classification of bleeding events was required to be reported by the investigators, however additional information was also collected to enable classification of the events with other scales as well. The CEC members adjudicated all bleeding events, independent of severity or location, on 3 different bleeding scales most widely used in cardiovascular clinical trials: TIMI, ISTH, and GUSTO scales. The TIMI bleeding classification (i.e., TIMI major, TIMI minor, TIMI bleeding requiring medical attention and TIMI insignificant bleeding) was the primary classification. The detailed classification of each bleeding scale is provided in [Appendix 1](#).

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. The incidence of clinically significant bleeding (including TIMI major, TIMI minor and TIMI bleeding requiring medical attention) for All Strata was 11.5%, 14.6%, and 6.4% for the rivaroxaban 2.5 mg b.i.d., 5 mg b.i.d., and placebo group; for Stratum 2, the incidence was 11.9%, 15.2%, and 6.6% for rivaroxaban 2.5 mg b.i.d., 5 mg b.i.d., and placebo groups ([Table 35](#)). The results in Stratum 2 were similar to All Strata, since 93% of study subjects were enrolled into Stratum 2.

**Table 35: (from TBL21) Incidence of Treatment–Emergent Bleeding Events as Adjudicated by the CEC
(Study RIVAROXACS3001; Treatment-Emergent Safety Analysis Set)**

Subject Stratum: All Strata

	----- Rivaroxaban -----			
	2.5 mg BID (N=5115)	5 mg BID (N=5110)	Combined (N=10225)	Placebo (N=5125)
	n (%)	n (%)	n (%)	n (%)
TIMI major bleeding	68 (1.3)	85 (1.7)	153 (1.5)	27 (0.5)
Non-CABG TIMI major bleeding* ***	65 (1.3)	82 (1.6)	147 (1.4)	19 (0.4)
Non-CABG TIMI major bleeding - fatal	6 (0.1)	13 (0.3)	19 (0.2)	3 (0.1)
Non-CABG TIMI major bleeding - non-fatal**	59 (1.2)	69 (1.4)	128 (1.3)	16 (0.3)
CABG related TIMI major bleeding	3 (0.1)	3 (0.1)	6 (0.1)	8 (0.2)
TIMI minor bleeding	32 (0.6)	49 (1.0)	81 (0.8)	20 (0.4)
Non-CABG TIMI major or minor bleeding	97 (1.9)	129 (2.5)	226 (2.2)	38 (0.7)
TIMI bleeding requiring medical attention	492 (9.6)	637 (12.5)	1129 (11.0)	282 (5.5)
Clinically significant bleeding***	586 (11.5)	748 (14.6)	1334 (13.0)	327 (6.4)
Fatal bleeding	6 (0.1)	15 (0.3)	21 (0.2)	9 (0.2)
Non-fatal bleeding	580 (11.3)	733 (14.3)	1313 (12.8)	318 (6.2)
Intracranial bleeding	14 (0.3)	18 (0.4)	32 (0.3)	5 (0.1)
Intra-parenchymal	13 (0.3)	13 (0.3)	26 (0.3)	4 (0.1)
Intra-ventricular	2 (<0.1)	7 (0.1)	9 (0.1)	0
Epidural	0	1 (<0.1)	1 (<0.1)	0
Subdural	1 (<0.1)	3 (0.1)	4 (<0.1)	1 (<0.1)
Subarachnoid	3 (0.1)	4 (0.1)	7 (0.1)	2 (<0.1)
Hemorrhagic stroke	13 (0.3)	17 (0.3)	30 (0.3)	4 (0.1)
Primary hemorrhagic intraparenchymal hemorrhage (including subarachnoid hemorrhage)	13 (0.3)	15 (0.3)	28 (0.3)	4 (0.1)
Primary hemorrhagic subdural hematoma	0	2 (<0.1)	2 (<0.1)	0
Primary hemorrhagic epidural hematoma	0	0	0	0

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: Percentages calculated with the number of subjects in each treatment group as denominator.

Note: Incidences are based on the number of subjects, not the number of events. Although a subject may have had 2 or more bleeding events, the subject is counted only once in a category. The same subject may appear in different categories.

Note: * Primary safety endpoint; ** Subjects did not have any fatal non-CABG TIMI major bleeding.

Note: *** If one subject has both fatal and non-fatal bleedings, only fatal bleeding is counted.

Note: ASA = Acetylsalicylic acid; Thieno = Thienopyridine; CABG = Coronary artery bypass grafting.

Table 35 Continued (TBL21): Incidence of Treatment-Emergent Bleeding Events as Adjudicated by the CEC
(Study RIVAROXACS3001: Treatment-Emergent Safety Analysis Set)
Subject Stratum: ASA + Thieno

	----- Rivaroxaban -----			
	2.5 mg BID (N=4772) n (%)	5 mg BID (N=4768) n (%)	Combined (N=9540) n (%)	Placebo (N=4773) n (%)
TIMI major bleeding	66 (1.4)	81 (1.7)	147 (1.5)	25 (0.5)
Non-CABG TIMI major bleeding* ***	63 (1.3)	78 (1.6)	141 (1.5)	19 (0.4)
Non-CABG TIMI major bleeding - fatal	5 (0.1)	13 (0.3)	18 (0.2)	3 (0.1)
Non-CABG TIMI major bleeding - non-fatal**	58 (1.2)	65 (1.4)	123 (1.3)	16 (0.3)
CABG related TIMI major bleeding	3 (0.1)	3 (0.1)	6 (0.1)	6 (0.1)
TIMI minor bleeding	31 (0.6)	49 (1.0)	80 (0.8)	20 (0.4)
Non-CABG TIMI major or minor bleeding	94 (2.0)	125 (2.6)	219 (2.3)	38 (0.8)
TIMI bleeding requiring medical attention	476 (10.0)	618 (13.0)	1094 (11.5)	273 (5.7)
Clinically significant bleeding***	567 (11.9)	725 (15.2)	1292 (13.5)	316 (6.6)
Fatal bleeding	5 (0.1)	15 (0.3)	20 (0.2)	8 (0.2)
Non-fatal bleeding	562 (11.8)	710 (14.9)	1272 (13.3)	308 (6.5)
Intracranial bleeding	13 (0.3)	16 (0.3)	29 (0.3)	5 (0.1)
Intra-parenchymal	12 (0.3)	11 (0.2)	23 (0.2)	4 (0.1)
Intra-ventricular	2 (<0.1)	6 (0.1)	8 (0.1)	0
Epidural	0	1 (<0.1)	1 (<0.1)	0
Subdural	1 (<0.1)	3 (0.1)	4 (<0.1)	1 (<0.1)
Subarachnoid	3 (0.1)	4 (0.1)	7 (0.1)	2 (<0.1)
Hemorrhagic stroke	12 (0.3)	15 (0.3)	27 (0.3)	4 (0.1)
Primary hemorrhagic intraparenchymal hemorrhage (including subarachnoid hemorrhage)	12 (0.3)	13 (0.3)	25 (0.3)	4 (0.1)
Primary hemorrhagic subdural hematoma	0	2 (<0.1)	2 (<0.1)	0
Primary hemorrhagic epidural hematoma	0	0	0	0

See footnotes on the first page of the table.

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7.2.1. Primary Safety Endpoint

The primary safety endpoint was non-CABG TIMI major bleeding in the treatment-emergent safety analysis set, which comprises events that occurred from the first dose of the study drug up to 2 days after discontinuation, inclusive.

The effect of rivaroxaban compared with placebo on treatment-emergent bleeding events of all TIMI scale categories, including the primary safety endpoint (non-CABG-related TIMI major bleeding), is shown in [Table 36](#) by treatment group and stratum.

For all subjects cross strata, the occurrence of the primary safety endpoint was significantly higher in both the 2.5 mg b.i.d. group (1.3% vs. 0.4% placebo; HR: 3.46, 95% CI: 2.08, 5.77;

p<0.001) and the 5 mg b.i.d. group (1.6% 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 again significantly higher in both the 2.5 mg b.i.d. group (1.3% 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% vs. 0.4% placebo; HR: 4.26, 95% CI: 2.58, 7.03; p<0.001) compared with placebo.

Kaplan-Meier estimates of the cumulative risk of the first occurrence of the primary safety endpoint by treatment group are shown for Stratum 1, Stratum 2 and All Strata in [Figure 17](#) for the treatment-emergent safety analysis set. Throughout the treatment period, the cumulative risk of the first occurrence of non-CABG-related TIMI major bleeding was higher with either dose of rivaroxaban compared with placebo, but was highest with the 5 mg b.i.d. rivaroxaban dose.

Table 36: (TBL01) 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)

Subject Stratum Parameter	----- Rivaroxaban -----				-- 2.5 mg BID vs. Placebo --		--- 5 mg BID vs. Placebo ---		-- Combined vs. Placebo --	
	2.5 mg BID (N=5115) n(%)	5 mg BID (N=5110) n(%)	Combined (N=10225) n(%)	Placebo (N=5125) n(%)	HR (95% CI)	Log-Rank P-value	HR (95% CI)	Log-Rank P-value	HR (95% CI)	Log-Rank P-value
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)	<0.001	4.47 (2.71,7.36)	<0.001	3.96 (2.46,6.38)	<0.001
Clinical Sig.	586(11.5)	748(14.6)	1334(13.0)	327(6.4)	1.84 (1.61,2.11)	<0.001	2.43 (2.13,2.76)	<0.001	2.13 (1.89,2.40)	<0.001
TIMI Ma or Mi	100(2.0)	132(2.6)	232(2.3)	46(0.9)	2.20 (1.55,3.11)	<0.001	2.96 (2.12,4.14)	<0.001	2.58 (1.88,3.54)	<0.001
TIMI Major	68(1.3)	85(1.7)	153(1.5)	27(0.5)	2.55 (1.63,3.98)	<0.001	3.25 (2.11,5.02)	<0.001	2.90 (1.92,4.36)	<0.001
TIMI Minor	32(0.6)	49(1.0)	81(0.8)	20(0.4)	1.62 (0.92,2.82)	0.090	2.52 (1.50,4.24)	<0.001	2.07 (1.27,3.37)	0.003
TIMI Med. Attent.	492(9.6)	637(12.5)	1129(11.0)	282(5.5)	1.79 (1.55,2.07)	<0.001	2.39 (2.08,2.75)	<0.001	2.09 (1.83,2.38)	<0.001
ASA	343	342	685	352						
Primary	2(0.6)	4(1.2)	6(0.9)	0		0.154		0.046		0.083
Clinical Sig.	19(5.5)	23(6.7)	42(6.1)	11(3.1)	1.77 (0.84,3.71)	0.128	2.10 (1.02,4.31)	0.038	1.93 (0.99,3.75)	0.048
TIMI Ma or Mi	3(0.9)	4(1.2)	7(1.0)	2(0.6)	1.53 (0.26,9.16)	0.638	2.00 (0.37,10.94)	0.413	1.77 (0.37,8.50)	0.472
TIMI Major	2(0.6)	4(1.2)	6(0.9)	2(0.6)	1.02 (0.14,7.22)	0.987	2.00 (0.37,10.94)	0.413	1.51 (0.30,7.47)	0.612
TIMI Minor	1(0.3)	0	1(0.1)	0		0.308				0.472
TIMI Med. Attent.	16(4.7)	19(5.6)	35(5.1)	9(2.6)	1.82 (0.81,4.13)	0.144	2.13 (0.96,4.70)	0.056	1.97 (0.95,4.10)	0.064
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)	<0.001	4.26 (2.58,7.03)	<0.001	3.80 (2.35,6.14)	<0.001
Clinical Sig.	567(11.9)	725(15.2)	1292(13.5)	316(6.6)	1.84 (1.61,2.12)	<0.001	2.44 (2.14,2.78)	<0.001	2.14 (1.89,2.42)	<0.001
TIMI Ma or Mi	97(2.0)	128(2.7)	225(2.4)	44(0.9)	2.23 (1.56,3.18)	<0.001	3.01 (2.13,4.23)	<0.001	2.62 (1.89,3.61)	<0.001
TIMI Major	66(1.4)	81(1.7)	147(1.5)	25(0.5)	2.67 (1.68,4.23)	<0.001	3.35 (2.14,5.25)	<0.001	3.01 (1.97,4.60)	<0.001
TIMI Minor	31(0.6)	49(1.0)	80(0.8)	20(0.4)	1.56 (0.89,2.74)	0.116	2.52 (1.50,4.24)	<0.001	2.04 (1.25,3.33)	0.004
TIMI Med. Attent.	476(10.0)	618(13.0)	1094(11.5)	273(5.7)	1.79 (1.54,2.07)	<0.001	2.40 (2.08,2.77)	<0.001	2.09 (1.83,2.39)	<0.001

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.

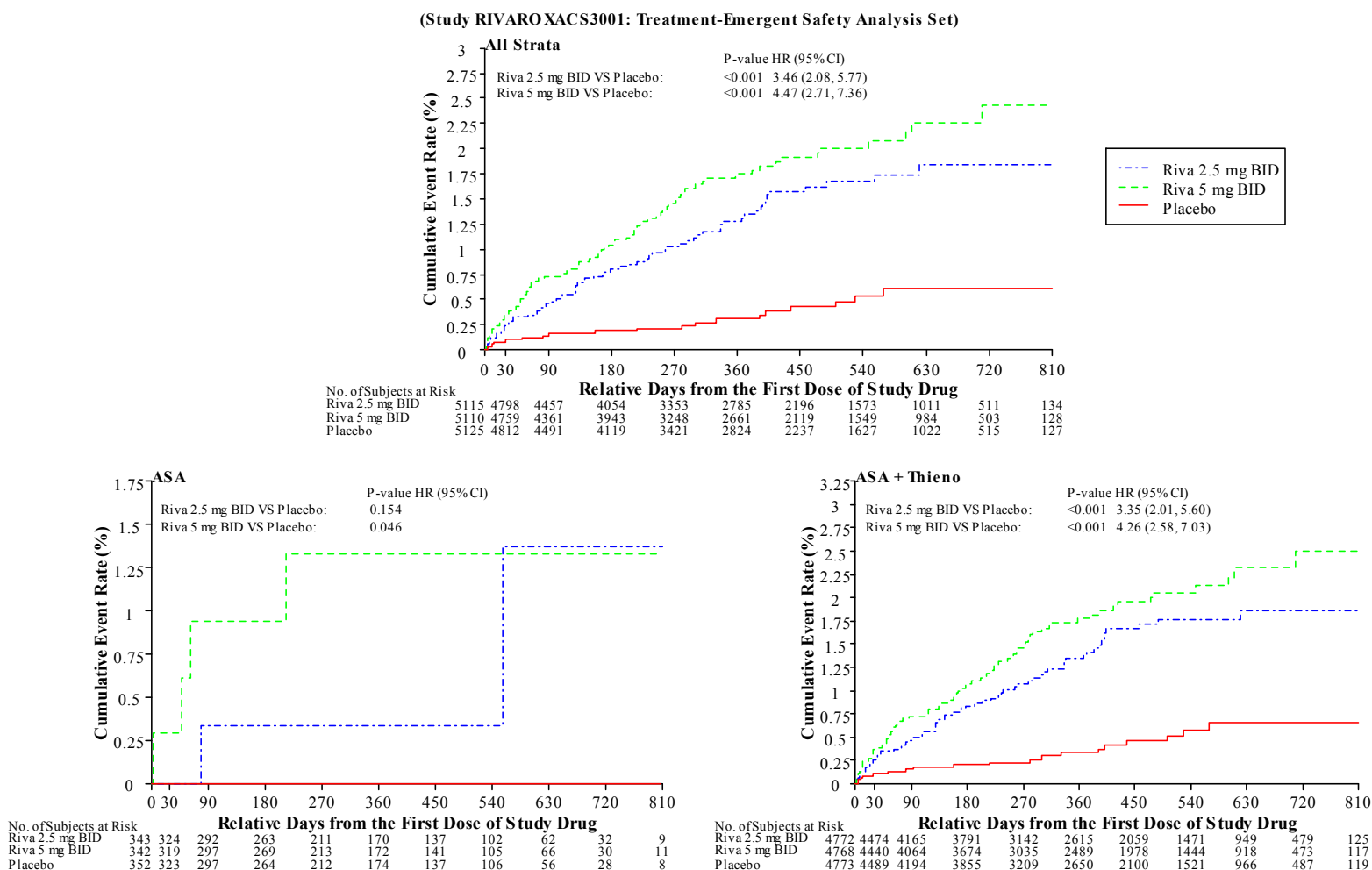
Note: HR (95% CI): Hazard ratios (95% confidence interval) as compared with placebo arm are based on the (stratified, only for all strata) Cox proportional hazards model.

Note: Log-Rank P-value: P-values (two-sided) as compared with placebo arm are based on the (stratified, only for all strata) log rank test.

Note: ASA = Acetylsalicylic acid; Thieno = Thienopyridine; CABG = Coronary artery bypass grafting.

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Figure 17: (FBL01A) Kaplan-Meier Estimates of the First Occurrence of Treatment-Emergent Non-CABG TIMI Major Bleeding Events as Adjudicated by the CEC (Study RIVAROXACS3001; Treatment-Emergent Safety Analysis Set)



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: P-value is based on (stratified, only for all strata) log-rank test and HR (95% CI) is based on (stratified, only for all strata) Cox proportional hazards model.

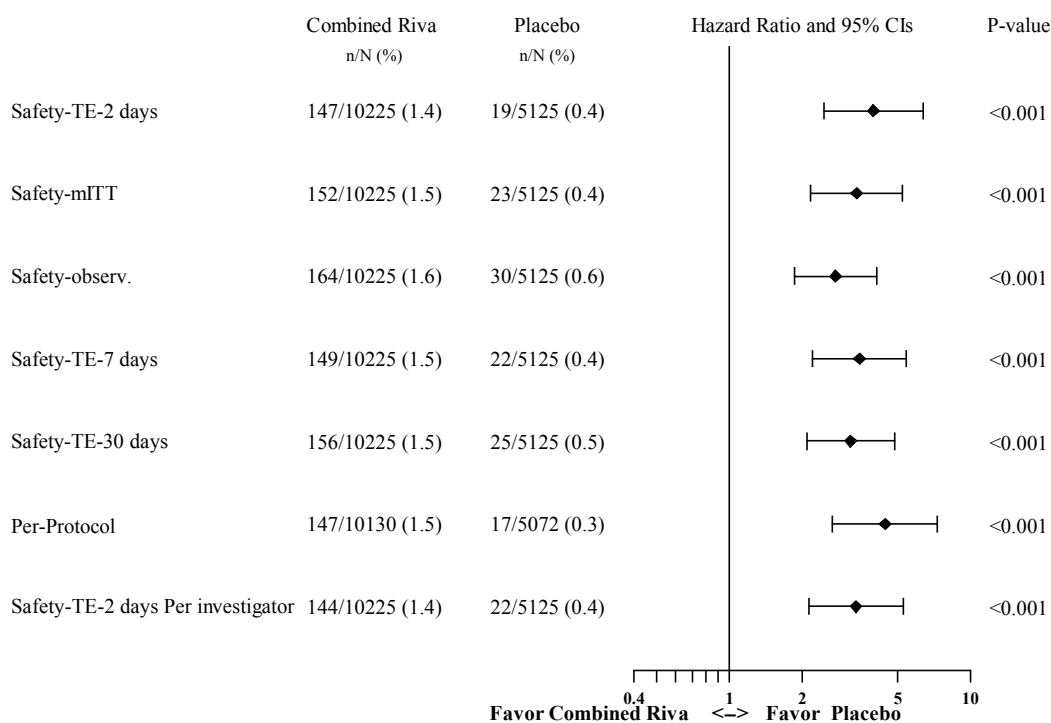
Note: KM curves for all treatment groups are not displayed when number of subjects at risk in any treatment group reaches less than 50 or 1 percent of that at the starting time point whichever is less.

7.2.1.1. Sensitivity Analyses of the Primary Safety Endpoint

The primary safety endpoint was analyzed, using the same methods as those used for the primary safety analysis in the treatment-emergent safety analysis set, in an array of additional analysis sets. Forest plots of the sensitivity analyses for the combined rivaroxaban doses in All Strata are shown in [Figure 18](#).

Results of the sensitivity analyses were generally consistent with the results of the primary safety analysis in showing significantly increased bleeding in the rivaroxaban group.

Figure 18: (FBL07A) Effect of Combined Rivaroxaban Compared with Placebo on First Occurrence of Non-CABG TIMI Major Bleeding Events in All Strata (Study RIVAROXACS3001)



Note: Other than 'Safety-TE-2 days Per investigator', the analysis is based on data as adjudicated by CEC.
 Note: P-value is based on stratified log-rank test and HR (95% confidence interval) is based on stratified Cox proportional hazards model.
 Note: Scale of X axis was based on log transformation of the ratio. Tick labels of X axis are in the original ratio scale.

Page 1 of 1 for figure FBL07A

7.2.2. Fatal Bleeding

As shown in [Table 37](#), the overall incidence of fatal bleeding events in the study was low (21/10225 for combined rivaroxaban and 9/5125 for placebo in All Strata). In All Strata, the frequency of fatal bleeding events was similar in the rivaroxaban 2.5 mg b.i.d. group (6/5115) and placebo (9/5125), and numerically higher in the rivaroxaban 5 mg b.i.d. (15/5110) group compared with the 2.5 mg b.i.d. group and placebo. The HR (95% CI) vs. placebo was 0.67 (0.24, 1.89) for rivaroxaban 2.5 mg b.i.d. group, and 1.72 (0.75, 3.92) for rivaroxaban 5 mg b.i.d. group ([Appendix DBL04](#)). Results in Stratum 2 were similar to All Strata.

In All Strata, the majority of fatal bleeding events were intracranial or gastrointestinal (GI). Fatal intracranial bleeding events occurred in 5 of 5115 subjects in the 2.5 mg b.i.d. group, 8 of 5110

subjects in the 5 mg b.i.d. group, and 4 of 5125 placebo subjects. Fatal GI bleeding occurred in 1 of 5115 subjects in the 2.5 mg b.i.d. group, 6 of 5110 subjects in the 5 mg b.i.d. and 0 placebo subjects. None of the fatal pericardial bleeding events was in the 2.5 mg b.i.d. group; 1 of 5110 occurred in the 5 mg b.i.d. group compared with 3 of 5125 events in the placebo group. These results were mirrored in Stratum 2 (Table 37).

Table 37: (TBL03D) Treatment-Emergent Fatal Bleeding using TIMI Scale by Location Reported by the CEC (Study RIVAROXACS3001; Treatment-Emergent Safety Analysis Set)

Subject Stratum Bleeding Location	----- Rivaroxaban -----			
	2.5 mg BID (N=5115) n (%)	5 mg BID (N=5110) n (%)	Combined (N=10225) n (%)	Placebo (N=5125) n (%)
All Strata	5115	5110	10225	5125
Total No. of Subjects with Treatment-Emergent Fatal Bleeding	6 (0.1)	15 (0.3)	21 (0.2)	9 (0.2)
Gastrointestinal (Hematemesis or Melena)	1 (<0.1)	6 (0.1)	7 (0.1)	0
Internal Bleeding (Non-Incisional Site)	0	0	0	1 (<0.1)
Associated with CABG				
Intracranial	5 (0.1)	8 (0.2)	13 (0.1)	4 (0.1)
Pericardial	0	1 (<0.1)	1 (<0.1)	3 (0.1)
Other	0	0	0	1 (<0.1)
ASA + Thieno	4772	4768	9540	4773
Total No. of Subjects with Treatment-Emergent Fatal Bleeding	5 (0.1)	15 (0.3)	20 (0.2)	8 (0.2)
Gastrointestinal (Hematemesis or Melena)	1 (<0.1)	6 (0.1)	7 (0.1)	0
Internal Bleeding (Non-Incisional Site)	0	0	0	0
Associated with CABG				
Intracranial	4 (0.1)	8 (0.2)	12 (0.1)	4 (0.1)
Pericardial	0	1 (<0.1)	1 (<0.1)	3 (0.1)
Other	0	0	0	1 (<0.1)

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: Percentages calculated with the number of subjects in each treatment group as denominator.

Note: Incidences are based on the number of subjects, not the number of events. Although a subject may have had 2 or more bleedings in the same location, the subject is counted only once in a category. The same subject may appear in different categories.

Note: ASA = Acetylsalicylic acid; Thieno = Thienopyridine; CABG = Coronary artery bypass grafting.

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7.2.3. Intracranial Bleeding

In general, the incidence of treatment-emergent intracranial bleeding and hemorrhagic stroke was low, 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 in placebo group and rivaroxaban 2.5 mg b.i.d. group.

In All Strata, 5 of 5125 subjects in placebo group compared with 14 of 5115 subjects in the 2.5 mg b.i.d. group and 18 of 5110 subjects in the 5 mg b.i.d. group had intracranial bleeding

events ([Table 35](#)). The HR (95% CI) vs. placebo was 2.83 (1.02, 7.86) for rivaroxaban 2.5 mg b.i.d. group, and 3.74 (1.39, 10.07) for rivaroxaban 5 mg b.i.d. group ([Appendix DBL04](#)).

In Stratum 2, 5 of 4773 subjects in placebo group compared with 13 of 4772 subjects in the 2.5 mg b.i.d. group and 16 of 4768 subjects in the 5 mg b.i.d. group had intracranial bleeding events ([Table 35](#)). The HR (95% CI) vs. placebo was 2.63 (0.94, 7.38) for rivaroxaban 2.5 mg b.i.d. group, and 3.34 (1.22, 9.12) for rivaroxaban 5 mg b.i.d. group ([Appendix DBL04](#)).

In All Strata, 5/14 subjects in the 2.5 mg b.i.d. group, 8/18 subjects in the 5 mg b.i.d. group, and 4/5 placebo subjects with intracranial bleeding events had fatal outcomes ([Table 37](#)). The incidence rates of hemorrhagic stroke across strata were similar to those for intracranial bleeding events ([Table 35](#)).

In All Strata, all but 1 case of intracranial bleeding events were non-CABG TIMI major bleeding events. The majority of cases of non-CABG TIMI major treatment-emergent intracranial bleeding were spontaneous: 8/14 intracranial bleeds in the 2.5 mg b.i.d. group, 13/18 intracranial bleeds in the 5 mg b.i.d. group, and 4/4 intracranial bleeds in the placebo group. The remaining cases were intracranial bleeding events due to trauma ([Appendix DBL30](#)).

7.2.4. Bleeding Events by Location of Bleeding

The most frequently reported sites of treatment-emergent TIMI major bleeding were GI and intracranial. In All Strata, 42 of 5115 subjects in the rivaroxaban 2.5 mg b.i.d dose, 46 of 5110 subjects in the rivaroxaban 5 mg b.i.d dose, and 13 of 5125 placebo subjects reported GI bleeding, and 14 of 5115 subjects in the rivaroxaban 2.5 mg b.i.d dose, 18 of 5110 subjects in the rivaroxaban 5 mg b.i.d dose, and 5 of 5125 placebo subjects reported intracranial bleeding. These event rates were consistent in Stratum 2 ([Table 38](#)).

**Table 38: (TBL03A) Treatment–Emergent TIMI Major Bleeding Events by Location Reported by the CEC
(Study RIVAROXACS3001; Treatment-Emergent Safety Analysis Set)**

Bleeding Location	----- Rivaroxaban -----			
	2.5 mg BID (N=5115) n (%)	5 mg BID (N=5110) n (%)	Combined (N=10225) n (%)	Placebo (N=5125) n (%)
Subject Stratum: All Strata	5115	5110	10225	5125
Total no. of subjects with treatment-emergent TIMI major bleeding	68 (1.3)	85 (1.7)	153 (1.5)	27 (0.5)
Bleeding associated with cardiac catheterization access site	2 (<0.1)	1 (<0.1)	3 (<0.1)	0
Bleeding from any location associated with non-cardiac surgery	2 (<0.1)	1 (<0.1)	3 (<0.1)	2 (<0.1)
Epistaxis	1 (<0.1)	1 (<0.1)	2 (<0.1)	0
Gastrointestinal (hematemesis or melena)	42 (0.8)	46 (0.9)	88 (0.9)	13 (0.3)
Incision site bleeding associated with CABG	0	0	0	1 (<0.1)
Increased or prolonged menstrual or abnormal vaginal bleeding	1 (<0.1)	1 (<0.1)	2 (<0.1)	0
Internal bleeding (non-incisional site) associated with CABG	3 (0.1)	3 (0.1)	6 (0.1)	6 (0.1)
Intracranial	14 (0.3)	18 (0.4)	32 (0.3)	5 (0.1)
Intramuscular (with compartment syndrome)	1 (<0.1)	1 (<0.1)	2 (<0.1)	0
Macroscopic (gross) hematuria	0	2 (<0.1)	2 (<0.1)	0
Pericardial	0	1 (<0.1)	1 (<0.1)	0
Rectal	1 (<0.1)	6 (0.1)	7 (0.1)	0
Retroperitoneal	1 (<0.1)	3 (0.1)	4 (<0.1)	0
Skin (ecchymosis other than at instrumented site)	0	1 (<0.1)	1 (<0.1)	0
Other	1 (<0.1)	1 (<0.1)	2 (<0.1)	0

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(continued))

Table 38 (continued): Treatment–Emergent TIMI Major Bleeding Events by Location Reported by the CEC (Study RIVAROXACS3001; Treatment–Emergent Safety Analysis Set)

Bleeding Location	----- Rivaroxaban -----			
	2.5 mg BID (N=5115) n (%)	5 mg BID (N=5110) n (%)	Combined (N=10225) n (%)	Placebo (N=5125) n (%)
Subject Stratum: ASA + Thieno	4772	4768	9540	4773
Total no. of subjects with treatment-emergent TIMI major bleeding	66 (1.4)	81 (1.7)	147 (1.5)	25 (0.5)
Bleeding associated with cardiac catheterization access site	2 (<0.1)	1 (<0.1)	3 (<0.1)	0
Bleeding from any location associated with non-cardiac surgery	2 (<0.1)	1 (<0.1)	3 (<0.1)	2 (<0.1)
Epistaxis	1 (<0.1)	1 (<0.1)	2 (<0.1)	0
Gastrointestinal (hematemesis or melena)	41 (0.9)	44 (0.9)	85 (0.9)	13 (0.3)
Incision site bleeding associated with CABG	0	0	0	1 (<0.1)
Increased or prolonged menstrual or abnormal vaginal bleeding	1 (<0.1)	1 (<0.1)	2 (<0.1)	0
Internal bleeding (non-incisional site) associated with CABG	3 (0.1)	3 (0.1)	6 (0.1)	4 (0.1)
Intracranial	13 (0.3)	16 (0.3)	29 (0.3)	5 (0.1)
Intramuscular (with compartment syndrome)	1 (<0.1)	1 (<0.1)	2 (<0.1)	0
Macroscopic (gross) hematuria	0	2 (<0.1)	2 (<0.1)	0
Pericardial	0	1 (<0.1)	1 (<0.1)	0
Rectal	1 (<0.1)	6 (0.1)	7 (0.1)	0
Retroperitoneal	1 (<0.1)	3 (0.1)	4 (<0.1)	0
Skin (ecchymosis other than at instrumented site)	0	1 (<0.1)	1 (<0.1)	0
Other	1 (<0.1)	1 (<0.1)	2 (<0.1)	0

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: Percentages calculated with the number of subjects in each treatment group as denominator.

Note: Incidences are based on the number of subjects, not the number of events. Although a subject may have had 2 or more bleedings in the same location, the subject is counted only once in a category. The same subject may appear in different categories.

Note: ASA = Acetylsalicylic acid; Thieno = Thienopyridine; CABG = Coronary artery bypass grafting.

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7.2.5. TIMI Life-Threatening Bleeding Events

Within the TIMI bleeding classification, the CEC categorized bleeding events as life-threatening. The incidence of life-threatening bleeding in All Strata increased in both rivaroxaban dose groups: 41 of 5115 subjects in the 2.5 mg b.i.d. group, 57 of 5110 subjects in the 5 mg b.i.d. group and 19 of 5125 placebo subjects (Table 39). These results were mirrored in Stratum 2.

Of the subjects with life-threatening bleeding in All Strata and Stratum 2, fatal bleeding events were similar in the rivaroxaban 2.5 mg b.i.d. group (6/5115) and placebo (9/5125), and bleeding requiring intravenous inotropic support or surgical intervention was balanced with placebo (3 for both groups). There were more symptomatic intracranial hemorrhages in the rivaroxaban 2.5 mg b.i.d. group (14/5115) compared with placebo (5/5125). There were also more transfusions of 4 or more units of blood over a 48 hour period in the rivaroxaban 2.5 mg b.i.d. group (19/5115) compared with placebo (6/5125).

In contrast, the rivaroxaban 5 mg b.i.d. group had a higher rate of any life-threatening bleeding subcategory, with the exception of those requiring surgical intervention.

Results in Stratum 2 mirror those in All Strata.

Table 39: (TBL28) Incidence of Treatment-Emergent TIMI Life-Threatening Bleeding as Adjudicated by the CEC
(Study RIVAROXACS3001; Treatment-Emergent Safety Analysis Set)

Subject Stratum Parameter Category	----- Rivaroxaban -----			
	2.5 mg BID (N=5115)	5 mg BID (N=5110)	Combined (N=10225)	Placebo (N=5125)
	n (%)	n (%)	n (%)	n (%)
All Strata	5115	5110	10225	5125
TIMI life-threatening bleeding *	41 (0.8)	57 (1.1)	98 (1.0)	19 (0.4)
Fatal	6 (0.1)	15 (0.3)	21 (0.2)	9 (0.2)
TIMI classification: TIMI major	6 (0.1)	13 (0.3)	19 (0.2)	5 (0.1)
TIMI classification: TIMI minor	0	1 (<0.1)	1 (<0.1)	0
TIMI classification: bleeding requiring medical attention	0	1 (<0.1)	1 (<0.1)	4 (0.1)
-provocation of bleeding event: instrumented	0	0	0	2 (<0.1)
-provocation of bleeding event: spontaneous	6 (0.1)	13 (0.3)	19 (0.2)	7 (0.1)
-provocation of bleeding event: trauma	0	2 (<0.1)	2 (<0.1)	0
Symptomatic intracranial hemorrhage	14 (0.3)	18 (0.4)	32 (0.3)	5 (0.1)
Hypotension requiring treatment with intravenous inotropic agents	3 (0.1)	8 (0.2)	11 (0.1)	3 (0.1)
Surgical intervention for ongoing bleeding	7 (0.1)	6 (0.1)	13 (0.1)	9 (0.2)
Transfusion of 4 or more units of blood over a 48 hour period	19 (0.4)	29 (0.6)	48 (0.5)	6 (0.1)
ASA + Thieno	4772	4768	9540	4773
TIMI life-threatening bleeding *	40 (0.8)	54 (1.1)	94 (1.0)	18 (0.4)
Fatal	5 (0.1)	15 (0.3)	20 (0.2)	8 (0.2)
TIMI classification: TIMI major	5 (0.1)	13 (0.3)	18 (0.2)	4 (0.1)
TIMI classification: TIMI minor	0	1 (<0.1)	1 (<0.1)	0
TIMI classification: bleeding requiring medical attention	0	1 (<0.1)	1 (<0.1)	4 (0.1)
-provocation of bleeding event: instrumented	0	0	0	1 (<0.1)
-provocation of bleeding event: spontaneous	5 (0.1)	13 (0.3)	18 (0.2)	7 (0.1)
-provocation of bleeding event: trauma	0	2 (<0.1)	2 (<0.1)	0
Symptomatic intracranial hemorrhage	13 (0.3)	16 (0.3)	29 (0.3)	5 (0.1)
Hypotension requiring treatment with intravenous inotropic agents	3 (0.1)	8 (0.2)	11 (0.1)	2 (<0.1)
Surgical intervention for ongoing bleeding	7 (0.1)	6 (0.1)	13 (0.1)	8 (0.2)
Transfusion of 4 or more units of blood over a 48 hour period	19 (0.4)	28 (0.6)	47 (0.5)	5 (0.1)

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: Percentages calculated with the number of subjects in each subject stratum and treatment group as denominator.

Note: * Incidences are based on the number of subjects, not the number of events. Although a subject may have had 2 or more bleeding events, the subject is counted only once in a category. The same subject may appear in different sub-categories.

Note: ASA = Acetylsalicylic acid; Thieno = Thienopyridine.

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7.2.6. Treatment-Emergent Bleeding Using TIMI, ISTH and GUSTO Scales

The TIMI bleeding classification was the primary classification as defined in the ATLAS ACS 2 TIMI 51 study protocol. In addition, all bleeding events were also adjudicated by the CEC using the ISTH and GUSTO scales.

The majority of bleeding events categorized as TIMI clinically significant (the composite of TIMI major, minor or bleeding requiring medical attention) were in the bleeding requiring medical attention category (1129/1334 [85%]) (Table 35). In All Strata and Stratum 2, the differences between the rivaroxaban groups compared with placebo in treatment-emergent clinically significant, TIMI major and minor, and TIMI bleeding requiring medical attention categories were all statistically significant favoring placebo (Table 36).

The majority of ISTH major bleeding events across all treatment groups were those that led to hemoglobin decreases ≥ 2 g/dL or the requirement of blood transfusions of 2 or more units of packed red blood cells or whole blood; the incidence of critical organ and fatal bleeding was low overall. In All Strata, the incidence rates of bleeding into a critical organ were balanced between the 2.5 mg b.i.d. (25/5115) and placebo (21/5125) groups, and were numerically higher in the 5 mg b.i.d. group (41/5110). The incidence rates of decreases in hemoglobin greater or equal to 2 g/dL and transfusions requiring 2 or more units were 2 to 3 times greater in both rivaroxaban groups than in the placebo group (Table 40).

Table 40: (TBL27) Incidence of Treatment-Emergent ISTH Major Bleeding as Adjudicated by the CEC (Study RIVAROXACS3001; Treatment-Emergent Safety Analysis Set)

Subject Stratum Parameter Category	----- Rivaroxaban -----			
	2.5 mg BID (N=5115)	5 mg BID (N=5110)	Combined (N=10225)	Placebo (N=5125)
	n (%)	n (%)	n (%)	n (%)
All Strata	5115	5110	10225	5125
ISTH major bleeding *	146 (2.9)	191 (3.7)	337 (3.3)	87 (1.7)
Hemoglobin drop greater or equal to 2 g/dL	121 (2.4)	151 (3.0)	272 (2.7)	62 (1.2)
Requiring transfusion of two or more units	66 (1.3)	79 (1.5)	145 (1.4)	25 (0.5)
Bleeding in a critical organ	25 (0.5)	41 (0.8)	66 (0.6)	21 (0.4)
Bleeding with a fatal outcome	6 (0.1)	15 (0.3)	21 (0.2)	9 (0.2)
ASA + Thieno	4772	4768	9540	4773
ISTH major bleeding *	140 (2.9)	180 (3.8)	320 (3.4)	80 (1.7)
Hemoglobin drop greater or equal to 2 g/dL	116 (2.4)	143 (3.0)	259 (2.7)	57 (1.2)
Requiring transfusion of two or more units	66 (1.4)	73 (1.5)	139 (1.5)	20 (0.4)
Bleeding in a critical organ	24 (0.5)	39 (0.8)	63 (0.7)	20 (0.4)
Bleeding with a fatal outcome	5 (0.1)	15 (0.3)	20 (0.2)	8 (0.2)

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: Percentages calculated with the number of subjects in each subject stratum and treatment group as denominator.

Note: * Incidences are based on the number of subjects, not the number of events. Although a subject may have had 2 or more bleeding events, the subject is counted only once in a category. The same subject may appear in different sub-categories.

Note: ASA = Acetylsalicylic acid; Thieno = Thienopyridine.

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The results using the GUSTO scale confirmed the findings of the TIMI life-threatening subcategories: in All Strata, for the rivaroxaban 2.5 mg b.i.d. group, similar rates compared with placebo were seen for fatal bleeding and severe bleeding subcategories (bleeding events requiring intervention for hemodynamic support, and bleeding events with hemodynamic compromise with a decrease in systolic blood pressure <90 mmHg), while the rates of non-fatal ICH and bleeding requiring transfusion or fluid replacement (moderate bleeding) were numerically higher in the 2.5 mg b.i.d. group compared with placebo. In the 5 mg b.i.d. group, event rates for all categories of GUSTO bleeding were numerically higher compared with placebo ([Appendix DBL29](#)).

7.2.7. Bleeding-Related Treatment Emergent Adverse Events

A total of 2,252 (22%) of rivaroxaban subjects and 643 (12.5%) of placebo subjects had treatment-emergent bleeding-related adverse events. For rivaroxaban and placebo treatment groups, gastrointestinal bleeding-related adverse events (most commonly gingival bleeding and rectal hemorrhage) and respiratory bleeding-related adverse events (primarily epistaxis) were the most common. Gastrointestinal bleeding-related adverse events occurred in 5.7% of the subjects in the rivaroxaban 2.5 mg group, 8.4% in the rivaroxaban 5 mg group, and 3.4% of the placebo group; respiratory bleeding-related events occurred in 5.8% of the subjects in the rivaroxaban 2.5 mg group, 7.7% in the rivaroxaban 5 mg group, and 3.0% of the placebo group. These results were consistent in Stratum 2 ([Table 41](#)).

Table 41: (TAE19A) Treatment-Emergent Bleeding-Related Adverse Events in at Least 1% of Subjects in Any Treatment Group by System Organ Class and Preferred Term (Study RIVAROXACS3001; Safety Analysis Set)

Subject Stratum: All Strata				
	----- Rivaroxaban -----			
	2.5 mg BID	5 mg BID	Combined	Placebo
	(N=5115)	(N=5110)	(N=10225)	(N=5125)
Body System Or Organ Class				
Preferred Term	n (%)	n (%)	n (%)	n (%)
Total no. subjects with treatment-emergent bleeding-related adverse events	974 (19.0)	1278 (25.0)	2252 (22.0)	643 (12.5)
Gastrointestinal Disorders	293 (5.7)	430 (8.4)	723 (7.1)	172 (3.4)
Gingival Bleeding	104 (2.0)	192 (3.8)	296 (2.9)	63 (1.2)
Rectal Haemorrhage	63 (1.2)	59 (1.2)	122 (1.2)	41 (0.8)
Respiratory, Thoracic and Mediastinal Disorders	295 (5.8)	391 (7.7)	686 (6.7)	154 (3.0)
Epistaxis	268 (5.2)	350 (6.8)	618 (6.0)	141 (2.8)
Injury, Poisoning and Procedural Complications	161 (3.1)	225 (4.4)	386 (3.8)	125 (2.4)
Contusion	75 (1.5)	92 (1.8)	167 (1.6)	53 (1.0)
Skin and Subcutaneous Tissue Disorders	145 (2.8)	163 (3.2)	308 (3.0)	91 (1.8)
Ecchymosis	82 (1.6)	89 (1.7)	171 (1.7)	53 (1.0)
Vascular Disorders	115 (2.2)	148 (2.9)	263 (2.6)	90 (1.8)
Haematoma	103 (2.0)	125 (2.4)	228 (2.2)	79 (1.5)
Renal and Urinary Disorders	77 (1.5)	124 (2.4)	201 (2.0)	32 (0.6)
Haematuria	69 (1.3)	121 (2.4)	190 (1.9)	31 (0.6)

Note: Percentages calculated with the number of subjects in each treatment group as denominator.

Note: AE coding is based on MedDRA version 14.0.

Note: Incidences are based on the number of subjects, not the number of events. Although a subject may have had 2 or more clinical AEs, the subject is counted only once in a category. The same subject may appear in different body system categories.

Note: Treatment-emergent AE is defined as the AE occurred after the first dose and up to 2 days after the last dose of study drug.

Note: Bleeding related AEs as identified through a search of the AE database using the preferred term contained within the Standardized MedDRA Query (SMQ): main SMQ term = 'HAEMORRHAGES (SMQ)' and sub SMQ term = 'HAEMORRHAGE TERMS (EXCL LABORATORY TERMS) (SMQ)'.

Note: AE is sorted in descending order by percentage in Combined Rivaroxaban group.

Note: ASA = Acetylsalicylic acid; Thieno = Thienopyridine.

Table 41 Continued (TAE19A): Treatment-Emergent Bleeding-Related Adverse Events in at Least 1% of Subjects in any Treatment Group by System Organ Class and Preferred Term (continued)
(Study RIVAROXACS3001: Safety Analysis Set)
Subject Stratum: ASA + Thieno

Body System Or Organ Class Preferred Term	----- Rivaroxaban -----			Placebo (N=4773) n (%)
	2.5 mg BID (N=4772) n (%)	5 mg BID (N=4768) n (%)	Combined (N=9540) n (%)	
Total no. subjects with treatment-emergent bleeding-related adverse events	948 (19.9)	1235 (25.9)	2183 (22.9)	616 (12.9)
Gastrointestinal Disorders	288 (6.0)	419 (8.8)	707 (7.4)	166 (3.5)
Gingival Bleeding	104 (2.2)	188 (3.9)	292 (3.1)	60 (1.3)
Rectal Haemorrhage	60 (1.3)	58 (1.2)	118 (1.2)	39 (0.8)
Respiratory, Thoracic and Mediastinal Disorders	291 (6.1)	380 (8.0)	671 (7.0)	151 (3.2)
Epistaxis	264 (5.5)	341 (7.2)	605 (6.3)	138 (2.9)
Haemoptysis	25 (0.5)	46 (1.0)	71 (0.7)	16 (0.3)
Injury, Poisoning and Procedural Complications	156 (3.3)	217 (4.6)	373 (3.9)	118 (2.5)
Contusion	74 (1.6)	90 (1.9)	164 (1.7)	53 (1.1)
Skin and Subcutaneous Tissue Disorders	141 (3.0)	158 (3.3)	299 (3.1)	86 (1.8)
Ecchymosis	79 (1.7)	86 (1.8)	165 (1.7)	49 (1.0)
Vascular Disorders	113 (2.4)	145 (3.0)	258 (2.7)	86 (1.8)
Haematoma	101 (2.1)	123 (2.6)	224 (2.3)	76 (1.6)
Renal and Urinary Disorders	72 (1.5)	122 (2.6)	194 (2.0)	30 (0.6)
Haematuria	64 (1.3)	119 (2.5)	183 (1.9)	29 (0.6)

See footnotes on the first page of the table.

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In All Strata, serious treatment-emergent bleeding-related adverse events occurred in 118 (2.3%) subjects in the rivaroxaban 2.5 mg b.i.d group, 178 (3.5%) subjects in the rivaroxaban 5 mg b.i.d group, and 60 (1.2%) the placebo group. The most common bleeding-related serious adverse events were gastrointestinal bleeding-related serious adverse events and occurred in 64 (1.3%) subjects in the rivaroxaban 2.5 mg b.i.d group, 94 (1.8%) subjects in the rivaroxaban 5 mg b.i.d group, and 32 (0.6%) subjects in the placebo group. Results for Stratum 2 mirrored those for All Strata. In All Strata and Stratum 2, the incidence of treatment-emergent bleeding-related serious adverse events was consistently higher in subjects receiving rivaroxaban 5 mg b.i.d. compared with rivaroxaban 2.5 mg b.i.d. or placebo.

In All Strata, a total of 183 (3.6%) subjects in the rivaroxaban 2.5 mg b.i.d group, 255 (5.0%) subjects in the rivaroxaban 5 mg b.i.d group, and 92 (1.8%) placebo subjects had treatment-emergent bleeding-related adverse events that resulted in permanent discontinuation from study drug. The most common events were GI bleeding-related adverse events that occurred in 63 (1.2%) subjects in the rivaroxaban 2.5 mg b.i.d group, 114 (2.2%) subjects in the rivaroxaban 5 mg b.i.d group, and 40 (0.8%) subjects in the placebo group. Gingival bleeding was the most common bleeding-related adverse event causing discontinuation, occurring in 13 (0.3%) subjects

in the rivaroxaban 2.5 mg b.i.d group, 33 (0.6%) subjects in the rivaroxaban 5 mg b.i.d group, and 6 (0.1%) placebo subjects. Results for Stratum 2 mirrored those for All Strata.

7.2.8. Bleeding in Subgroups

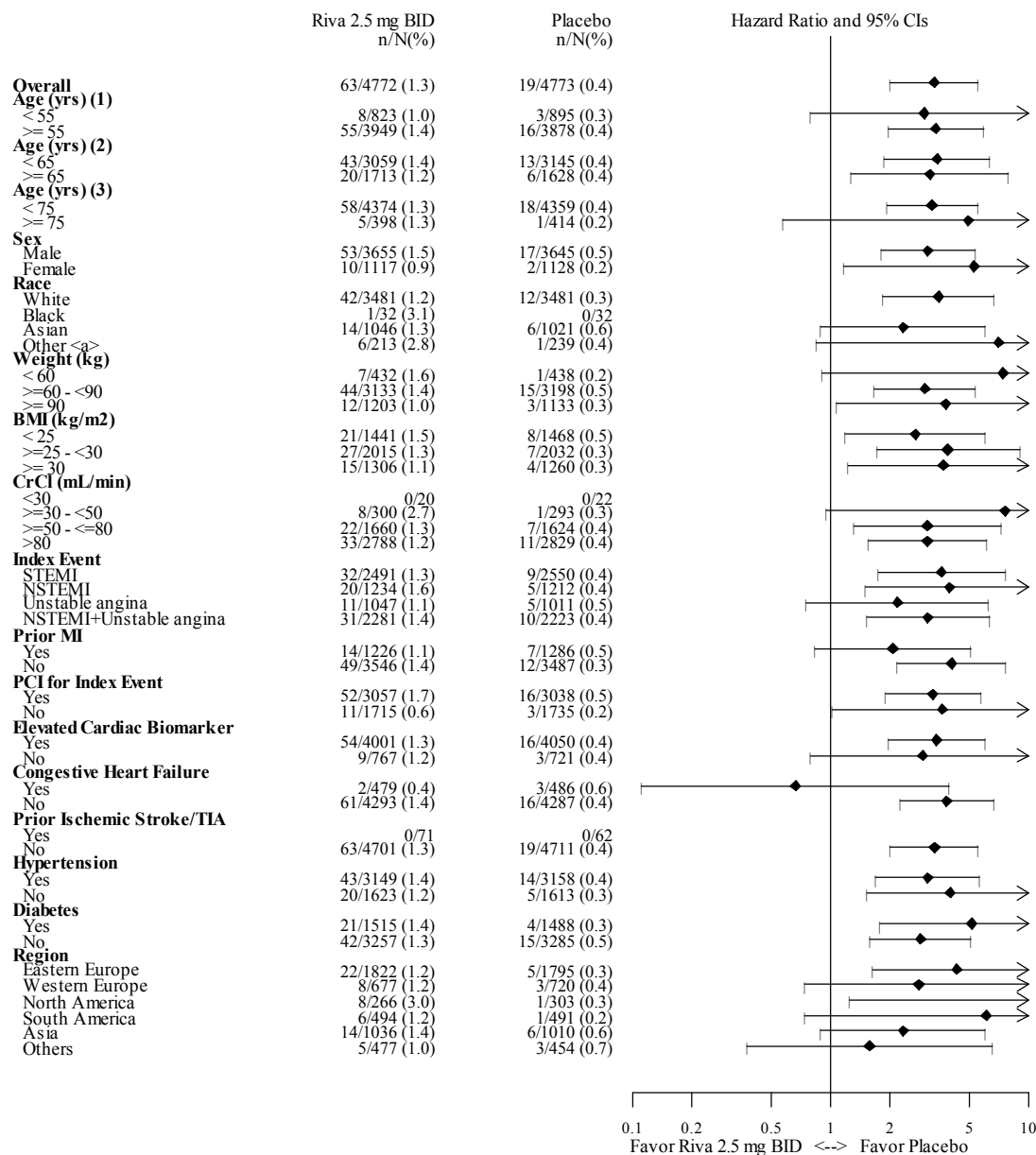
Subgroup analyses on the primary safety endpoint (non-CABG TIMI major bleeding) were performed by baseline characteristics. The results of the subgroup analyses were generally consistent with the results of the overall primary safety endpoint analysis, showing a consistent pattern of increased non-CABG-related TIMI major bleeding in the rivaroxaban groups compared with placebo across all major subgroups. There were no significant treatment interactions with any of the subgroups based on demographics, baseline characteristics, medical history, index event (STEMI, NSTEMI or UA) or region; all interaction p-values were >0.05.

Forest plots of the hazard ratio by baseline characteristics in the Treatment-emergent Safety analysis set for the primary safety endpoint are presented for rivaroxaban 2.5 mg b.i.d. dose, Stratum 2 in [Figure 19](#). A forest plot for the combined doses in All Strata is included in [Appendix FBL10A](#).

Three populations of subjects were identified and defined post hoc as “fragile” using the following criteria: 1) subjects with CrCl values <50 mL/min at screening; 2) subjects \geq 75 years old at screening; and 3) subjects with weight less than 60 kg. The interaction testing methods and results of the analysis of the primary safety endpoint in the “fragile” population in 2.5 mg b.i.d. group for All Strata and Stratum 2 are shown in [Table 42](#). In general, subgroups meeting the 3 criteria had very small number of events, but all subgroups had HRs favoring placebo.

In addition, subgroup analyses on clinically significant bleeding (i.e., the composite endpoint of TIMI major bleeding event, TIMI minor bleeding event, or bleeding event requiring medical attention) were also performed by baseline characteristics. There were no significant treatment interactions with any of the subgroups based on demographics, baseline characteristics, medical history, index event (STEMI, NSTEMI or UA) or region; all interaction p-values were >0.05. Forest plots for combined doses in All Strata and for the 2.5 mg b.i.d. dose in Stratum 2 are included in [Appendices FBL15a](#) and [FBL15h](#).

**Figure 19: (FBL10h) Hazard Ratios and Rates of the First Occurrence of Treatment–Emergent Non–CABG related TIMI Major Bleeding Events by Subgroup for Rivaroxaban 2.5 mg B.I.D. Group Compared With Placebo in Stratum 2
(Study RIVAROXACS3001; Treatment–Emergent Safety Analysis Set)**



Note: Hazard Ratio and 95% confidence interval as compared to placebo arm is based on the unstratified Cox proportional hazards model.
Note: Scale of X axis was based on log transformation of the ratio. Tick labels of X axis are in the original ratio scale.
Note: <a> Including 'American Indian or Alaska Native', 'Native Hawaiian or Other Pacific Islander' and 'Other' per CRF.
Note: Arrow (< or >) of a line indicates that the confidence interval limit exceeds the X-axis range.

**Table 42: (TBLPH05B): Effect of Rivaroxaban 2.5 mg Compared with Placebo on Non-CABG TIMI Major Bleeding Events in Fragile Populations
(Study RIVAROXACS3001: Treatment-Emergent Safety Analysis Set)**

Subject Stratum: All Strata		Riva 2.5 mg BID	-- Placebo -		P-value	P-value
Baseline Covariates	Categories	k/N (%)	k/N (%)	HR (95% CI)	(a)	(b)
CrCL <50 mL/min	Yes	8/369(2.2)	1/380(0.3)	7.60 (0.95,60.81)	0.422	-
	No	57/4742(1.2)	18/4740(0.4)	3.21 (1.89,5.46)		
Age ≥ 75 years	Yes	6/451(1.3)	1/488(0.2)	6.21 (0.75,51.61)	0.566	-
	No	59/4664(1.3)	18/4637(0.4)	3.31 (1.95,5.60)		
Weight <60 kg	Yes	7/468(1.5)	1/484(0.2)	7.43 (0.91,60.37)	0.440	-
	No	58/4643(1.2)	18/4637(0.4)	3.24 (1.91,5.50)		
Age ≥ 75 years and CrCL <50 mL/min	Yes	3/159(1.9)	0/182		0.977	-
	No	62/4952(1.3)	19/4938(0.4)	3.30 (1.97,5.52)		
Age ≥ 75 years and Weight <60 kg	Yes	0/70	1/84(1.2)	0.00	0.973	-
	No	65/5041(1.3)	18/5037(0.4)	3.65 (2.16,6.14)		
Age ≥ 75 years and CrCL <50 mL/min and Weight <60 kg	Yes	0/44	0/66		0.999	-
	No	65/5063(1.3)	19/5050(0.4)	3.45 (2.07,5.75)		
Subject Stratum: ASA + Thieno		Riva 2.5 mg BID	-- Placebo -		P-value	P-value
Baseline Covariates	Categories	k/N (%)	k/N (%)	HR (95% CI)	(a)	(b)
CrCL <50 mL/min	Yes	8/320(2.5)	1/315(0.3)	7.60 (0.95,60.81)	0.414	-
	No	55/4448(1.2)	18/4453(0.4)	3.10 (1.82,5.28)		
Age ≥ 75 years	Yes	5/398(1.3)	1/414(0.2)	4.96 (0.58,42.45)	0.689	-
	No	58/4374(1.3)	18/4359(0.4)	3.25 (1.92,5.52)		
Weight <60 kg	Yes	7/432(1.6)	1/438(0.2)	7.43 (0.91,60.37)	0.425	-
	No	56/4336(1.3)	18/4331(0.4)	3.13 (1.84,5.32)		
Age ≥ 75 years and CrCL <50 mL/min	Yes	3/134(2.2)	0/146		0.978	-
	No	60/4634(1.3)	19/4622(0.4)	3.20 (1.91,5.35)		
Age ≥ 75 years and Weight <60 kg	Yes	0/59	1/69(1.4)	0.00	0.974	-
	No	63/4709(1.3)	18/4700(0.4)	3.53 (2.09,5.96)		
Age ≥ 75 years and CrCL <50 mL/min and Weight <60 kg	Yes	0/35	0/53		0.999	-
	No	63/4729(1.3)	19/4711(0.4)	3.34 (2.00,5.58)		

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: k/N: Number of subjects having events / number of subjects at risk; % = 100 * k / N.

Note: HR (95% CI): Hazard ratio (95% confidence interval) as compared with placebo arm is based on the (stratified, only for all strata) Cox proportional hazards model.

Note: (a) P-value (two-sided) for the interaction of treatment group and each baseline subgroup based on the Cox proportional hazards model including treatment group, baseline subgroup and their interaction.

Note: (b) Gail Simon P-value (two-sided) for the interaction of treatment group and the baseline subgroup is provided when proportional hazards model p-value is significant at 0.05 level.

Note: ASA = Acetylsalicylic acid; Thieno = Thienopyridine; CABG = Coronary artery bypass grafting.

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7.3. Adverse Events Overall

Given the extensive background of existing safety data from the previously completed Phase 3 rivaroxaban trials, along with the safety data from 3462 subjects in the Phase 2 ATLAS ACS TIMI 46 clinical trial, the ATLAS ACS 2 TIMI 51 study only collected serious adverse events, adverse events leading to discontinuation of study drug, and adverse events of special interest were collected in ATLAS ACS 2 TIMI 51 study, with the exception of sites in Japan, where data on all adverse events were collected (see Section 4.2.2).

7.3.1. Most Common Adverse Events

Overall, treatment emergent adverse events were balanced between treatments. A total of 5667 (55.4%) subjects in the combined rivaroxaban groups and 2694 (52.6%) subjects in the placebo group reported treatment-emergent adverse events. In the rivaroxaban and placebo groups, events in the System Organ Classes of cardiac disorders and GI disorders were most common. Most GI events were bleeding-related. As expected for the population with ACS, cardiac disorders were commonly reported adverse events and occurred in 18.0% of subjects in the combined rivaroxaban groups and 19.0% of the subjects in the placebo group; gastrointestinal disorders occurred in 12.0% of subjects in the combined rivaroxaban groups and 9.3% of subjects in the placebo group. Angina pectoris was the most common cardiac event and occurred in 5.9% of subjects in the combined rivaroxaban groups and 6.6% of subjects in the placebo group. Gingival bleeding was the most common gastrointestinal event and occurred in 2.9% of subjects in the combined rivaroxaban groups and 1.2% of subjects in the placebo group.

When only non-bleeding treatment-emergent adverse events were considered, the 5 most common events based on any treatment group were angina pectoris, angina unstable, PCI, chest pain and acute MI, these events were generally balanced between rivaroxaban and placebo treatment groups.

7.3.2. Other Adverse Events

Per FDA request, the Sponsor searched the database for cases of hypersensitivity using high level group terms of 'Allergic conditions' and 'Angioedema and urticaria', and high level terms of 'Dermatitis ascribed to specific agent', 'Exfoliative conditions' and 'Skin vasculitides'. There were rare cases meeting the terms identified, including 6/5115 cases in the rivaroxaban 2.5 mg b.i.d. group, 1/5110 cases in the rivaroxaban 5 mg b.i.d., and 2/5125 cases in the placebo group.

7.3.3. Deaths

All deaths that occurred post randomization were adjudicated by CEC. Table 43 summarizes all deaths by primary cause for the safety analysis set in All Strata. There were a total of 532 deaths reported in the safety analysis set. Fewer all-cause and CV deaths occurred in subjects in the rivaroxaban 2.5 mg b.i.d. group than in the placebo group in the safety analysis set. The reduction in death observed in the 2.5 mg b.i.d. group was due to a numerical reduction in sudden or unwitnessed deaths and deaths due to congestive heart failure/cardiogenic shock vs. placebo. In the rivaroxaban 5 mg b.i.d. group, fewer sudden or unwitnessed deaths were also seen compared with the placebo group, but in contrast to the 2.5 mg b.i.d. group, no reduction

was seen on death due to heart failure/cardiogenic shock, and there was a numerical increase in the deaths due to MI compared with placebo.

Table 43: (TAE16A) Summary of All-Cause Deaths by Primary Cause as Adjudicated by CEC in All Strata (Study RIVAROXACS3001: Safety Analysis Set)

Subject Stratum: All Strata	----- Rivaroxaban -----			
	2.5 mg BID (N=5115) n (%)	5 mg BID (N=5110) n (%)	Combined (N=10225) n (%)	Placebo (N=5125) n (%)
All Cause Death	145 (2.8)	194 (3.8)	339 (3.3)	193 (3.8)
Cardiovascular Deaths	118 (2.3)	161 (3.2)	279 (2.7)	164 (3.2)
Non-hemorrhagic stroke	2 (<0.1)	5 (0.1)	7 (0.1)	4 (0.1)
Intracranial hemorrhage	7 (0.1)	7 (0.1)	14 (0.1)	6 (0.1)
Atherosclerotic vascular disease (excluding coronary)	1 (<0.1)	3 (0.1)	4 (<0.1)	1 (<0.1)
Congestive heart failure / Cardiogenic shock	12 (0.2)	27 (0.5)	39 (0.4)	19 (0.4)
Directly related to revascularization (CABG or PCI)	3 (0.1)	2 (<0.1)	5 (<0.1)	5 (0.1)
Cardiac arrhythmia	1 (<0.1)	4 (0.1)	5 (<0.1)	6 (0.1)
Pulmonary embolism	0	0	0	3 (0.1)
Sudden or unwitnessed death	69 (1.3)	74 (1.4)	143 (1.4)	96 (1.9)
Hemorrhage, not intracranial	1 (<0.1)	5 (0.1)	6 (0.1)	1 (<0.1)
Myocardial infarction	22 (0.4)	34 (0.7)	56 (0.5)	23 (0.4)
Other vascular	0	0	0	0
Non-Cardiovascular Deaths	22 (0.4)	29 (0.6)	51 (0.5)	24 (0.5)
Accidental / trauma	2 (<0.1)	2 (<0.1)	4 (<0.1)	4 (0.1)
Respiratory failure	1 (<0.1)	2 (<0.1)	3 (<0.1)	2 (<0.1)
Infection	2 (<0.1)	10 (0.2)	12 (0.1)	2 (<0.1)
Malignancy	17 (0.3)	13 (0.3)	30 (0.3)	14 (0.3)
Suicide	0	1 (<0.1)	1 (<0.1)	1 (<0.1)
Liver failure	0	0	0	0
Renal failure	0	0	0	1 (<0.1)
Other non-vascular	0	1 (<0.1)	1 (<0.1)	0
Unknown	5 (0.1)	4 (0.1)	9 (0.1)	5 (0.1)

Note: Percentages calculated with the number of subjects in each treatment group as denominator.

Note: Death events occur at or after the first study drug administration.

Note: ASA = Acetylsalicylic acid; Thieno = Thienopyridine; CABG = Coronary artery bypass grafting.

7.3.4. Adverse Events that Occurred Within 30 Days Prior to Permanent Discontinuation of Study Drug

In All Strata, a total of 772 (26.8%) subjects in the combined rivaroxaban groups and 314 (23.2%) subjects in the placebo group had postbaseline adverse events within 30 days prior to discontinuation of study drug. Overall, the incidence of postbaseline adverse events occurring within 30 days prior to discontinuation of study drug was numerically higher in the rivaroxaban 5 mg b.i.d. group (438 [29.1%]) than in the rivaroxaban 2.5 mg b.i.d. group (334 [24.3%]). The most common postbaseline adverse events occurring within 30 days prior to discontinuation of study drug were events in the System Organ Classes of gastrointestinal disorders and cardiac disorders. Gingival bleeding was the most common gastrointestinal event occurring within

30 days prior to discontinuation of study drug and occurred in 43 (1.5%) subjects in the combined rivaroxaban groups and 4 (0.3%) subjects in the placebo group. More gingival bleeding events occurred within 30 days prior to discontinuation of study drug in the 5 mg b.i.d. group than in the 2.5 mg b.i.d. group. Angina pectoris was the most common cardiac event occurring within 30 days prior to discontinuation of study drug and occurred in 32 (1.1%) subjects in the combined rivaroxaban groups and 19 (1.4%) subjects in the placebo group. Results in Stratum 2 were similar to those for All Strata.

7.4. Safety in Stratum 1

Overall, the use of rivaroxaban increased the risk of bleeding in subjects with ACS, and this risk was higher in those subjects receiving aspirin plus a thienopyridine as the standard care (Stratum 2), compared with those subjects receiving aspirin alone (Stratum 1).

For the primary safety endpoint, non-CABG TIMI major bleeding, as in Stratum 2, the event rate was increased in the rivaroxaban groups compared with placebo in Stratum 1, but with fewer events. There were 2 of 343 subjects in the 2.5 mg b.i.d. group, 4 of 342 subjects in the 5 mg b.i.d. group, and 0 for the placebo group who had non-CABG TIMI major bleeding ([Table 44](#)).

In Stratum 1, intracranial bleeding events occurred in 1 of 343 subjects in the 2.5 mg b.i.d. group, 2 of 342 subjects in the 5 mg b.i.d. group and 0 subjects in the placebo group ([Table 44](#)).

There was 1 fatal bleeding in the 2.5 mg b.i.d. group, 0 in the 5 mg b.i.d. group and 1 in the placebo group ([Table 44](#)).

The incidence of clinically significant bleeding in Stratum 1 was 6.1% for the combined rivaroxaban group and 3.1% for placebo, both lower than in Stratum 2 (13.0% and 6.4%, respectively) ([Table 44](#) and [Table 35](#)).

Table 44: (TBL21) Incidence of Treatment-Emergent Bleeding Events as Adjudicated by the CEC in Stratum 1 (Study RIVAROXACS001: Treatment-Emergent Safety Analysis Set)

Subject Stratum: ASA

	----- Rivaroxaban -----			
	2.5 mg BID (N=343)	5 mg BID (N=342)	Combined (N=685)	Placebo (N=352)
	n (%)	n (%)	n (%)	n (%)
TIMI major bleeding	2 (0.6)	4 (1.2)	6 (0.9)	2 (0.6)
Non-CABG TIMI major bleeding* ***	2 (0.6)	4 (1.2)	6 (0.9)	0
Non-CABG TIMI major bleeding - fatal	1 (0.3)	0	1 (0.1)	0
Non-CABG TIMI major bleeding - non-fatal**	1 (0.3)	4 (1.2)	5 (0.7)	0
CABG related TIMI major bleeding	0	0	0	2 (0.6)
TIMI minor bleeding	1 (0.3)	0	1 (0.1)	0
Non-CABG TIMI major or minor bleeding	3 (0.9)	4 (1.2)	7 (1.0)	0
TIMI bleeding requiring medical attention	16 (4.7)	19 (5.6)	35 (5.1)	9 (2.6)
Clinically significant bleeding***	19 (5.5)	23 (6.7)	42 (6.1)	11 (3.1)
Fatal bleeding	1 (0.3)	0	1 (0.1)	1 (0.3)
Non-fatal bleeding	18 (5.2)	23 (6.7)	41 (6.0)	10 (2.8)
Intracranial bleeding	1 (0.3)	2 (0.6)	3 (0.4)	0
Intra-parenchymal	1 (0.3)	2 (0.6)	3 (0.4)	0
Intra-ventricular	0	1 (0.3)	1 (0.1)	0
Epidural	0	0	0	0
Subdural	0	0	0	0
Subarachnoid	0	0	0	0
Hemorrhagic stroke	1 (0.3)	2 (0.6)	3 (0.4)	0
Primary hemorrhagic intraparenchymal hemorrhage (including subarachnoid hemorrhage)	1 (0.3)	2 (0.6)	3 (0.4)	0
Primary hemorrhagic subdural hematoma	0	0	0	0
Primary hemorrhagic epidural hematoma	0	0	0	0

See footnotes on the first page of the table.

7.5. Dose Response

In study ATLAS ACS 2 TIMI 51, a lower incidence of bleeding events was observed with the 2.5 mg b.i.d. dose compared with the 5 mg b.i.d. dose, for all bleeding categories in All Strata, Stratum 1, and Stratum 2. In All Strata, the occurrence of the primary safety endpoint (non-CABG TIMI major bleeding) was higher in the 5 mg b.i.d. group (1.6%) compared with the 2.5 mg b.i.d. group (1.3%; HR: 1.29, 95% CI: 0.93, 1.79). The same was true in Stratum 2 (1.6% for the 5 mg b.i.d. group vs. 1.3% for the 2.5 mg b.i.d. group; HR: 1.27; 95% CI: 0.91, 1.77) ([Appendix DBLPH00](#)).

7.6. Safety Across Studies In The Rivaroxaban Clinical Development Program

In the overall clinical development program, the safety of rivaroxaban has been assessed and demonstrated in multiple indications, with over 40,000 subjects exposed to rivaroxaban in completed and ongoing clinical studies to date. In NDA 22406 (approved in July 2011) for the

prophylaxis of DVT, which may lead to PE in patients undergoing knee or hip replacement surgery, the safety population for the 4 pivotal studies (RECORD 1-4) included a total of 6,183 subjects who received rivaroxaban. NDA 202439 (approved in November 2011) for the reduction of the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation, the pivotal Phase 3 study ROCKET AF and supportive Phase 3 study J-ROCKET included a total of 7,750 subjects who received rivaroxaban. The overall safety profile of rivaroxaban showed no safety signals other than the expected bleeding risks.

7.7. Summary of Clinical Risks

The overall safety profile of rivaroxaban showed no safety signals other than bleeding risks. There were no new safety findings in the ATLAS ACS 2 TIMI 51 study. [Table 45](#) summarizes the key safety results of the study.

Increased bleeding is an expected consequence of an anticoagulant such as rivaroxaban when added to single or dual antiplatelet therapy to improve the efficacy benefit. In the Phase 3 ATLAS ACS 2 TIMI 51 study, in the safety analysis set, rivaroxaban at a dose of 2.5 mg b.i.d. increased the risk of non-CABG TIMI major bleeding (primary safety endpoint) in ACS patients from 0.4% to 1.3%, representing an absolute increase of 0.9% and a HR of 3.46 (95% CI: 2.08, 5.77), and the 5 mg b.i.d. dose increased the risk of non-CABG TIMI major bleeding in ACS patients to 1.6%, representing an absolute increase of 1.2% and a HR of 4.47 (95% CI: 2.71, 7.36). This finding is consistent with the observed data from the Phase 2 ATLAS ACS TIMI 46 study, and the published data from other novel anticoagulants that have been tested in ACS patients². The rates of non-CABG TIMI major bleeding observed in the ATLAS ACS 2 TIMI 51 study were low overall, and lower than that observed in other contemporary trials of antithrombotic agents such as the TRITON and PLATO trials^{42,46}.

In ATLAS ACS 2 TIMI 51, although the incidence of bleeding was higher with rivaroxaban treatment compared with placebo, the overall incidence of TIMI major bleeding (CABG or non-CABG) and TIMI minor bleeding were low, and the majority of the clinically significant bleeding events were categorized in the less severe TIMI bleeding requiring medical attention category.

The overall incidence of treatment-emergent fatal bleeding in the study was low, and similar in the rivaroxaban 2.5 mg b.i.d. group (6/5115 subjects) compared with placebo (9/5125 subjects), but numerically higher in the rivaroxaban 5 mg b.i.d. group (15/5110 subjects).

The rates of ICH and hemorrhagic stroke were low overall, but significantly higher in the rivaroxaban groups compared with the placebo group, particularly in Stratum 2, where 13/5115 subjects in the 2.5 mg b.i.d. group and 16/5110 subjects in the 5 mg b.i.d. group had intracranial bleeding events, compared with 5/5125 placebo subjects. However, fatal intracranial bleeding events were similarly low. In All Strata, 5/14 subjects in the 2.5 mg b.i.d. group, 8/18 subjects in the 5 mg b.i.d. group, and 4/5 placebo subjects with intracranial bleeding events had fatal outcomes.

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 were 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 bleeding requiring surgical intervention.

**Table 45: Comparison of Key Safety Results of the 2.5 mg b.i.d. and 5 mg b.i.d. Treatment Groups in All Strata and Stratum 2
(Study RIVAROXACS3001: Treatment-Emergent Safety Analysis Set)**

	Rivaroxaban 2.5 mg b.i.d. (N=5115 for All Strata; N= 4772 for Stratum 2)	Rivaroxaban 5 mg b.i.d. (N=5110 for All Strata; N= 4768 for Stratum 2)	Placebo (N=5125 for All Strata; N= 4773 for Stratum 2)
Primary Safety Endpoint (non-CABG TIMI major bleeding)			
All Strata			
Event Incidence (n [%])	65 (1.3%)	82 (1.6%)	19 (0.4%)
HR (95% CI) vs Placebo	3.46 (2.08,5.77)	4.47 (2.71,7.36)	-
Stratum 2			
Event Incidence (n [%])	63 (1.3%)	78 (1.6%)	19 (0.4%)
HR (95% CI) vs Placebo	3.35 (2.01,5.60)	4.26 (2.58,7.03)	-
Intracranial Bleeding			
All Strata			
Event Incidence (n)	14	18	5
- With Fatal Outcome	5/14	8/18	4/5
HR (95% CI) vs Placebo	2.83 (1.02,7.86)	3.74 (1.39,10.07)	-
Stratum 2			
Event Incidence	13	16	5
- With Fatal Outcome	4/13	8/16	4/5
HR (95% CI) vs Placebo	2.63 (0.94,7.38)	3.34 (1.22,9.12)	-
Fatal Bleeding			
All Strata			
Event Incidence (n)	6	15	9
HR (95% CI) vs Placebo	0.67 (0.24,1.89)	1.72 (0.75,3.92)	-
Stratum 2			
Event Incidence (n [%])	5	15	8
HR (95% CI) vs Placebo	0.63 (0.21,1.93)	1.93 (0.82,4.56)	-
TIMI Clinically Significant Bleeding (the composite of TIMI major, minor or bleeding requiring medical attention)			
All Strata			
Event Incidence (n [%])	586 (11.5%)	748 (14.6%)	327 (6.4%)
HR (95% CI) vs Placebo	1.84 (1.61,2.11)	2.43 (2.13,2.76)	-
Stratum 2			
Event Incidence (n [%])	567 (11.9%)	725 (15.2%)	316 (6.6%)
HR (95% CI) vs Placebo	1.84 (1.61,2.12)	2.44 (2.14,2.78)	-
TIMI Life Threatening Bleeding (categorized by the CEC)			
All Strata			
Event Incidence (n [%])	41 (0.8%)	57 (1.1%)	19 (0.4%)
HR (95% CI) vs Placebo	2.18 (1.26,3.75)	3.09 (1.84,5.20)	-
Stratum 2			
Event Incidence (n [%])	40 (0.8%)	54 (1.1%)	18 (0.4%)
HR (95% CI) vs Placebo	2.24 (1.29,3.91)	3.10 (1.82,5.28)	-
ISTH Major Bleeding			
All Strata			
Event Incidence (n [%])	146 (2.9%)	191 (3.7%)	87 (1.7%)
HR (95% CI) vs Placebo	1.70 (1.30,2.21)	2.26 (1.76,2.92)	-
Stratum 2			
Event Incidence (n [%])	140 (2.9%)	180 (3.8%)	80 (1.7%)
HR (95% CI) vs Placebo	1.77 (1.34,2.33)	2.32 (1.79,3.02)	-

Table 45 (continued): Comparison of Key Safety Results of the 2.5 mg b.i.d. and 5 mg b.i.d. Treatment Groups in All Strata and Stratum 2 (continued)
(Study RIVAROXACS3001: Treatment-Emergent Safety Analysis Set)

	Rivaroxaban 2.5 mg b.i.d. (N=5115 for All Strata; N= 4772 for Stratum 2)	Rivaroxaban 5 mg b.i.d. (N=5110 for All Strata; N= 4768 for Stratum 2)	Placebo (N=5125 for All Strata; N= 4773 for Stratum 2)
Treatment Emergent Bleeding-related Adverse Event Resulting in Permanent Discontinuation of Study Drug			
All Strata			
Event Incidence (n [%])	183 (3.6%)	255 (5.0%)	92 (1.8%)
Stratum 2			
Event Incidence (n [%])	177 (3.7%)	247 (5.2%)	88 (1.8%)

Note: CABG= coronary artery bypass graft; ISTH=International Society on Thrombosis and Haemostasis; TIMI= thrombolysis in myocardial infarction;

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. Bleeding events were adjudicated by the Clinical Endpoint Committee.

Note: percentages were not shown for events with frequency < 1% in all treatment groups.

Source outputs: DBL01, DBL04, DAE21A,

7.8. Safety Discussion

Although the risk of bleeding was increased with rivaroxaban, the rates of the most important bleeding categories (i.e., fatal bleeding and fatal ICH) were low, and similar between the placebo and rivaroxaban 2.5 mg b.i.d. groups. In the the clinical trial protocol, physicians were advised to use supportive measures to deal with bleeding events, and subsequently to use agents such as recombinant factor 7, prothrombin complex concentrate or activated prothrombin complex concentrate. An analysis of the concomitant medication database did not reveal the use of any of these agents during the duration of the trial. Recently, Eerenberg et al reported that prothrombin complex concentrate effectively reverses the effect of rivaroxaban in a small clinical trial (NTR2272). While no antidote is currently available for rivaroxaban, the result reported by Eerenberg and colleagues suggests that PCC may reverse the effect of rivaroxaban¹⁰.

The available data demonstrate that rivaroxaban use in ACS patients increases the risk of bleeding; and this risk is predictable and manageable. As will be discussed in Section 8, the overall balance of benefit and risk for rivaroxaban 2.5mg b.i.d. dose is positive.

8. BENEFIT-RISK ANALYSIS – ATLAS ACS 2 TIMI 51

8.1. Quantitative Benefit-Risk Assessment

As described earlier in the document, the significant benefits of rivaroxaban as compared with placebo in reducing the incidence of CV death, MI, or stroke (primarily driven by CV death and MI) were accompanied with a greater risk for bleeding.

The tradeoff between benefits and risks can be assessed quantitatively, and the Net Clinical Outcome (NCO) endpoint (Secondary Efficacy Endpoint 2) was one approach intended to assess this balance. This endpoint combined the benefits and risks in a single composite endpoint and included the components of CV death, MI, ischemic stroke and non-CABG TIMI major

bleeding. The results for this endpoint, while not statistically significant, directionally favored rivaroxaban 2.5 mg b.i.d. in All Strata and in Stratum 2 (Section 6.3.2).

An alternative approach to assessing the balance of benefit and risk in the setting of the ATLAS ACS 2 TIMI 51 can be based on the approach outlined by Unger^{4,41}. These additional post hoc analyses focus on events that are fatal or lead to irreversible harm, and also minimize double-counting of events between endpoints. A variety of sensitivity analyses in which events with a greater range of clinical import are also included.

The benefits and risks summarized in previous Sections 6.8 and 7.7 encompassed a spectrum of outcomes with a wide range of clinical significance. In addition, some events were included under both efficacy and safety outcomes (e.g., fatal bleed and hemorrhagic stroke were included in both the primary efficacy and primary safety endpoints), which further complicated direct comparison of benefits and risks. To enable a more direct comparison of comparable benefits and harms, a post hoc analysis was performed to show all key efficacy and safety endpoints with all ischemic events included under the efficacy measure and all hemorrhagic events included under the safety measure (Sections 8.1.1 and 8.1.2). Events such as CV death, MI, hemorrhagic, ischemic and uncertain stroke represent irreversible tissue damage and are generally regarded as being more clinically important than those bleeding events with no irreversible consequences⁴¹. For this reason, several endpoints were further decomposed and endpoints that were fatal or likely to lead to irreversible harm were shown separately so as to enable comparing events of similar clinical importance. Where appropriate, events were confined to one outcome in the decompositions, so double-counting of events was minimized. Events were categorized to the possible category with the highest clinical importance.

8.1.1. Excess Number of Events and NNT/NNH

Benefit-risk results are discussed here in detail for the 2.5 mg b.i.d. dose in All Strata and Stratum 2. Table 46 below shows event rates, between-treatment differences (excess number of events/10,000 patient-years) and NNT (number needed to treat) and NNH (number needed to harm). For this study, the NNT denotes the number of patient-years exposure (based on all events over the course of the study) needed with rivaroxaban treatment vs. placebo to prevent 1 additional efficacy event, while the NNH denotes the number of patient-years exposure needed with rivaroxaban treatment vs. placebo to cause 1 additional safety event. A negative excess number of events favors rivaroxaban, and a positive excess number of events favors placebo

The composite efficacy endpoint includes ischemic and other non-bleeding events: non-bleeding CV death, MI, and ischemic stroke. The composite safety endpoint includes TIMI life-threatening bleeding and TIMI major bleeding events. TIMI life-threatening bleeding and TIMI major bleeding events both include a range of clinically significant bleeding events; however, they do not completely overlap. Using a composite of these two endpoints includes all non-minor bleeds in the benefit-risk assessment. Because the interpretation of outcomes may vary depending on the severity and associated clinical consequences, bleeding events were further grouped into 3 main categories that were mutually exclusive and in an order of relatively decreasing clinical importance: 1) fatal bleeding and ICH, 2) non-fatal and non-ICH TIMI life-

threatening bleeding, and 3) TIMI major bleeding that was not life-threatening. Based on these definitions, there is no overlap between events under the efficacy and safety categories.

Compared with placebo, rivaroxaban 2.5 mg b.i.d. prevented 125 (95% CI: 30, 221) non-bleeding CV death, MI and ischemic stroke events per 10,000 patient-years, while causing 10 (95% CI: -11, 30) fatal bleeding or ICH events. These results (125 vs. 10) suggest that approximately 12-13 non-bleeding CV events were prevented for 1 hemorrhagic event caused (i.e., approximately a favorable “benefit-risk ratio” of 12-13 to 1). This comparison is clinically important, since both these benefits and harms are considered fatal or generally irreversible. From an NNT/NNH perspective, treatment of ACS patients with rivaroxaban 2.5 mg b.i.d. instead of placebo would result in 1 fewer non-bleeding CV death, MI or ischemic stroke event per 80 patient-years; while there would be 1 additional fatal bleeding or ICH event every 1052 patient-years. This favorable benefit-risk profile is strengthened by noting that 68% of the efficacy events prevented are non-bleeding CV death (85 out of 125), while there are very few fatal bleeding events ([Table 46](#)).

In addition to fatal bleeding and ICH events, rivaroxaban 2.5 mg b.i.d. caused 28 (95% CI 5, 51) non-fatal, non-ICH TIMI life-threatening bleeding events and 35 (95% CI: 10, 61) non-life-threatening TIMI major bleeding events per 10,000 patients-years compared with placebo. The first endpoint was primarily driven by bleeding requiring transfusion ≥ 4 units, while the second endpoint consisted of bleeding events that reduced hemoglobin by 5 g/dL or more but resulted in no surgical, IV inotropic or transfusion intervention of 4 units or more ([Appendix DNCB055](#)). From a clinical perspective, those events considered less severe than fatal bleeding and ICH (i.e., bleeding events with irreversible harm), but they were presented for completeness. As a conservative benefit-risk assessment, the 125 (95% CI 30, 221) composite efficacy endpoint of non-bleeding CV death, MI or ischemic stroke events prevented per 10,000 patient-years might also be compared with the 69 (95% CI: 30, 109) composite safety endpoint of TIMI life-threatening bleeding or TIMI major bleeding events caused ([Table 46](#)). Regardless how the risk of bleeding was assessed, rivaroxaban consistently demonstrated a favorable benefit-risk profile (particularly dominated by a significant reduction in CV death) compared with placebo.

Results for 2.5 mg b.i.d. dose are similar for Stratum 2 ([Table 46](#)). In Stratum 2, compared with treatment with placebo, rivaroxaban 2.5 mg b.i.d. treatment prevented 115 (95% CI: 18, 212) non-bleeding CV death, MI or ischemic stroke events per 10,000 patient-years, while causing an additional 10 (95% CI: -11, 32) fatal bleeding or ICH events. These results (115 vs. 10) suggest a favorable “benefit-risk ratio” of 11-12 to 1 (i.e., 11-12 fatal or generally irreversible events prevented per 1 fatal or generally irreversible events caused). From a NNT/NNH perspective, treatment of ACS patients with rivaroxaban 2.5 mg b.i.d. instead of placebo would result in 1 fewer non-bleeding CV death, MI and ischemic stroke event per 87 patient-years; while there would be 1 additional fatal bleeding or ICH event every 984 patient-years. This favorable benefit-risk profile is strengthened by noting that 82.6% of the efficacy events prevented are non-bleeding CV death (95 out of 115), while there are very few fatal bleeding events.

A forest plot showing the risk differences of the ischemic and hemorrhagic endpoints for rivaroxaban 2.5 mg vs. placebo in Stratum 2 is shown in [Figure 20](#).

Additionally, results for the 5 mg b.i.d. dose are included in [Appendix DNCB055](#).

8.1.2. Temporal Course of Benefit-Risk

Excess number of events of non-bleeding CV death, MI, and ischemic stroke by treatment duration was estimated by the difference of Kaplan-Meier estimates of the event rate between treatment groups. Excess number of events of fatal bleeding and symptomatic ICH was estimated similarly. Results for the 2.5 mg b.i.d. group in Stratum 2 are shown in [Figure 21](#). The benefit or efficacy endpoint exceeded the harm or safety endpoint early in treatment course and showed a considerable advantage to rivaroxaban throughout the course of treatment. The plots for the rivaroxaban 2.5 mg b.i.d in All Strata are included in [Appendix FNCB1009a](#).

**Table 46: (RNCB055) Decomposition of Ischemic and Hemorrhagic Events for Rivaroxaban 2.5 mg BID Dose
(Study RIVAROXACS3001: Modified Intent-to-Treat (Excluding Sites 091001, 091019 and 091026) Analysis Set)**

Subject Stratum: All Strata						
Rivaroxaban: 2.5 mg						
Analysis Set: Modified Intent-to-Treat (Excluding Sites 091001, 091019 and 091026)						
Time to		----- Event Rate(a) -----		----- Excess Number of Events -----		
Event		----- (/100 Pt-yrs) -----		----- (Rivaroxaban - Placebo) -----		
Category	Endpoints	Rivaroxaban	Placebo	Excess # events for 10,000 pt-yrs	95% CI	NNT/NNH(b)
Efficacy	Non-bleeding CV death, MI or ischemic stroke	5.62	6.87	-125 *	(-221, -30)	-80
	Non-bleeding CV death	1.58	2.43	-85 *	(-139, -32)	-117
	MI excl CV death	3.64	3.98	-34	(-108, 41)	-297
	Ischemic stroke excl CV death	0.53	0.56	-3	(-31, 25)	-3380
	Non-CV death excl fatal bleed	0.17	0.16	0	(-16, 16)	47435
Safety	TIMI life threatening bleeding + TIMI major bleeding	1.42	0.73	69 *	(30, 109)	144
	Fatal Bleeding + symptomatic ICH	0.33	0.24	10	(-11, 30)	1052
	Fatal Bleeding	0.17	0.20	-3	(-20, 13)	-2921
	Intracranial Bleeding (ICH)	0.28	0.11	17	(-1, 34)	599
	Fatal ICH	0.11	0.07	4	(-9, 16)	2649
	Non-fatal ICH	0.17	0.04	13	(-1, 26)	773
	Non-fatal, non-ICH TIMI life threatening bleeding	0.50	0.22	28 *	(5, 51)	358
	TIMI Major Bleeding, non-life threatening	0.63	0.27	35 *	(10, 61)	282

(a): Event rate (/100 Pt-yrs): Number of events per 100 patient years of follow up.

(b): A negative number denotes the number of patient years needed to be treated with rivaroxaban instead of placebo to prevent one additional harmful event (NNT). A positive number denotes the number of patient years needed to be treated with rivaroxaban instead of placebo to observe one additional harmful event (NNH).

Note: CI = Confidence Interval; CV =Cardiovascular; MI = Myocardial infarction; ICH =Intracranial Hemorrhage.

Note: * Nominal 2-sided p-value < 0.05 (not adjusted for multiplicity).

Note: The 95% CI is based on constant hazard assumption. Under this assumption the number of events observed has a Poisson distribution. The calculation is carried out using normal approximation to Poisson distribution, conditional on the total duration of treatment exposure.

Note: Non-bleeding CV death excludes deaths adjudicated as due to non-bleeding causes that have fatal bleeding complications (e.g. trauma, malignancy).

All hemorrhagic CV deaths and non-hemorrhage CV deaths with fatal bleeding complications are included under fatal bleeding.

Note: CV deaths include deaths adjudicated as Unknown.

Note: No CI provided if the number of events is 0 or 1 in either group; There are no asymptomatic ICHs.

Table 46 continued RNCB055: Decomposition of Ischemic and Hemorrhagic Events
(Study RIVAROXACS3001: Modified Intent-to-Treat (Excluding Sites 091001, 091019 and 091026) Analysis Set)

Subject Stratum: ASA + Thieno

Rivaroxaban: 2.5 mg

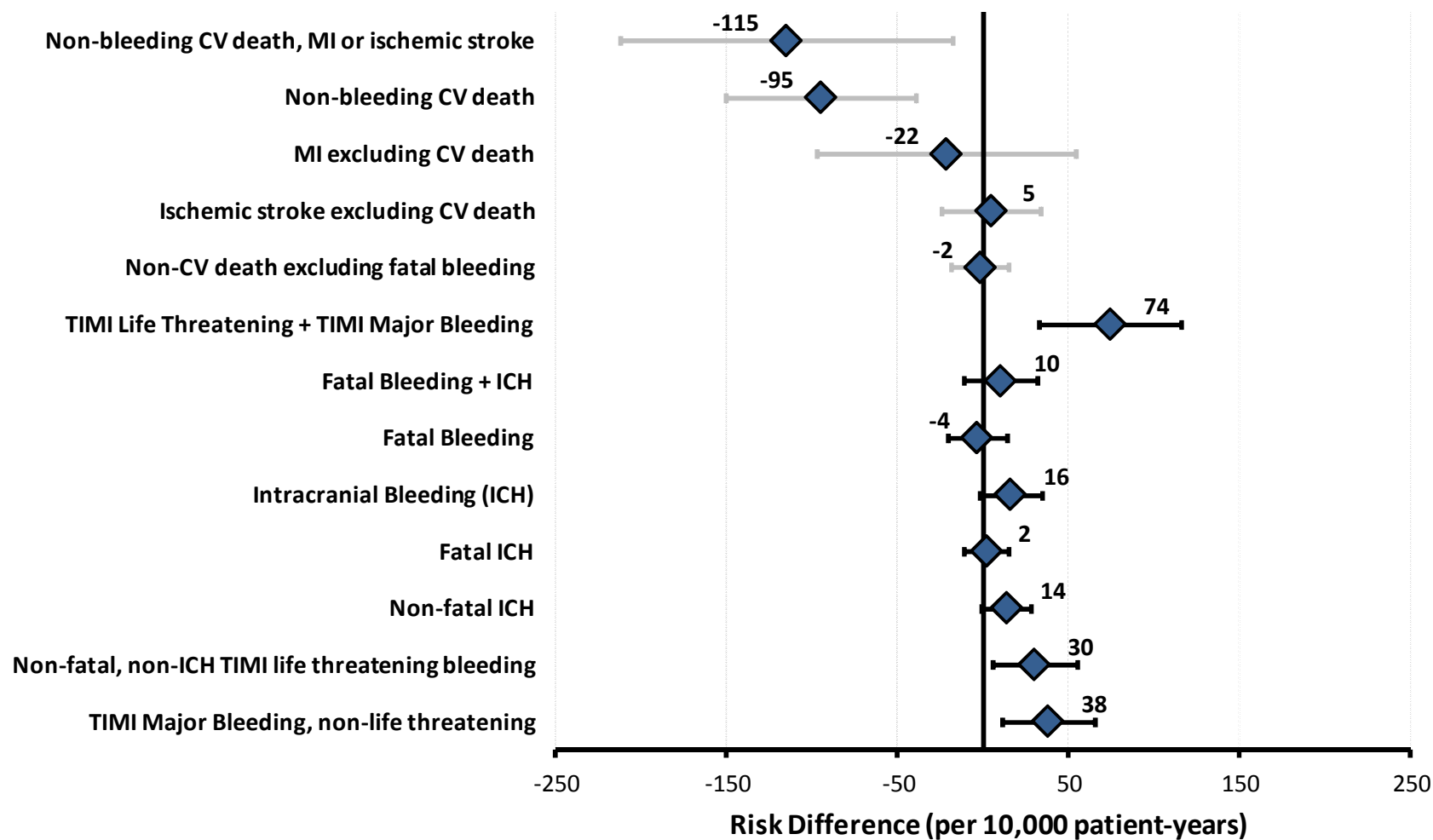
Analysis Set: Modified Intent-to-Treat (Excluding Sites 091001, 091019 and 091026)

Time to Event Category	Endpoints	----- Event Rate(a) ----- ----- (/100 Pt-yrs) -----		----- Excess Number of Events ----- ----- (Rivaroxaban - Placebo) ----- Excess # events for		
		Rivaroxaban	Placebo	10,000 pt-yrs	95% CI	NNT/NNH(b)
Efficacy	Non-bleeding CV death, MI or ischemic stroke	5.48	6.63	-115 *	(-212, -18)	-87
	Non-bleeding CV death	1.48	2.43	-95 *	(-149, -41)	-105
	MI excl CV death	3.59	3.81	-22	(-97, 54)	-462
	Ischemic stroke excl CV death	0.55	0.51	5	(-24, 33)	2150
	Non-CV death excl fatal bleed	0.16	0.17	-2	(-19, 15)	-5790
Safety	TIMI life threatening bleeding + TIMI major bleeding	1.48	0.74	74 *	(33, 116)	135
	Fatal Bleeding + symptomatic ICH	0.33	0.23	10	(-11, 32)	984
	Fatal Bleeding	0.16	0.19	-4	(-21, 14)	-2726
	Intracranial Bleeding (ICH)	0.28	0.12	16	(-2, 34)	629
	Fatal ICH	0.10	0.08	2	(-11, 15)	4819
	Non-fatal ICH	0.18	0.04	14	(-1, 28)	723
	Non-fatal, non-ICH TIMI life threatening bleeding	0.53	0.23	30 *	(5, 55)	334
	TIMI Major Bleeding, non-life threatening	0.65	0.27	38 *	(11, 65)	264

See footnotes on front page.

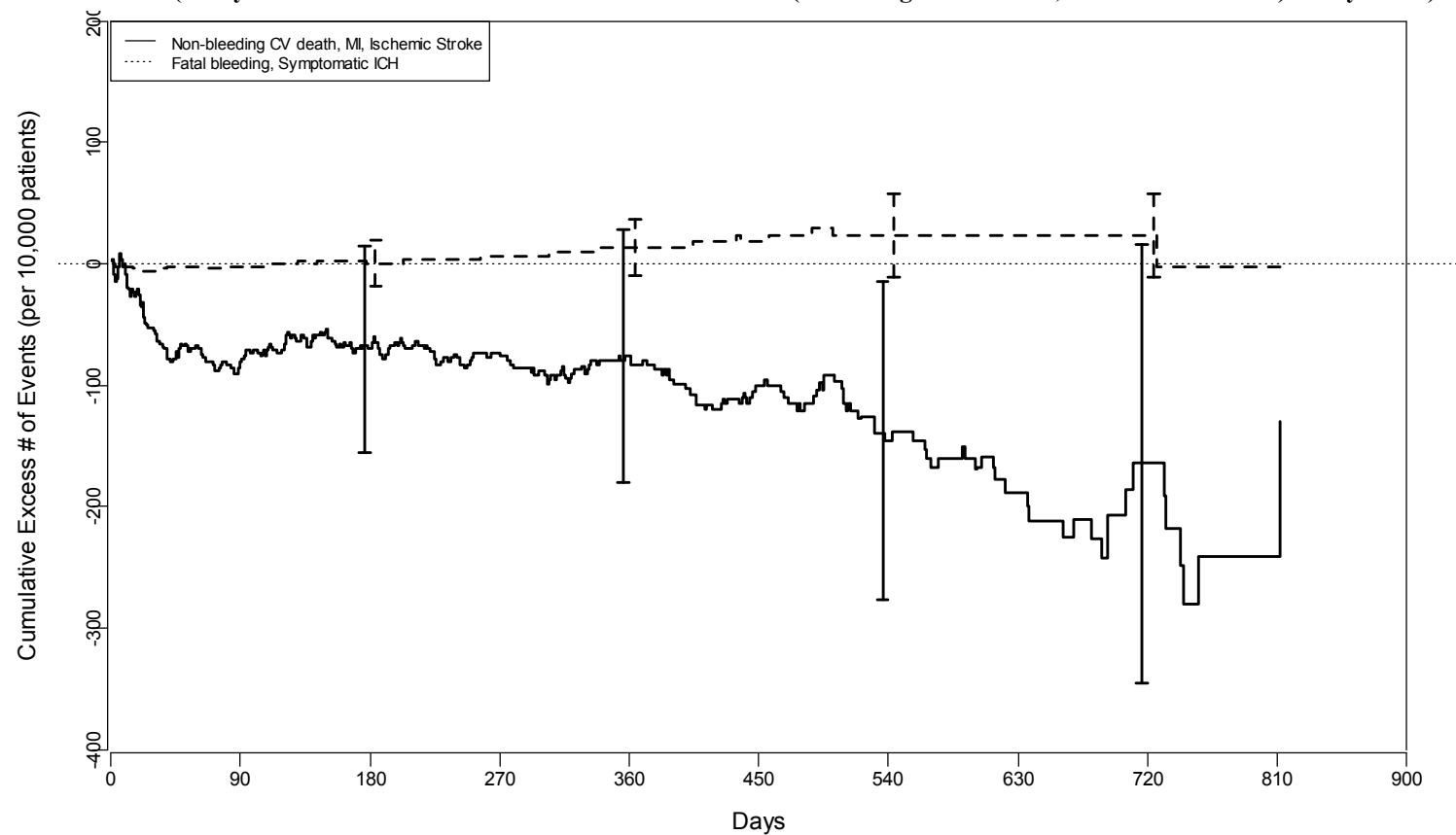
Source: mcb055.rtf generated by rncb055.sas, 11APR2012 15:42

Figure 20: Risk Differences (per 10,000 patient-years) of Ischemic and Hemorrhagic Events for Rivaroxaban 2.5 mg BID Dose in Stratum 2 (Study RIVAROXACS3001: Modified Intent-to-Treat (Excluding Sites 091001, 091019 and 091026) Analysis Set)



Note: Diamonds indicate point estimates. Grey and black bars show 95% CIs for ischemic and hemorrhagic endpoints respectively.
Data source: RNCB055.

**Figure 21: (FNCB1008a) Cumulative Excess Number of Events Based on Kaplan-Meier Method for the Composite of Non-bleeding CV death, MI and Ischemic Stroke Versus Fatal Bleeding and Symptomatic ICH as Adjudicated by the CEC
Rivaroxaban 2.5 mg b.i.d. Versus Placebo, Stratum 2
(Study RIVAROXACS3001: Modified Intent-to-Treat (Excluding Sites 091001, 091019 and 091026) Analysis Set)**



8.2. Quantitative Benefit-Risk Assessment Conclusions

In summary, using approaches that compare efficacy against several different levels of bleeding severity, rivaroxaban consistently prevented more fatal and irreversible non-bleeding CV events than bleeding events caused. These quantitative benefit-risk analyses confirm the positive benefit-risk profile of rivaroxaban as compared with placebo.

9. Overall Summary

The following conclusions can be drawn based on the data from the ATLAS ACS 2 TIMI 51 study:

- The addition of rivaroxaban, at a dose of 2.5 mg b.i.d., to standard care antiplatelet therapy is effective in reducing the risk of the composite of CV death, myocardial infarction or stroke compared with standard care antiplatelet therapy alone in subjects with recent ACS.
 - The results were driven by a nominally statistically significant reduction in the incidence of CV deaths, and a reduction of lesser magnitude in MI. In addition, reduction in all cause mortality in ITT analysis set showed nominal statistical significance.
 - This effect of rivaroxaban treatment was consistently observed across most major subgroups.
- 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 standard care antiplatelet therapy alone.
 - The rates of all types of bleeding events were incrementally increased with rivaroxaban at a dose of 5 mg b.i.d compared with 2.5 mg b.i.d.
 - 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 similar fatal bleeding events in subjects treated with 2.5 mg b.i.d. and in

subjects treated with placebo, but numerically more fatal bleeding events were observed with the 5 mg b.i.d. dose.

In conclusion, the data from the ATLAS ACS clinical development program, and the ATLAS ACS 2 TIMI 51 study in particular, show a compelling balance of benefit and risk for rivaroxaban 2.5 mg twice daily, and support the recommendation of this rivaroxaban regimen for reducing the risk of thrombotic CV events in patients with ACS.

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Appendix 1: Bleeding Scales

Three bleeding event scales were used to assess bleeding events in this study. The TIMI scale was the primary bleeding scale for this study; it has categories of major, minor, requiring medical attention, and insignificant bleeding events. The primary safety endpoint in this study was the incidence of non-CABG TIMI major bleeding events. Two other bleeding scales were also used to provide additional information on bleeding. The rivaroxaban program scale uses the ISTH major bleeding event classification and has categories of major bleeding events, clinically relevant nonmajor bleeding events, and minimal bleeding events. Bleeding events associated with CABG were evaluated separately for the ISTH scale. Finally, the GUSTO scale was also used to categorize bleeding events.

To account for transfusion, hemoglobin measurements were adjusted for any packed red blood cells (PRBC) or whole blood transfused between the pre- and postbleeding hemoglobin measurements. The number of units of PRBC and whole blood combined were added to the change in hemoglobin. If only a hematocrit value was known, the corresponding hemoglobin value was assumed to be one-third of the hematocrit value (in g/dL).

1. TIMI Bleeding Event Classification Scale

TIMI Major Bleeding Event

In the case of a TIMI major bleed, the adjudicator would determine if it was a coronary artery bypass graft (CABG) surgery related or non-CABG surgery related bleeding event. If the bleed was non-CABG related, then the following criteria were required to qualify as a TIMI major bleed:

1. Any symptomatic intracranial hemorrhage, or
2. Clinically overt signs of hemorrhage (including imaging) associated with a drop in hemoglobin of ≥ 5 g/dL (or when the hemoglobin concentration was not available, an absolute drop in hematocrit of $\geq 15\%$).

A TIMI major CABG-related bleed would include CABG-related: fatal bleeding (i.e., bleeding that directly results in death), perioperative intracranial bleeding, reoperation following closure of the sternotomy incision to control bleeding, transfusion of greater than or equal to 5 units of whole blood or PRBCs within a 48 hour period (cell saver transfusion would not be counted in calculations of blood products), or chest tube output > 2 L within a 24 hour period. For the TIMI scale, bleeding that occurred in the setting of CABG would be classified as a CABG-related TIMI major bleed, or as not a CABG-related TIMI Major Bleed. Events associated with CABG would not be classified as TIMI minor bleeding or bleeding requiring medical attention.

TIMI Minor Bleeding Event

A TIMI minor bleeding event was defined as any clinically overt sign of hemorrhage (including imaging) that was associated with a fall in hemoglobin concentration of 3 to <5 g/dL (or, when hemoglobin concentration was not available, a fall in hematocrit of 9 to <15%).

Bleeding Events Requiring Medical Attention

A bleeding event requiring medical attention was defined as any bleeding event that required medical treatment, surgical treatment, or laboratory evaluation and did not meet criteria for a major or minor bleeding event, as defined above.

Insignificant Bleeding Events

An insignificant bleeding event was defined as a reported blood loss or bleeding event episode not meeting any of the above criteria.

Clinically Significant Bleeding Events

The composite endpoint of TIMI major bleeding event, TIMI minor bleeding event, or bleeding event requiring medical attention was considered clinically significant for the TIMI scale.

TIMI Life-threatening Bleeding Event

Within the TIMI bleeding classification, the CEC categorized bleeding events as life-threatening.

2. Rivaroxaban Program Bleeding Event Scale

ISTH Major Bleeding Events

A major bleeding event was defined using ISTH **Error! Reference source not found.**²⁴ criteria as clinically overt bleeding that was associated with:

- A fall in hemoglobin of 2 g/dL or more, or
- A transfusion of 2 or more units of packed red blood cells or whole blood, or
- A critical site: intracranial, intraspinal, intraocular, pericardial, intra-articular, intramuscular with compartment syndrome, retroperitoneal, or
- A fatal outcome

Clinically Relevant Nonmajor Bleeding Events

A clinically relevant nonmajor bleeding event was defined as an overt bleeding event that did not meet the criteria for a major bleeding event, but was associated with medical intervention, unscheduled contact (visit or telephone call) with a physician, (temporary) cessation of study drug treatment, or was associated with discomfort for the subject such as pain or impairment of activities of daily life.

Examples of nonmajor clinically relevant bleeding events were:

- Epistaxis if it lasted for more than 5 minutes, if it was repetitive (i.e., 2 or more episodes of true bleeding, i.e., no spots on a handkerchief, within 24 hours), or led to an intervention (packing, electrocautery, etc.)
- Gingival bleeding if it occurred spontaneously (i.e., unrelated to tooth brushing or eating), or if it lasted for more than 5 minutes
- Hematuria if it was macroscopic, and either spontaneous or lasted for more than 24 hours after instrumentation (e.g., catheter placement or surgery) of the urogenital tract
- Macroscopic gastrointestinal hemorrhage: at least 1 episode of melena or hematemesis, if clinically apparent
- Rectal blood loss, if more than a few spots
- Hemoptysis, if more than a few speckles in the sputum, or
- Intramuscular hematoma
- Subcutaneous hematoma if the size was larger than 25 cm² or larger than 100 cm² if provoked
- Multiple source bleeding events

Minimal Bleeding Events

All other overt bleeding events not meeting the criteria for major or clinically relevant nonmajor bleeding events were classified as minimal bleeding events.

3. GUSTO Bleeding Event Scale

The GUSTO bleeding event scale has 3 classes: severe, moderate, and mild.

Severe Bleeding

Severe bleeding was defined as either an intracranial hemorrhage or bleeding that caused hemodynamic compromise and required intervention.

Moderate Bleeding

Moderate bleeding was defined as bleeding that required blood transfusion but did not result in hemodynamic compromise.

Mild Bleeding

Mild bleeding was defined as bleeding that did not meet criteria for either severe or moderate bleeding.

LIST OF APPENDICES

Output DSUB04A:	Demographic and Baseline Characteristics	144
Output DSUB24B:	Extent of Exposure to Concomitant Aspirin between the First Dose of Study Drug and the Last Dose of Study Drug	153
Output DBL04:	Effect of Rivaroxaban Compared with Placebo on Treatment-Emergent Bleeding using the TIMI, GUSTO and ISTH Scales as Adjudicated by the CEC	155
Output DBL29:	Incidence of Treatment-Emergent GUSTO Severe Bleeding as Adjudicated by the CEC	157
Output DBL30:	Incidence of Treatment-Emergent of Non-CABG TIMI Major Bleeding Events by Provocation as Adjudicated by the CEC	158
Output DBLPH00:	Comparison between Treatment Groups on Bleeding Events Using TIMI Scale as Adjudicated by the CEC	161
Output DNCB055:	Decomposition of Ischemic and Hemorrhagic Events	162
Figure FNCB1009a:	Cumulative Excess Number of Events Based on Kaplan–Meier Method for Composite of Non–bleeding CV death, MI, Ischemic Stroke vs. Fatal Bleeding, Symptomatic ICH (Adjudicated by CEC), MITT, Rivaroxaban 2.5mg vs Placebo (Stratum = All Strata)	171
Figure FBL10A:	Hazard Ratios and Rates of First Occurrence of Treatment–Emergent Non–CABG-related TIMI Major Bleeding Events by Subgroups for Combined Rivaroxaban Dose Groups Compared with Placebo in All Stratum	172
Figure FBL15A:	Hazard Ratios and Rates of First Occurrence of Treatment–Emergent Clinically Significant Bleeding Events by Subgroups for Combined Rivaroxaban Dose Groups Compared with Placebo in All Stratum	173
Figure FBL15H:	Hazard Ratios and Rates of First Occurrence of Treatment–Emergent Clinically Significant Bleeding Events by Subgroups for Rivaroxaban 2.5 mg BID Group Compared with Placebo in ASA + Thieno Stratum	174
Figure FEF20A:	Hazard Ratios and Rates of the Primary Efficacy Endpoint (First Occurrence Cardiovascular Death, MI, Stroke) by Subgroup for Combined Rivaroxaban Dose Groups Compared with Placebo in All Strata	175

Page 1 of 9

09NOV2011 16:55
System Used: Arrow6.1(U)/rdm01a_t

Study RIVAROXACS3001

Output DSUB04A: Demographic and Baseline Characteristics

Analysis Set: All Randomized Subjects

Subject Stratum: All Strata

	Rivaroxaban				
	2.5 mg BID (N=5174)	5 mg BID (N=5176)	Combined (N=10350)	Placebo (N=5176)	Total (N=15526)

Sex, n (%)					
~~~~~					
N	5174	5176	10350	5176	15526
FEMALE	1299 (25.1)	1333 (25.8)	2632 (25.4)	1294 (25.0)	3926 (25.3)
MALE	3875 (74.9)	3843 (74.2)	7718 (74.6)	3882 (75.0)	11600 (74.7)
Race, n (%)					
~~~~~					
N	5174	5176	10350	5176	15526
WHITE	3798 (73.4)	3815 (73.7)	7613 (73.6)	3796 (73.3)	11409 (73.5)
BLACK OR AFRICAN AMERICAN	34 (0.7)	34 (0.7)	68 (0.7)	39 (0.8)	107 (0.7)
ASIAN	1099 (21.2)	1055 (20.4)	2154 (20.8)	1075 (20.8)	3229 (20.8)
AMERICAN INDIAN OR ALASKA NATIVE	0	3 (0.1)	3 (<0.1)	5 (0.1)	8 (0.1)
NATIVE HAWAIIAN OR OTHER PACIFIC ISLANDER	0	2 (<0.1)	2 (<0.1)	3 (0.1)	5 (<0.1)
OTHER	243 (4.7)	267 (5.2)	510 (4.9)	258 (5.0)	768 (4.9)
Age (yrs)					
~~~~~					
N	5174	5176	10350	5176	15526
Mean	61.8	61.9	61.9	61.5	61.8
SD	9.23	9.03	9.13	9.39	9.22
Median	61.0	61.0	61.0	61.0	61.0
Minimum	25	26	25	22	22
Maximum	91	93	93	98	98
Age (yrs), n (%)					
~~~~~					
N	5174	5176	10350	5176	15526
>= 75	466 (9.0)	441 (8.5)	907 (8.8)	498 (9.6)	1405 (9.0)
>= 65	1905 (36.8)	1921 (37.1)	3826 (37.0)	1835 (35.5)	5661 (36.5)
>= 55	4298 (83.1)	4326 (83.6)	8624 (83.3)	4216 (81.5)	12840 (82.7)
< 55	876 (16.9)	850 (16.4)	1726 (16.7)	960 (18.5)	2686 (17.3)

Note: Percentages calculated with the number of subjects in each parameter and treatment group as denominator.

Note: ASA = Acetylsalicylic acid; Thieno = Thienopyridine; MI = Myocardial infarction.

Page 2 of 9

09NOV2011 16:55
System Used: Arrow6.1(U)/rdm01a_t

Study RIVAROXACS3001

Output DSUB04A: Demographic and Baseline Characteristics (continued)

Analysis Set: All Randomized Subjects
Subject Stratum: All Strata

	Rivaroxaban				
	2.5 mg BID (N=5174)	5 mg BID (N=5176)	Combined (N=10350)	Placebo (N=5176)	Total (N=15526)

Baseline Creatinine Clearance (mL/min), n (%)					
~~~~~					
N	5111	5104	10215	5120	15335
<30	25 ( 0.5)	22 ( 0.4)	47 ( 0.5)	30 ( 0.6)	77 ( 0.5)
>=30 - <50	344 ( 6.7)	315 ( 6.2)	659 ( 6.5)	350 ( 6.8)	1009 ( 6.6)
>=50 - <=80	1779 (34.8)	1847 (36.2)	3626 (35.5)	1748 (34.1)	5374 (35.0)
>80	2963 (58.0)	2920 (57.2)	5883 (57.6)	2992 (58.4)	8875 (57.9)
Admitting Diagnosis, n (%)					
~~~~~					
N	5174	5176	10350	5176	15526
STEMI	2601 (50.3)	2584 (49.9)	5185 (50.1)	2632 (50.9)	7817 (50.3)
NSTEMI	1321 (25.5)	1335 (25.8)	2656 (25.7)	1323 (25.6)	3979 (25.6)
Unstable Angina	1252 (24.2)	1257 (24.3)	2509 (24.2)	1221 (23.6)	3730 (24.0)
Time from Index Event to Randomization (days)					
~~~~~					
N	5174	5176	10350	5176	15526
Mean	4.7	4.6	4.7	4.7	4.7
SD	1.78	1.77	1.78	1.79	1.78
Median	4.7	4.7	4.7	4.7	4.7
Minimum	0	0	0	0	0
Maximum	15	13	15	19	19
Revascularization procedure for index event, n (%)					
~~~~~					
N	5174	5175	10349	5176	15525
YES	3138 (60.6)	3123 (60.3)	6261 (60.5)	3126 (60.4)	9387 (60.5)
Baseline PCI for Index Event, n (%)					
~~~~~					
N	5174	5175	10349	5176	15525
YES	3117 (60.2)	3106 (60.0)	6223 (60.1)	3101 (59.9)	9324 (60.1)

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Page 3 of 9

09NOV2011 16:55  
System Used: Arrow6.1(U)/rdm01a_t

Study RIVAROXACS3001

Output DSUB04A: Demographic and Baseline Characteristics (continued)

Analysis Set: All Randomized Subjects

Subject Stratum: All Strata

	Rivaroxaban				
	2.5 mg BID (N=5174)	5 mg BID (N=5176)	Combined (N=10350)	Placebo (N=5176)	Total (N=15526)
-----					
Baseline Diabetes Mellitus, n (%)					
~~~~~					
N	5174	5176	10350	5176	15526
YES	1669 (32.3)	1648 (31.8)	3317 (32.0)	1647 (31.8)	4964 (32.0)
Prior MI, n (%)					
~~~~~					
N	5174	5176	10350	5176	15526
YES	1363 (26.3)	1403 (27.1)	2766 (26.7)	1415 (27.3)	4181 (26.9)
Prior Stroke, n (%)					
~~~~~					
N	5174	5176	10350	5176	15526
YES	100 (1.9)	98 (1.9)	198 (1.9)	88 (1.7)	286 (1.8)
Prior TIA, n (%)					
~~~~~					
N	5174	5176	10350	5176	15526
YES	42 ( 0.8)	52 ( 1.0)	94 ( 0.9)	47 ( 0.9)	141 ( 0.9)
Prior Hypertension, n (%)					
~~~~~					
N	5174	5176	10350	5174	15524
YES	3470 (67.1)	3499 (67.6)	6969 (67.3)	3494 (67.5)	10463 (67.4)

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Page 4 of 9

09NOV2011 16:55
System Used: Arrow6.1(U)/rdm01a_t

Study RIVAROXACS3001

Output DSUB04A: Demographic and Baseline Characteristics (continued)

Analysis Set: All Randomized Subjects
Subject Stratum: ASA

	Rivaroxaban		Combined	Placebo	Total
	2.5 mg BID (N=349)	5 mg BID (N=349)	(N=698)	(N=355)	(N=1053)

Sex, n (%)					
~~~~~					
N	349	349	698	355	1053
FEMALE	168 (48.1)	157 (45.0)	325 (46.6)	153 (43.1)	478 (45.4)
MALE	181 (51.9)	192 (55.0)	373 (53.4)	202 (56.9)	575 (54.6)
Race, n (%)					
~~~~~					
N	349	349	698	355	1053
WHITE	276 (79.1)	275 (78.8)	551 (78.9)	276 (77.7)	827 (78.5)
BLACK OR AFRICAN AMERICAN	2 (0.6)	4 (1.1)	6 (0.9)	7 (2.0)	13 (1.2)
ASIAN	42 (12.0)	41 (11.7)	83 (11.9)	47 (13.2)	130 (12.3)
AMERICAN INDIAN OR ALASKA NATIVE	0	0	0	0	0
NATIVE HAWAIIAN OR OTHER PACIFIC ISLANDER	0	0	0	0	0
OTHER	29 (8.3)	29 (8.3)	58 (8.3)	25 (7.0)	83 (7.9)
Age (yrs)					
~~~~~					
N	349	349	698	355	1053
Mean	64.4	63.3	63.8	64.7	64.1
SD	10.00	9.36	9.70	10.74	10.06
Median	63.0	63.0	63.0	65.0	64.0
Minimum	35	26	26	22	22
Maximum	89	88	89	93	93
Age (yrs), n (%)					
~~~~~					
N	349	349	698	355	1053
>= 75	55 (15.8)	37 (10.6)	92 (13.2)	75 (21.1)	167 (15.9)
>= 65	167 (47.9)	154 (44.1)	321 (46.0)	179 (50.4)	500 (47.5)
>= 55	301 (86.2)	294 (84.2)	595 (85.2)	298 (83.9)	893 (84.8)
< 55	48 (13.8)	55 (15.8)	103 (14.8)	57 (16.1)	160 (15.2)

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Page 5 of 9

09NOV2011 16:55
System Used: Arrow6.1(U)/rdm01a_t

Study RIVAROXACS3001

Output DSUB04A: Demographic and Baseline Characteristics (continued)

Analysis Set: All Randomized Subjects
Subject Stratum: ASA

	Rivaroxaban				
	2.5 mg BID (N=349)	5 mg BID (N=349)	Combined (N=698)	Placebo (N=355)	Total (N=1053)

Baseline Creatinine Clearance (mL/min), n (%)					
~~~~~					
N	343	341	684	352	1036
<30	5 ( 1.5)	2 ( 0.6)	7 ( 1.0)	8 ( 2.3)	15 ( 1.4)
>=30 - <50	44 (12.8)	30 ( 8.8)	74 (10.8)	57 (16.2)	131 (12.6)
>=50 - <=80	119 (34.7)	146 (42.8)	265 (38.7)	124 (35.2)	389 (37.5)
>80	175 (51.0)	163 (47.8)	338 (49.4)	163 (46.3)	501 (48.4)
Admitting Diagnosis, n (%)					
~~~~~					
N	349	349	698	355	1053
STEMI	77 (22.1)	47 (13.5)	124 (17.8)	58 (16.3)	182 (17.3)
NSTEMI	77 (22.1)	78 (22.3)	155 (22.2)	95 (26.8)	250 (23.7)
Unstable Angina	195 (55.9)	224 (64.2)	419 (60.0)	202 (56.9)	621 (59.0)
Time from Index Event to Randomization (days)					
~~~~~					
N	349	349	698	355	1053
Mean	4.9	4.7	4.8	4.8	4.8
SD	1.69	1.68	1.69	1.75	1.71
Median	5.0	4.9	5.0	4.9	4.9
Minimum	1	1	1	1	1
Maximum	10	13	13	11	13
Revascularization procedure for index event, n (%)					
~~~~~					
N	349	349	698	355	1053
YES	24 (6.9)	13 (3.7)	37 (5.3)	33 (9.3)	70 (6.6)
Baseline PCI for Index Event, n (%)					
~~~~~					
N	349	349	698	355	1053
YES	20 ( 5.7)	8 ( 2.3)	28 ( 4.0)	23 ( 6.5)	51 ( 4.8)

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Page 6 of 9

09NOV2011 16:55  
System Used: Arrow6.1(U)/rdm01a_t

Study RIVAROXACS3001

Output DSUB04A: Demographic and Baseline Characteristics (continued)

Analysis Set: All Randomized Subjects

Subject Stratum: ASA

	Rivaroxaban				
	2.5 mg BID (N=349)	5 mg BID (N=349)	Combined (N=698)	Placebo (N=355)	Total (N=1053)
-----					
Baseline Diabetes Mellitus, n (%)					
~~~~~					
N	349	349	698	355	1053
YES	139 (39.8)	137 (39.3)	276 (39.5)	142 (40.0)	418 (39.7)
Prior MI, n (%)					
~~~~~					
N	349	349	698	355	1053
YES	134 (38.4)	143 (41.0)	277 (39.7)	118 (33.2)	395 (37.5)
Prior Stroke, n (%)					
~~~~~					
N	349	349	698	355	1053
YES	57 (16.3)	53 (15.2)	110 (15.8)	49 (13.8)	159 (15.1)
Prior TIA, n (%)					
~~~~~					
N	349	349	698	355	1053
YES	13 ( 3.7)	14 ( 4.0)	27 ( 3.9)	20 ( 5.6)	47 ( 4.5)
Prior Hypertension, n (%)					
~~~~~					
N	349	349	698	355	1053
YES	290 (83.1)	298 (85.4)	588 (84.2)	310 (87.3)	898 (85.3)

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Page 7 of 9

09NOV2011 16:55
System Used: Arrow6.1(U)/rdm01a_t

Study RIVAROXACS3001

Output DSUB04A: Demographic and Baseline Characteristics (continued)

Analysis Set: All Randomized Subjects
Subject Stratum: ASA + Thieno

	Rivaroxaban				
	2.5 mg BID (N=4825)	5 mg BID (N=4827)	Combined (N=9652)	Placebo (N=4821)	Total (N=14473)

Sex, n (%)					
~~~~~					
N	4825	4827	9652	4821	14473
FEMALE	1131 (23.4)	1176 (24.4)	2307 (23.9)	1141 (23.7)	3448 (23.8)
MALE	3694 (76.6)	3651 (75.6)	7345 (76.1)	3680 (76.3)	11025 (76.2)
Race, n (%)					
~~~~~					
N	4825	4827	9652	4821	14473
WHITE	3522 (73.0)	3540 (73.3)	7062 (73.2)	3520 (73.0)	10582 (73.1)
BLACK OR AFRICAN AMERICAN	32 (0.7)	30 (0.6)	62 (0.6)	32 (0.7)	94 (0.6)
ASIAN	1057 (21.9)	1014 (21.0)	2071 (21.5)	1028 (21.3)	3099 (21.4)
AMERICAN INDIAN OR ALASKA NATIVE	0	3 (0.1)	3 (<0.1)	5 (0.1)	8 (0.1)
NATIVE HAWAIIAN OR OTHER PACIFIC ISLANDER	0	2 (<0.1)	2 (<0.1)	3 (0.1)	5 (<0.1)
OTHER	214 (4.4)	238 (4.9)	452 (4.7)	233 (4.8)	685 (4.7)
Age (yrs)					
~~~~~					
N	4825	4827	9652	4821	14473
Mean	61.7	61.8	61.7	61.3	61.6
SD	9.15	9.00	9.07	9.24	9.13
Median	61.0	61.0	61.0	61.0	61.0
Minimum	25	29	25	30	25
Maximum	91	93	93	98	98
Age (yrs), n (%)					
~~~~~					
N	4825	4827	9652	4821	14473
>= 75	411 (8.5)	404 (8.4)	815 (8.4)	423 (8.8)	1238 (8.6)
>= 65	1738 (36.0)	1767 (36.6)	3505 (36.3)	1656 (34.3)	5161 (35.7)
>= 55	3997 (82.8)	4032 (83.5)	8029 (83.2)	3918 (81.3)	11947 (82.5)
< 55	828 (17.2)	795 (16.5)	1623 (16.8)	903 (18.7)	2526 (17.5)

See footnotes on the first page of the table.

Page 8 of 9

09NOV2011 16:55
System Used: Arrow6.1(U)/rdm01a_t

Study RIVAROXACS3001

Output DSUB04A: Demographic and Baseline Characteristics (continued)

Analysis Set: All Randomized Subjects

Subject Stratum: ASA + Thieno

	Rivaroxaban				
	2.5 mg BID (N=4825)	5 mg BID (N=4827)	Combined (N=9652)	Placebo (N=4821)	Total (N=14473)
Baseline Creatinine Clearance (mL/min), n (%)					
N	4768	4763	9531	4768	14299
<30	20 (0.4)	20 (0.4)	40 (0.4)	22 (0.5)	62 (0.4)
>=30 - <50	300 (6.3)	285 (6.0)	585 (6.1)	293 (6.1)	878 (6.1)
>=50 - <=80	1660 (34.8)	1701 (35.7)	3361 (35.3)	1624 (34.1)	4985 (34.9)
>80	2788 (58.5)	2757 (57.9)	5545 (58.2)	2829 (59.3)	8374 (58.6)
Admitting Diagnosis, n (%)					
N	4825	4827	9652	4821	14473
STEMI	2524 (52.3)	2537 (52.6)	5061 (52.4)	2574 (53.4)	7635 (52.8)
NSTEMI	1244 (25.8)	1257 (26.0)	2501 (25.9)	1228 (25.5)	3729 (25.8)
Unstable Angina	1057 (21.9)	1033 (21.4)	2090 (21.7)	1019 (21.1)	3109 (21.5)
Time from Index Event to Randomization (days)					
N	4825	4827	9652	4821	14473
Mean	4.7	4.6	4.7	4.7	4.7
SD	1.78	1.78	1.78	1.79	1.78
Median	4.7	4.7	4.7	4.7	4.7
Minimum	0	0	0	0	0
Maximum	15	13	15	19	19
Revascularization procedure for index event, n (%)					
N	4825	4826	9651	4821	14472
YES	3114 (64.5)	3110 (64.4)	6224 (64.5)	3093 (64.2)	9317 (64.4)
Baseline PCI for Index Event, n (%)					
N	4825	4826	9651	4821	14472
YES	3097 (64.2)	3098 (64.2)	6195 (64.2)	3078 (63.8)	9273 (64.1)

See footnotes on the first page of the table.

Page 9 of 9

09NOV2011 16:55
System Used: Arrow6.1(U)/rdm01a_t

Study RIVAROXACS3001

Output DSUB04A: Demographic and Baseline Characteristics (continued)

Analysis Set: All Randomized Subjects
Subject Stratum: ASA + Thieno

	Rivaroxaban				
	2.5 mg BID (N=4825)	5 mg BID (N=4827)	Combined (N=9652)	Placebo (N=4821)	Total (N=14473)

Baseline Diabetes Mellitus, n (%)					
~~~~~					
N	4825	4827	9652	4821	14473
YES	1530 (31.7)	1511 (31.3)	3041 (31.5)	1505 (31.2)	4546 (31.4)
Prior MI, n (%)					
~~~~~					
N	4825	4827	9652	4821	14473
YES	1229 (25.5)	1260 (26.1)	2489 (25.8)	1297 (26.9)	3786 (26.2)
Prior Stroke, n (%)					
~~~~~					
N	4825	4827	9652	4821	14473
YES	43 ( 0.9)	45 ( 0.9)	88 ( 0.9)	39 ( 0.8)	127 ( 0.9)
Prior TIA, n (%)					
~~~~~					
N	4825	4827	9652	4821	14473
YES	29 (0.6)	38 (0.8)	67 (0.7)	27 (0.6)	94 (0.6)
Prior Hypertension, n (%)					
~~~~~					
N	4825	4827	9652	4819	14471
YES	3180 (65.9)	3201 (66.3)	6381 (66.1)	3184 (66.1)	9565 (66.1)

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See footnotes on the first page of the table.

Page 1 of 2

09NOV2011 16:56  
System Used: Arrow6.1(U)/rcm03

Study RIVAROXACS3001

Output DSUB24B: Extent of Exposure to Concomitant Aspirin between the First Dose of Study Drug and the Last Dose of Study Drug

-----  
Analysis Set: Safety

	----- Rivaroxaban -----			Placebo	Total
	2.5 mg BID (N=5115)	5 mg BID (N=5110)	Combined (N=10225)	(N=5125)	(N=15350)
-----					
All Strata					
~~~~~					
N	5114	5107	10221	5119	15340
Mean	395.3	385.5	390.4	399.9	393.6
SD	233.37	237.19	235.32	232.34	234.37
Median	395.0	376.0	386.0	399.0	390.0
Minimum	1	1	1	1	1
Maximum	927	929	929	932	932
Total Exposure (patient years)	5534.8	5389.7	10924.5	5605.0	16529.5
Cumulative Duration, n (%)					
N	5114	5107	10221	5119	15340
>= 3 months	4445 (86.9)	4340 (85.0)	8785 (86.0)	4463 (87.2)	13248 (86.4)
>= 6 months	4046 (79.1)	3941 (77.2)	7987 (78.1)	4108 (80.3)	12095 (78.8)
>= 12 months	2782 (54.4)	2655 (52.0)	5437 (53.2)	2812 (54.9)	8249 (53.8)
>= 18 months	1569 (30.7)	1545 (30.3)	3114 (30.5)	1619 (31.6)	4733 (30.9)
>= 24 months	508 (9.9)	496 (9.7)	1004 (9.8)	507 (9.9)	1511 (9.9)
ASA					
~~~					
N	343	342	685	352	1037
Mean	377.9	383.4	380.6	369.9	377.0
SD	235.71	234.36	234.88	236.68	235.43
Median	350.0	364.0	351.0	348.5	351.0
Minimum	1	1	1	2	1
Maximum	864	909	909	882	909
Total Exposure (patient years)	354.9	359.0	713.9	356.5	1070.4

-----  
Note: Total duration (including days off aspirin) = date of the last aspirin administration - date of the first aspirin administration + 1.

Note: Percentages calculated with the number of subjects in each subject stratum and treatment group as denominator.

Note: The unit for duration is days.

Note: ASA = Acetylsalicylic acid; Thieno = Thienopyridine.

Page 2 of 2

09NOV2011 16:56  
System Used: Arrow6.1(U)/rcm03

Study RIVAROXACS3001

Output DSUB24B: Extent of Exposure to Concomitant Aspirin between the First Dose of Study Drug and the Last Dose of Study Drug (continued)

-----  
Analysis Set: Safety

	----- Rivaroxaban -----				
	2.5 mg BID (N=5115)	5 mg BID (N=5110)	Combined (N=10225)	Placebo (N=5125)	Total (N=15350)
-----					
ASA					
~~~					
Cumulative Duration, n (%)					
N	343	342	685	352	1037
>= 3 months	292 (85.1)	294 (86.0)	586 (85.5)	294 (83.5)	880 (84.9)
>= 6 months	262 (76.4)	269 (78.7)	531 (77.5)	264 (75.0)	795 (76.7)
>= 12 months	170 (49.6)	171 (50.0)	341 (49.8)	173 (49.1)	514 (49.6)
>= 18 months	102 (29.7)	105 (30.7)	207 (30.2)	104 (29.5)	311 (30.0)
>= 24 months	32 (9.3)	29 (8.5)	61 (8.9)	28 (8.0)	89 (8.6)
ASA + Thieno					
~~~~~					
N	4771	4765	9536	4767	14303
Mean	396.6	385.6	391.1	402.1	394.8
SD	233.18	237.41	235.35	231.89	234.26
Median	399.0	377.0	387.0	401.0	392.0
Minimum	1	1	1	1	1
Maximum	927	929	929	932	932
Total Exposure (patient years)	5179.9	5030.7	10210.6	5248.5	15459.1
Cumulative Duration, n (%)					
N	4771	4765	9536	4767	14303
>= 3 months	4153 (87.0)	4046 (84.9)	8199 (86.0)	4169 (87.5)	12368 (86.5)
>= 6 months	3784 (79.3)	3672 (77.1)	7456 (78.2)	3844 (80.6)	11300 (79.0)
>= 12 months	2612 (54.7)	2484 (52.1)	5096 (53.4)	2639 (55.4)	7735 (54.1)
>= 18 months	1467 (30.7)	1440 (30.2)	2907 (30.5)	1515 (31.8)	4422 (30.9)
>= 24 months	476 (10.0)	467 ( 9.8)	943 ( 9.9)	479 (10.0)	1422 ( 9.9)

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See footnotes on the first page of the table.



Page 1 of 2

09NOV2011 16:54  
System Used: Arrow6.1(U)/rbl02_t

Study RIVAROXACS3001

Output DBL04: Effect of Rivaroxaban Compared with Placebo on Treatment-Emergent Bleeding using the TIMI, GUSTO and ISTH Scales as Adjudicated by the CEC

Analysis Set: Treatment-Emergent Safety

Subject Stratum Parameter	----- Rivaroxaban -----				-- 2.5 mg BID vs. Placebo --		-- 5 mg BID vs. Placebo --		-- Combined vs. Placebo --	
	2.5 mg BID (N=5115) n(%)	5 mg BID (N=5110) n(%)	Combined (N=10225) n(%)	Placebo (N=5125) n(%)	HR (95% CI)	Log-Rank P-value	HR (95% CI)	Log-Rank P-value	HR (95% CI)	Log-Rank P-value
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)	<0.001	4.47 (2.71,7.36)	<0.001	3.96 (2.46,6.38)	<0.001
TIMI Life-threatening	41(0.8)	57(1.1)	98(1.0)	19(0.4)	2.18 (1.26,3.75)	0.004	3.09 (1.84,5.20)	<0.001	2.63 (1.61,4.30)	<0.001
TIMI Major	68(1.3)	85(1.7)	153(1.5)	27(0.5)	2.55 (1.63,3.98)	<0.001	3.25 (2.11,5.02)	<0.001	2.90 (1.92,4.36)	<0.001
TIMI Minor	32(0.6)	49(1.0)	81(0.8)	20(0.4)	1.62 (0.92,2.82)	0.090	2.52 (1.50,4.24)	<0.001	2.07 (1.27,3.37)	0.003
TIMI Med. Attent.	492(9.6)	637(12.5)	1129(11.0)	282(5.5)	1.79 (1.55,2.07)	<0.001	2.39 (2.08,2.75)	<0.001	2.09 (1.83,2.38)	<0.001
TIMI Insig.	551(10.8)	747(14.6)	1298(12.7)	385(7.5)	1.48 (1.29,1.68)	<0.001	2.08 (1.84,2.36)	<0.001	1.77 (1.58,1.99)	<0.001
GUSTO Severe	29(0.6)	43(0.8)	72(0.7)	19(0.4)	1.54 (0.86,2.75)	0.141	2.33 (1.36,4.00)	0.002	1.93 (1.17,3.20)	0.009
GUSTO Moderate	62(1.2)	81(1.6)	143(1.4)	27(0.5)	2.32 (1.48,3.65)	<0.001	3.09 (2.00,4.78)	<0.001	2.71 (1.80,4.09)	<0.001
GUSTO Mild	948(18.5)	1220(23.9)	2168(21.2)	615(12.0)	1.61 (1.45,1.78)	<0.001	2.17 (1.97,2.40)	<0.001	1.88 (1.72,2.06)	<0.001
ISTH Major	146(2.9)	191(3.7)	337(3.3)	87(1.7)	1.70 (1.30,2.21)	<0.001	2.26 (1.76,2.92)	<0.001	1.98 (1.56,2.51)	<0.001
ISTH Non-major	607(11.9)	806(15.8)	1413(13.8)	347(6.8)	1.80 (1.58,2.06)	<0.001	2.49 (2.20,2.83)	<0.001	2.14 (1.90,2.41)	<0.001
ISTH Minimal	427(8.3)	566(11.1)	993(9.7)	307(6.0)	1.42 (1.23,1.65)	<0.001	1.95 (1.70,2.25)	<0.001	1.68 (1.48,1.91)	<0.001
Intracranial	14(0.3)	18(0.4)	32(0.3)	5(<0.1)	2.83 (1.02,7.86)	0.037	3.74 (1.39,10.07)	0.005	3.28 (1.28,8.42)	0.009
Hemorrhagic Stroke	13(0.3)	17(0.3)	30(0.3)	4(<0.1)	3.29 (1.07,10.08)	0.027	4.41 (1.48,13.11)	0.003	3.84 (1.35,10.90)	0.006
Clinical Sig.-Fatal	6(0.1)	15(0.3)	21(0.2)	9(0.2)	0.67 (0.24,1.89)	0.450	1.72 (0.75,3.92)	0.195	1.19 (0.54,2.59)	0.664
ASA	343	342	685	352						
Primary	2(0.6)	4(1.2)	6(0.9)	0		0.154		0.046		0.083
TIMI Life-threatening	1(0.3)	3(0.9)	4(0.6)	1(0.3)	1.01 (0.06,16.09)	0.997	2.97 (0.31,28.59)	0.322	2.00 (0.22,17.86)	0.528
TIMI Major	2(0.6)	4(1.2)	6(0.9)	2(0.6)	1.02 (0.14,7.22)	0.987	2.00 (0.37,10.94)	0.413	1.51 (0.30,7.47)	0.612
TIMI Minor	1(0.3)	0	1(0.1)	0		0.308				0.472
TIMI Med. Attent.	16(4.7)	19(5.6)	35(5.1)	9(2.6)	1.82 (0.81,4.13)	0.144	2.13 (0.96,4.70)	0.056	1.97 (0.95,4.10)	0.064
TIMI Insig.	8(2.3)	17(5.0)	25(3.6)	11(3.1)	0.73 (0.29,1.81)	0.494	1.56 (0.73,3.33)	0.247	1.15 (0.56,2.33)	0.706
GUSTO Severe	1(0.3)	3(0.9)	4(0.6)	1(0.3)	1.01 (0.06,16.09)	0.997	3.02 (0.31,28.99)	0.315	2.02 (0.23,18.03)	0.522
GUSTO Moderate	1(0.3)	7(2.0)	8(1.2)	5(1.4)	0.20 (0.02,1.74)	0.107	1.42 (0.45,4.47)	0.548	0.81 (0.26,2.47)	0.710
GUSTO Mild	26(7.6)	34(9.9)	60(8.8)	20(5.7)	1.33 (0.74,2.39)	0.335	1.73 (1.00,3.01)	0.049	1.53 (0.92,2.54)	0.096
ISTH Major	6(1.7)	11(3.2)	17(2.5)	7(2.0)	0.87 (0.29,2.59)	0.800	1.60 (0.62,4.12)	0.329	1.23 (0.51,2.97)	0.642

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: n = number of subjects with events; N = number of subjects at risk; % = 100 * n / N.

Note: Primary: Non-CABG related TIMI major bleeding; TIMI Med. Attent.: TIMI bleeding events requiring medical attention; TIMI Insig.: TIMI insignificant bleeding.

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: Log-Rank P-value: P-values (two-sided) as compared to placebo arm are based on the (stratified, only for all strata) log rank test.

Note: ASA = Acetylsalicylic acid; Thieno = Thienopyridine; CABG = Coronary artery bypass grafting.

Page 2 of 2

09NOV2011 16:54  
System Used: Arrow6.1(U)/rbl02_t

Study RIVAROXACS3001

Output DBL04: Effect of Rivaroxaban Compared with Placebo on Treatment-Emergent Bleeding using the TIMI, GUSTO and ISTH Scales as Adjudicated by the CEC  
(continued)

Analysis Set: Treatment-Emergent Safety										
Subject Stratum Parameter	Rivaroxaban				-- 2.5 mg BID vs. Placebo --		-- 5 mg BID vs. Placebo --		-- Combined vs. Placebo --	
	2.5 mg BID (N=5115) n(%)	5 mg BID (N=5110) n(%)	Combined (N=10225) n(%)	Placebo (N=5125) n(%)	HR (95% CI)	Log-Rank P-value	HR (95% CI)	Log-Rank P-value	HR (95% CI)	Log-Rank P-value
ISTH Non-major	18(5.2)	23(6.7)	41(6.0)	12(3.4)	1.53 (0.74,3.18)	0.248	1.94 (0.97,3.90)	0.058	1.74 (0.91,3.30)	0.089
ISTH Minimal	6(1.7)	13(3.8)	19(2.8)	9(2.6)	0.67 (0.24,1.88)	0.445	1.46 (0.62,3.41)	0.383	1.06 (0.48,2.35)	0.877
Intracranial	1(0.3)	2(0.6)	3(0.4)	0		0.316		0.160		0.222
Hemorrhagic Stroke	1(0.3)	2(0.6)	3(0.4)	0		0.316		0.160		0.222
Clinical Sig.-Fatal	1(0.3)	0	1(0.1)	1(0.3)	1.01 (0.06,16.09)	0.997		0.319	0.50 (0.03,8.00)	0.618
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)	<0.001	4.26 (2.58,7.03)	<0.001	3.80 (2.35,6.14)	<0.001
TIMI Life-threatening	40(0.8)	54(1.1)	94(1.0)	18(0.4)	2.24 (1.29,3.91)	0.003	3.10 (1.82,5.28)	<0.001	2.67 (1.61,4.42)	<0.001
TIMI Major	66(1.4)	81(1.7)	147(1.5)	25(0.5)	2.67 (1.68,4.23)	<0.001	3.35 (2.14,5.25)	<0.001	3.01 (1.97,4.60)	<0.001
TIMI Minor	31(0.6)	49(1.0)	80(0.8)	20(0.4)	1.56 (0.89,2.74)	0.116	2.52 (1.50,4.24)	<0.001	2.04 (1.25,3.33)	0.004
TIMI Med. Attent.	476(10.0)	618(13.0)	1094(11.5)	273(5.7)	1.79 (1.54,2.07)	<0.001	2.40 (2.08,2.77)	<0.001	2.09 (1.83,2.39)	<0.001
TIMI Insig.	543(11.4)	730(15.3)	1273(13.3)	374(7.8)	1.50 (1.31,1.71)	<0.001	2.10 (1.85,2.38)	<0.001	1.79 (1.60,2.01)	<0.001
GUSTO Severe	28(0.6)	40(0.8)	68(0.7)	18(0.4)	1.57 (0.87,2.84)	0.133	2.29 (1.31,4.00)	0.003	1.93 (1.15,3.24)	0.012
GUSTO Moderate	61(1.3)	74(1.6)	135(1.4)	22(0.5)	2.81 (1.72,4.57)	<0.001	3.48 (2.16,5.59)	<0.001	3.14 (2.00,4.93)	<0.001
GUSTO Mild	922(19.3)	1186(24.9)	2108(22.1)	595(12.5)	1.62 (1.46,1.79)	<0.001	2.19 (1.98,2.42)	<0.001	1.90 (1.73,2.08)	<0.001
ISTH Major	140(2.9)	180(3.8)	320(3.4)	80(1.7)	1.77 (1.34,2.33)	<0.001	2.32 (1.79,3.02)	<0.001	2.05 (1.60,2.61)	<0.001
ISTH Non-major	589(12.3)	783(16.4)	1372(14.4)	335(7.0)	1.81 (1.59,2.07)	<0.001	2.51 (2.21,2.85)	<0.001	2.16 (1.91,2.43)	<0.001
ISTH Minimal	421(8.8)	553(11.6)	974(10.2)	298(6.2)	1.45 (1.25,1.68)	<0.001	1.97 (1.71,2.27)	<0.001	1.70 (1.50,1.94)	<0.001
Intracranial	13(0.3)	16(0.3)	29(0.3)	5(0.1)	2.63 (0.94,7.38)	0.056	3.34 (1.22,9.12)	0.012	2.98 (1.15,7.70)	0.018
Hemorrhagic Stroke	12(0.3)	15(0.3)	27(0.3)	4(<0.1)	3.04 (0.98,9.41)	0.043	3.91 (1.30,11.79)	0.009	3.47 (1.21,9.90)	0.013
Clinical Sig.-Fatal	5(0.1)	15(0.3)	20(0.2)	8(0.2)	0.63 (0.21,1.93)	0.416	1.93 (0.82,4.56)	0.126	1.27 (0.56,2.89)	0.561

See footnotes on the first page of the table.

Page 1 of 1

09NOV2011 16:54  
System Used: Arrow6.1(U)/rbl10

Study RIVAROXACS3001

Output DBL29: Incidence of Treatment-Emergent GUSTO Severe Bleeding as Adjudicated by the CEC

-----  
Analysis Set: Treatment-Emergent Safety

Subject Stratum Parameter Category	Rivaroxaban			
	2.5 mg BID (N=5115) n (%)	5 mg BID (N=5110) n (%)	Combined (N=10225) n (%)	Placebo (N=5125) n (%)
All Strata	5115	5110	10225	5125
GUSTO Severe Bleeding *	29 ( 0.6)	43 ( 0.8)	72 ( 0.7)	19 ( 0.4)
Fatal	6 ( 0.1)	15 ( 0.3)	21 ( 0.2)	9 ( 0.2)
Symptomatic Intracranial Hemorrhage	14 ( 0.3)	18 ( 0.4)	32 ( 0.3)	5 ( 0.1)
Causing Hemodynamic Compromise with Systolic Blood Pressure < 90 mm Hg	13 ( 0.3)	23 ( 0.5)	36 ( 0.4)	9 ( 0.2)
Causing Hemodynamic Compromise Requiring Transfusion or Fluid Replacement for Hemodynamic Reasons	14 ( 0.3)	20 ( 0.4)	34 ( 0.3)	8 ( 0.2)
Causing Hemodynamic Compromise with Intervention for Hemodynamic Support	3 ( 0.1)	9 ( 0.2)	12 ( 0.1)	4 ( 0.1)
ASA	343	342	685	352
GUSTO Severe Bleeding *	1 ( 0.3)	3 ( 0.9)	4 ( 0.6)	1 ( 0.3)
Fatal	1 ( 0.3)	0	1 ( 0.1)	1 ( 0.3)
Symptomatic Intracranial Hemorrhage	1 ( 0.3)	2 ( 0.6)	3 ( 0.4)	0
Causing Hemodynamic Compromise with Systolic Blood Pressure < 90 mm Hg	0	1 ( 0.3)	1 ( 0.1)	1 ( 0.3)
Causing Hemodynamic Compromise Requiring Transfusion or Fluid Replacement for Hemodynamic Reasons	0	1 ( 0.3)	1 ( 0.1)	1 ( 0.3)
Causing Hemodynamic Compromise with Intervention for Hemodynamic Support	0	0	0	1 ( 0.3)
ASA + Thieno	4772	4768	9540	4773
GUSTO Severe Bleeding *	28 ( 0.6)	40 ( 0.8)	68 ( 0.7)	18 ( 0.4)
Fatal	5 ( 0.1)	15 ( 0.3)	20 ( 0.2)	8 ( 0.2)
Symptomatic Intracranial Hemorrhage	13 ( 0.3)	16 ( 0.3)	29 ( 0.3)	5 ( 0.1)
Causing Hemodynamic Compromise with Systolic Blood Pressure < 90 mm Hg	13 ( 0.3)	22 ( 0.5)	35 ( 0.4)	8 ( 0.2)
Causing Hemodynamic Compromise Requiring Transfusion or Fluid Replacement for Hemodynamic Reasons	14 ( 0.3)	19 ( 0.4)	33 ( 0.3)	7 ( 0.1)
Causing Hemodynamic Compromise with Intervention for Hemodynamic Support	3 ( 0.1)	9 ( 0.2)	12 ( 0.1)	3 ( 0.1)

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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: Percentages calculated with the number of subjects in each subject stratum and treatment group as denominator.

Note: * Incidences are based on the number of subjects, not the number of events. Although a subject may have had 2 or more bleeding events, the subject is counted only once in a category. The same subject may appear in different sub-categories.

Note: ASA = Acetylsalicylic acid; Thieno = Thienopyridine.

Page 1 of 3

09NOV2011 16:54  
System Used: Arrow6.1(U)/rbl11

Study RIVAROXACS3001

Output DBL30: Incidence of Treatment-Emergent of Non-CABG TIMI Major Bleeding Events by Provocation as Adjudicated by the CEC

Analysis Set: Treatment-Emergent Safety

Subject Stratum: All Strata

	Rivaroxaban			Placebo
	2.5 mg BID (N=5115) n (%)	5 mg BID (N=5110) n (%)	Combined (N=10225) n (%)	(N=5125) n (%)
Non-CABG TIMI Major Bleeding*	65 ( 1.3)	82 ( 1.6)	147 ( 1.4)	19 ( 0.4)
Instrumented	5 ( 0.1)	3 ( 0.1)	8 ( 0.1)	2 (<0.1)
Spontaneous	53 ( 1.0)	71 ( 1.4)	124 ( 1.2)	17 ( 0.3)
Trauma	8 ( 0.2)	8 ( 0.2)	16 ( 0.2)	0
Non-CABG TIMI Major Life-threatening Bleeding	34 ( 0.7)	44 ( 0.9)	78 ( 0.8)	7 ( 0.1)
Instrumented	4 ( 0.1)	1 (<0.1)	5 (<0.1)	2 (<0.1)
Spontaneous	24 ( 0.5)	38 ( 0.7)	62 ( 0.6)	5 ( 0.1)
Trauma	6 ( 0.1)	5 ( 0.1)	11 ( 0.1)	0
Non-CABG TIMI Major Intracranial Bleeding	14 ( 0.3)	18 ( 0.4)	32 ( 0.3)	4 ( 0.1)
Instrumented	0	0	0	0
Spontaneous	8 ( 0.2)	13 ( 0.3)	21 ( 0.2)	4 ( 0.1)
Trauma	6 ( 0.1)	5 ( 0.1)	11 ( 0.1)	0

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: Percentages calculated with the number of subjects in each treatment group as denominator.

Note: Incidences are based on the number of subjects, not the number of events. Although a subject may have had 2 or more bleeding events, the subject is counted only once in a category. The same subject may appear in different categories.

Note: * Primary safety endpoint.

Note: ASA = Acetylsalicylic acid; Thieno = Thienopyridine; CABG = Coronary artery bypass grafting.

Page 2 of 3

09NOV2011 16:54  
System Used: Arrow6.1(U)/rbl11

Study RIVAROXACS3001

Output DBL30: Incidence of Treatment-Emergent of Non-CABG TIMI Major Bleeding Events by Provocation as Adjudicated by the CEC (continued)

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Analysis Set: Treatment-Emergent Safety  
Subject Stratum: ASA

	Rivaroxaban			Placebo
	2.5 mg BID (N=343)	5 mg BID (N=342)	Combined (N=685)	(N=352)
	n (%)	n (%)	n (%)	n (%)
Non-CABG TIMI Major Bleeding*	2 ( 0.6)	4 ( 1.2)	6 ( 0.9)	0
Instrumented	0	0	0	0
Spontaneous	2 ( 0.6)	4 ( 1.2)	6 ( 0.9)	0
Trauma	0	0	0	0
Non-CABG TIMI Major Life-threatening Bleeding	1 ( 0.3)	3 ( 0.9)	4 ( 0.6)	0
Instrumented	0	0	0	0
Spontaneous	1 ( 0.3)	3 ( 0.9)	4 ( 0.6)	0
Trauma	0	0	0	0
Non-CABG TIMI Major Intracranial Bleeding	1 ( 0.3)	2 ( 0.6)	3 ( 0.4)	0
Instrumented	0	0	0	0
Spontaneous	1 ( 0.3)	2 ( 0.6)	3 ( 0.4)	0
Trauma	0	0	0	0

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See footnotes on the first page of the table.

Page 3 of 3

09NOV2011 16:54  
System Used: Arrow6.1(U)/rbl11

Study RIVAROXACS3001

Output DBL30: Incidence of Treatment-Emergent of Non-CABG TIMI Major Bleeding Events by Provocation as Adjudicated by the CEC (continued)

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Analysis Set: Treatment-Emergent Safety  
Subject Stratum: ASA + Thieno

	Rivaroxaban				Placebo
	2.5 mg BID (N=4772)	5 mg BID (N=4768)	Combined (N=9540)		(N=4773)
	n (%)	n (%)	n (%)		n (%)
Non-CABG TIMI Major Bleeding*	63 ( 1.3)	78 ( 1.6)	141 ( 1.5)		19 ( 0.4)
Instrumented	5 ( 0.1)	3 ( 0.1)	8 ( 0.1)		2 (<0.1)
Spontaneous	51 ( 1.1)	67 ( 1.4)	118 ( 1.2)		17 ( 0.4)
Trauma	8 ( 0.2)	8 ( 0.2)	16 ( 0.2)		0
Non-CABG TIMI Major Life-threatening Bleeding	33 ( 0.7)	41 ( 0.9)	74 ( 0.8)		7 ( 0.1)
Instrumented	4 ( 0.1)	1 (<0.1)	5 ( 0.1)		2 (<0.1)
Spontaneous	23 ( 0.5)	35 ( 0.7)	58 ( 0.6)		5 ( 0.1)
Trauma	6 ( 0.1)	5 ( 0.1)	11 ( 0.1)		0
Non-CABG TIMI Major Intracranial Bleeding	13 ( 0.3)	16 ( 0.3)	29 ( 0.3)		4 ( 0.1)
Instrumented	0	0	0		0
Spontaneous	7 ( 0.1)	11 ( 0.2)	18 ( 0.2)		4 ( 0.1)
Trauma	6 ( 0.1)	5 ( 0.1)	11 ( 0.1)		0

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See footnotes on the first page of the table.

Page 1 of 1

09NOV2011 16:56  
System Used: Arrow6.1(U)/rbl01_post

Study RIVAROXACS3001

Output DBLPH00: Comparison between Treatment Groups on Bleeding Events Using TIMI Scale as Adjudicated by the CEC

Analysis Set: Treatment-Emergent Safety

Subject Stratum Parameter	----- Rivaroxaban -----		Combined (N=10225) n(%)	Placebo (N=5125) n(%)	2.5 mg BID vs. Placebo HR (95% CI)	5 mg BID vs. Placebo HR (95% CI)	5 mg BID vs. 2.5 mg BID HR (95% CI)
	2.5 mg BID (N=5115) n(%)	5 mg BID (N=5110) n(%)					
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)	1.29 (0.93,1.79)
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)	1.32 (1.19,1.47)
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)	1.35 (1.04,1.75)
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)	1.28 (0.93,1.76)
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)	1.57 (1.00,2.45)
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)	1.34 (1.19,1.51)
ASA	343	342	685	352			
Primary	2(0.6)	4(1.2)	6(0.9)	0			1.97 (0.36,10.73)
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)	1.20 (0.65,2.20)
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)	1.31 (0.29,5.87)
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)	1.97 (0.36,10.73)
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)	1.18 (0.61,2.29)
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)	1.27 (0.91,1.77)
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)	1.33 (1.19,1.48)
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)	1.35 (1.04,1.76)
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)	1.26 (0.91,1.74)
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)	1.62 (1.03,2.54)
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)	1.35 (1.19,1.52)

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.

Page 1 of 9

11APR2012 15:42  
System Used: Arrow6.1 (U) /rncb055

Study RIVAROXACS3001

Output DNCB055: Decomposition of Ischemic and Hemorrhagic Events

Subject Stratum: All Strata

Rivaroxaban: 2.5 mg

Analysis Set: Modified Intent-to-Treat (Excluding Sites 091001, 091019 and 091026)

				---- Excess Number of Events ----		
				---- (Rivaroxaban - Placebo) ----		
Time to		----- Event Rate(a) -----	----- Excess # events			
Event		----- (/100 Pt-yrs) -----	----- for 10,000			
Category	Endpoints	Rivaroxaban	Placebo	pt-yrs	95% CI	NNT/NNH (b)
Efficacy	Non-bleeding CV death, MI or ischemic stroke	5.62	6.87	-125 *	( -221, -30)	-80
	Non-bleeding CV death	1.58	2.43	-85 *	( -139, -32)	-117
	MI excl CV death	3.64	3.98	-34	( -108, 41)	-297
	Ischemic stroke excl CV death	0.53	0.56	-3	( -31, 25)	-3380
	Non-CV death excl fatal bleed	0.17	0.16	0	( -16, 16)	47435
	Severe Recurrent Ischemia	3.78	4.06	-29	( -104, 47)	-351
Safety	TIMI life threatening bleeding + TIMI major bleeding	1.42	0.73	69 *	( 30, 109)	144
	TIMI life threatening bleeding	0.83	0.45	38 *	( 7, 68)	267
	Fatal Bleeding + symptomatic ICH	0.33	0.24	10	( -11, 30)	1052
	Fatal Bleeding	0.17	0.20	-3	( -20, 13)	-2921
	Intracranial Bleeding (ICH)	0.28	0.11	17	( -1, 34)	599
	Fatal ICH	0.11	0.07	4	( -9, 16)	2649
	Non-fatal ICH	0.17	0.04	13	( -1, 26)	773
	Non-fatal, non-ICH TIMI life threatening bleeding	0.50	0.22	28 *	( 5, 51)	358
	Non-fatal, non-ICH bleeding requiring surgical intervention	0.11	0.11	0	( -13, 14)	76318
	Non-fatal, non-ICH bleeding requiring IV inotropic agents	0.04	0.04	0	( -10, 10)	207626
	Non-fatal, non-ICH bleeding requiring transfusion >=4 units	0.37	0.13	24 *	( 5, 44)	414
	TIMI Major Bleeding, non-life threatening	0.63	0.27	35 *	( 10, 61)	282
		TIMI Minor Bleeding	0.59	0.44	15	( -12, 43)

(a): Event rate (/100 Pt-yrs): Number of events per 100 patient years of follow up.

(b): A negative number denotes the number of patient years needed to be treated with rivaroxaban instead of placebo to prevent one additional harmful event (NNT). A positive number denotes the number of patient years needed to be treated with rivaroxaban instead of placebo to observe one additional harmful event (NNH).

Note: CI = Confidence Interval; CV =Cardiovascular; MI = Myocardial infarction; ICH =Intracranial Hemorrhage.

Note: * Nominal 2-sided p-value &lt; 0.05 (not adjusted for multiplicity).

Note: The 95% CI is based on constant hazard assumption. Under this assumption the number of events observed has a Poisson distribution. The calculation is carried out using normal approximation to Poisson distribution, conditional on the total duration of treatment exposure.

Note: Non-bleeding CV death excludes deaths adjudicated as due to non-hemorrhagic causes that have fatal bleeding complications (e.g. trauma, malignancy).

All hemorrhagic CV deaths and non-hemorrhage CV deaths with fatal bleeding complications are included under fatal bleeding.

Note: CV deaths include deaths adjudicated as Unknown.

Note: No CI provided if the number of events is 0 or 1 in either group; There are no asymptomatic ICHs.



Page 2 of 9

11APR2012 15:42  
System Used: Arrow6.1(U)/rncb055

Study RIVAROXACS3001

Output DNCB055: Decomposition of Ischemic and Hemorrhagic Events (continued)

Subject Stratum: All Strata

Rivaroxaban: 5.0 mg

Analysis Set: Modified Intent-to-Treat (Excluding Sites 091001, 091019 and 091026)

Time to Event Category	Endpoints	----- Event Rate(a) -----		----- Excess Number of Events --- ----- (Rivaroxaban - Placebo) -----			
		----- (/100 Pt-yrs) -----	----- for 10,000 pt-yrs -----	Excess # events	95% CI	NNT/NNH (b)	
Efficacy	Non-bleeding CV death, MI or ischemic stroke	5.58	6.87	-129 *	( -224, -33)	-78	
	Non-bleeding CV death	2.20	2.43	-23	( -81, 35)	-434	
	MI excl CV death	2.94	3.98	-104 *	( -175, -33)	-96	
	Ischemic stroke excl CV death	0.60	0.56	4	( -25, 33)	2466	
	Non-CV death excl fatal bleed	0.17	0.16	1	( -16, 17)	16573	
	Severe Recurrent Ischemia	3.96	4.06	-11	( -88, 66)	-936	
Safety	TIMI life threatening bleeding + TIMI major bleeding	1.89	0.73	116 *	( 73, 160)	86	
	TIMI life threatening bleeding	1.17	0.45	72 *	( 37, 106)	140	
	Fatal Bleeding + symptomatic ICH	0.51	0.24	27 *	( 4, 51)	367	
	Fatal Bleeding	0.30	0.20	10	( -9, 30)	984	
	Intracranial Bleeding (ICH)	0.34	0.11	23 *	( 4, 42)	434	
	Fatal ICH	0.13	0.07	6	( -7, 19)	1689	
	Non-fatal ICH	0.21	0.04	17 *	( 2, 32)	585	
	Non-fatal, non-ICH TIMI life threatening bleeding	0.66	0.22	44 *	( 19, 70)	226	
	Non-fatal, non-ICH bleeding requiring surgical intervention	0.13	0.11	2	( -12, 17)	4388	
	Non-fatal, non-ICH bleeding requiring IV inotropic agents	0.08	0.04	4	( -7, 15)	2563	
	Non-fatal, non-ICH bleeding requiring transfusion >=4 units	0.57	0.13	44 *	( 21, 67)	228	
	TIMI Major Bleeding, non-life threatening	0.74	0.27	46 *	( 19, 74)	216	
	TIMI Minor Bleeding	1.00	0.44	56 *	( 24, 89)	177	

See footnotes on the first page of the table.

Page 3 of 9

11APR2012 15:42  
System Used: Arrow6.1(U)/rncb055

Study RIVAROXACS3001

Output DNCB055: Decomposition of Ischemic and Hemorrhagic Events (continued)

Subject Stratum: All Strata

Rivaroxaban: Pooled

Analysis Set: Modified Intent-to-Treat (Excluding Sites 091001, 091019 and 091026)

Time to Event Category	Endpoints	----- Event Rate(a) -----		---- Excess Number of Events --- ---- (Rivaroxaban - Placebo) ----		Excess # events for 10,000		NNT/NNH (b)
		Rivaroxaban	Placebo	----- (/100 Pt-yrs) -----	pt-yrs	95% CI		
Efficacy	Non-bleeding CV death, MI or ischemic stroke	5.60	6.87	-127 *	(	-211,	-43)	-79
	Non-bleeding CV death	1.89	2.43	-54 *	(	-103,	-6)	-184
	MI excl CV death	3.29	3.98	-69 *	(	-133,	-5)	-145
	Ischemic stroke excl CV death	0.57	0.56	1	(	-24,	25)	19815
	Non-CV death excl fatal bleed	0.17	0.16	0	(	-13,	14)	24703
	Severe Recurrent Ischemia	3.87	4.06	-20	(	-86,	46)	-508
Safety	TIMI life threatening bleeding + TIMI major bleeding	1.65	0.73	93 *	(	59,	126)	108
	TIMI life threatening bleeding	1.00	0.45	54 *	(	28,	81)	184
	Fatal Bleeding + symptomatic ICH	0.42	0.24	18 *	(	0,	36)	547
	Fatal Bleeding	0.23	0.20	3	(	-12,	19)	3042
	Intracranial Bleeding (ICH)	0.31	0.11	20 *	(	6,	34)	504
	Fatal ICH	0.12	0.07	5	(	-6,	16)	2068
	Non-fatal ICH	0.19	0.04	15 *	(	4,	26)	667
	Non-fatal, non-ICH TIMI life threatening bleeding	0.58	0.22	36 *	(	17,	55)	278
	Non-fatal, non-ICH bleeding requiring surgical intervention	0.12	0.11	1	(	-11,	13)	8386
	Non-fatal, non-ICH bleeding requiring IV inotropic agents	0.06	0.04	2	(	-7,	11)	5120
	Non-fatal, non-ICH bleeding requiring transfusion >=4 units	0.47	0.13	34 *	(	17,	50)	295
	TIMI Major Bleeding, non-life threatening	0.68	0.27	41 *	(	20,	62)	245
	TIMI Minor Bleeding	0.79	0.44	36 *	(	11,	60)	281

See footnotes on the first page of the table.

Page 4 of 9

11APR2012 15:42  
System Used: Arrow6.1(U)/rncb055

Study RIVAROXACS3001

Output DNCB055: Decomposition of Ischemic and Hemorrhagic Events (continued)

Subject Stratum: ASA

Rivaroxaban: 2.5 mg

Analysis Set: Modified Intent-to-Treat (Excluding Sites 091001, 091019 and 091026)

Time to Event Category	Endpoints	----- Event Rate(a) -----		---- Excess Number of Events --- ---- (Rivaroxaban - Placebo) ----			
		----- (/100 Pt-yrs) -----	----- (/100 Pt-yrs) -----	Excess # events for 10,000 pt-yrs	95% CI	NNT/NNH (b)	
Efficacy	Non-bleeding CV death, MI or ischemic stroke	7.65	10.52	-287	( -751, 177)	-35	
	Non-bleeding CV death	3.12	2.56	57	( -206, 319)	176	
	MI excl CV death	4.39	6.56	-216	( -579, 146)	-46	
	Ischemic stroke excl CV death	0.29	1.43	-115		-87	
	Non-CV death excl fatal bleed	0.28	0.00	28		352	
	Severe Recurrent Ischemia	2.90	3.17	-27	( -300, 246)	-367	
Safety	TIMI life threatening bleeding + TIMI major bleeding	0.57	0.57	-0	( -158, 158)	-96914	
	TIMI life threatening bleeding	0.28	0.28	0		2515040	
	Fatal Bleeding + symptomatic ICH	0.28	0.28	0		2515040	
	Fatal Bleeding	0.28	0.28	0		2515040	
	Intracranial Bleeding (ICH)	0.28	0.00	28		352	
	Fatal ICH	0.28	0.00	28		352	
	Non-fatal ICH	0.00	0.00	0			
	Non-fatal, non-ICH TIMI life threatening bleeding	0.00	0.00	0			
	Non-fatal, non-ICH bleeding requiring surgical intervention	0.00	0.00	0			
	Non-fatal, non-ICH bleeding requiring IV inotropic agents	0.00	0.00	0			
	Non-fatal, non-ICH bleeding requiring transfusion >=4 units	0.00	0.00	0			
	TIMI Major Bleeding, non-life threatening	0.28	0.28	-0		-181399	
	TIMI Minor Bleeding	0.28	0.00	28		352	

See footnotes on the first page of the table.

Page 5 of 9

11APR2012 15:42  
System Used: Arrow6.1(U)/rncb055

Study RIVAROXACS3001

Output DNCB055: Decomposition of Ischemic and Hemorrhagic Events (continued)

Subject Stratum: ASA

Rivaroxaban: 5.0 mg

Analysis Set: Modified Intent-to-Treat (Excluding Sites 091001, 091019 and 091026)

Time to Event Category	Endpoints	----- Event Rate(a) -----		---- Excess Number of Events --- ---- (Rivaroxaban - Placebo) ----		NNT/NNH (b)
		----- (/100 Pt-yrs) -----	----- (/100 Pt-yrs) -----	Excess # events for 10,000 pt-yrs	95% CI	
Efficacy	Non-bleeding CV death, MI or ischemic stroke	6.03	10.52	-449 *	( -890, -7)	-22
	Non-bleeding CV death	2.54	2.56	-2	( -251, 248)	-5979
	MI excl CV death	2.28	6.56	-428 *	( -755, -100)	-23
	Ischemic stroke excl CV death	1.42	1.43	-1	( -199, 197)	-10271
	Non-CV death excl fatal bleed	0.00	0.00	0		
	Severe Recurrent Ischemia	3.16	3.17	-1	( -279, 276)	-7485
Safety	TIMI life threatening bleeding + TIMI major bleeding	1.13	0.57	56	( -114, 226)	178
	TIMI life threatening bleeding	0.85	0.28	56		178
	Fatal Bleeding + symptomatic ICH	0.56	0.28	28		356
	Fatal Bleeding	0.00	0.28	-28		-352
	Intracranial Bleeding (ICH)	0.56	0.00	56		177
	Fatal ICH	0.00	0.00	0		
	Non-fatal ICH	0.56	0.00	56		177
	Non-fatal, non-ICH TIMI life threatening bleeding	0.28	0.00	28		354
	Non-fatal, non-ICH bleeding requiring surgical intervention	0.00	0.00	0		
	Non-fatal, non-ICH bleeding requiring IV inotropic agents	0.00	0.00	0		
	Non-fatal, non-ICH bleeding requiring transfusion >=4 units	0.28	0.00	28		354
	TIMI Major Bleeding, non-life threatening	0.28	0.28	-0		-41409
	TIMI Minor Bleeding	0.00	0.00	0		

See footnotes on the first page of the table.

Page 6 of 9

11APR2012 15:42  
System Used: Arrow6.1(U)/rncb055

Study RIVAROXACS3001

Output DNCB055: Decomposition of Ischemic and Hemorrhagic Events (continued)

Subject Stratum: ASA

Rivaroxaban: Pooled

Analysis Set: Modified Intent-to-Treat (Excluding Sites 091001, 091019 and 091026)

Time to Event Category	Endpoints	----- Event Rate(a) -----		---- Excess Number of Events --- ---- (Rivaroxaban - Placebo) ----		NNT/NNH (b)
		----- (/100 Pt-yrs) -----	----- (/100 Pt-yrs) -----	Excess # events for 10,000 pt-yrs	95% CI	
Efficacy	Non-bleeding CV death, MI or ischemic stroke	6.83	10.52	-369	( -774, 36)	-27
	Non-bleeding CV death	2.83	2.56	27	( -191, 246)	364
	MI excl CV death	3.32	6.56	-324 *	( -637, -11)	-31
	Ischemic stroke excl CV death	0.85	1.43	-58	( -217, 101)	-173
	Non-CV death excl fatal bleed	0.14	0.00	14		706
	Severe Recurrent Ischemia	3.03	3.17	-14	( -251, 223)	-702
Safety	TIMI life threatening bleeding + TIMI major bleeding	0.85	0.57	28	( -106, 162)	357
	TIMI life threatening bleeding	0.57	0.28	28		354
	Fatal Bleeding + symptomatic ICH	0.42	0.28	14		711
	Fatal Bleeding	0.14	0.28	-14		-702
	Intracranial Bleeding (ICH)	0.42	0.00	42		235
	Fatal ICH	0.14	0.00	14		706
	Non-fatal ICH	0.28	0.00	28		353
	Non-fatal, non-ICH TIMI life threatening bleeding	0.14	0.00	14		706
	Non-fatal, non-ICH bleeding requiring surgical intervention	0.00	0.00	0		
	Non-fatal, non-ICH bleeding requiring IV inotropic agents	0.00	0.00	0		
	Non-fatal, non-ICH bleeding requiring transfusion >=4 units	0.14	0.00	14		706
	TIMI Major Bleeding, non-life threatening	0.28	0.28	-0		-67286
	TIMI Minor Bleeding	0.14	0.00	14		706

See footnotes on the first page of the table.

Page 7 of 9

11APR2012 15:42  
System Used: Arrow6.1(U)/rncb055

Study RIVAROXACS3001

Output DNCB055: Decomposition of Ischemic and Hemorrhagic Events (continued)

Subject Stratum: ASA + Thieno

Rivaroxaban: 2.5 mg

Analysis Set: Modified Intent-to-Treat (Excluding Sites 091001, 091019 and 091026)

Time to Event Category	Endpoints	----- Event Rate(a) -----		----- Excess Number of Events --- ----- (Rivaroxaban - Placebo) -----		Excess # events for 10,000		NNT/NNH (b)
		Rivaroxaban	Placebo	pt-yrs	95% CI			
Efficacy	Non-bleeding CV death, MI or ischemic stroke	5.48	6.63	-115 *	( -212, -18)			-87
	Non-bleeding CV death	1.48	2.43	-95 *	( -149, -41)			-105
	MI excl CV death	3.59	3.81	-22	( -97, 54)			-462
	Ischemic stroke excl CV death	0.55	0.51	5	( -24, 33)			2150
	Non-CV death excl fatal bleed	0.16	0.17	-2	( -19, 15)			-5790
	Severe Recurrent Ischemia	3.84	4.13	-29	( -107, 50)			-350
Safety	TIMI life threatening bleeding + TIMI major bleeding	1.48	0.74	74 *	( 33, 116)			135
	TIMI life threatening bleeding	0.87	0.47	40 *	( 8, 72)			249
	Fatal Bleeding + symptomatic ICH	0.33	0.23	10	( -11, 32)			984
	Fatal Bleeding	0.16	0.19	-4	( -21, 14)			-2726
	Intracranial Bleeding (ICH)	0.28	0.12	16	( -2, 34)			629
	Fatal ICH	0.10	0.08	2	( -11, 15)			4819
	Non-fatal ICH	0.18	0.04	14	( -1, 28)			723
	Non-fatal, non-ICH TIMI life threatening bleeding	0.53	0.23	30 *	( 5, 55)			334
	Non-fatal, non-ICH bleeding requiring surgical intervention	0.12	0.12	0	( -14, 15)			66806
	Non-fatal, non-ICH bleeding requiring IV inotropic agents	0.04	0.04	0	( -11, 11)			181756
	Non-fatal, non-ICH bleeding requiring transfusion >=4 units	0.39	0.14	26 *	( 5, 47)			387
	TIMI Major Bleeding, non-life threatening	0.65	0.27	38 *	( 11, 65)			264
	TIMI Minor Bleeding	0.61	0.47	14	( -15, 43)			691

See footnotes on the first page of the table.

Page 8 of 9

11APR2012 15:42  
System Used: Arrow6.1(U)/rncb055

Study RIVAROXACS3001

Output DNCB055: Decomposition of Ischemic and Hemorrhagic Events (continued)

Subject Stratum: ASA + Thieno

Rivaroxaban: 5.0 mg

Analysis Set: Modified Intent-to-Treat (Excluding Sites 091001, 091019 and 091026)

					---- Excess Number of Events ---- ---- (Rivaroxaban - Placebo) ----			
Time to Event Category	Endpoints	Event Rate(a) ---- (/100 Pt-yrs)	Placebo	Excess # events ---- for 10,000 pt-yrs	95% CI		NNT/NNH (b)	
Efficacy	Non-bleeding CV death, MI or ischemic stroke	5.55	6.63	-108 *	(	-205, -10)	-93	
	Non-bleeding CV death	2.18	2.43	-25	(	-84, 35)	-406	
	MI excl CV death	2.98	3.81	-82 *	(	-155, -10)	-121	
	Ischemic stroke excl CV death	0.55	0.51	4	(	-25, 33)	2424	
	Non-CV death excl fatal bleed	0.18	0.17	1	(	-17, 18)	14307	
	Severe Recurrent Ischemia	4.02	4.13	-11	(	-91, 69)	-902	
	Safety	TIMI life threatening bleeding + TIMI major bleeding	1.95	0.74	121 *	(	75, 167)	83
TIMI life threatening bleeding		1.19	0.47	73 *	(	37, 109)	138	
Fatal Bleeding + symptomatic ICH		0.50	0.23	27 *	(	3, 52)	368	
Fatal Bleeding		0.32	0.19	13	(	-8, 34)	776	
Intracranial Bleeding (ICH)		0.32	0.12	21 *	(	1, 40)	484	
Fatal ICH		0.14	0.08	6	(	-8, 21)	1571	
Non-fatal ICH		0.18	0.04	14	(	-0, 29)	700	
Non-fatal, non-ICH TIMI life threatening bleeding		0.69	0.23	45 *	(	18, 73)	220	
Non-fatal, non-ICH bleeding requiring surgical intervention		0.14	0.12	2	(	-13, 18)	4038	
Non-fatal, non-ICH bleeding requiring IV inotropic agents		0.08	0.04	4	(	-8, 16)	2385	
Non-fatal, non-ICH bleeding requiring transfusion >=4 units		0.59	0.14	45 *	(	21, 69)	222	
TIMI Major Bleeding, non-life threatening		0.77	0.27	50 *	(	21, 79)	201	
		TIMI Minor Bleeding	1.07	0.47	61 *	(	26, 96)	165

See footnotes on the first page of the table.

Page 9 of 9

11APR2012 15:42  
System Used: Arrow6.1(U)/rncb055

Study RIVAROXACS3001

Output DNCB055: Decomposition of Ischemic and Hemorrhagic Events (continued)

Subject Stratum: ASA + Thieno

Rivaroxaban: Pooled

Analysis Set: Modified Intent-to-Treat (Excluding Sites 091001, 091019 and 091026)

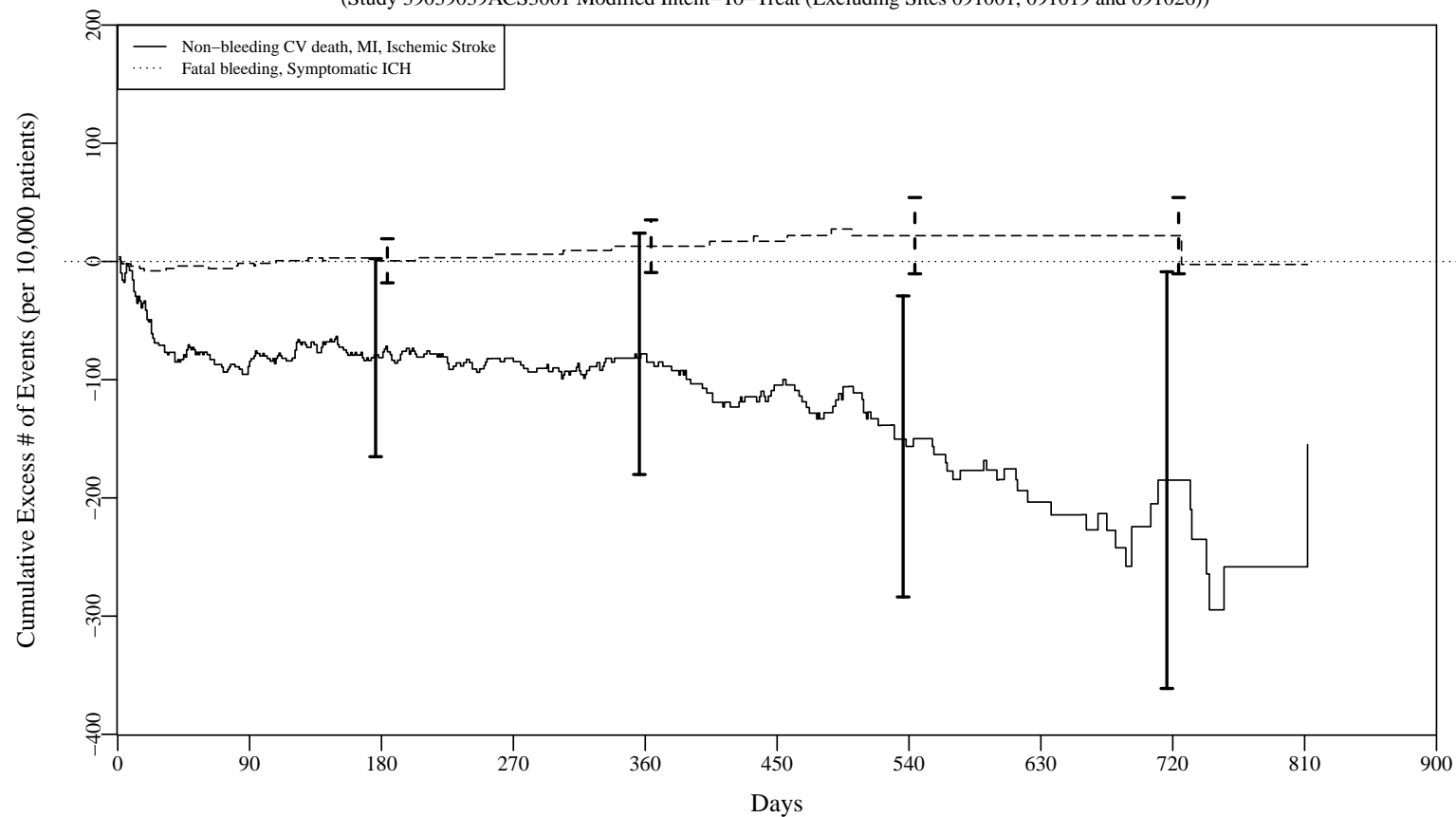
Time to Event Category	Endpoints	----- Event Rate(a) -----		----- Excess Number of Events --- ----- (Rivaroxaban - Placebo) -----		Excess # events for 10,000		NNT/NNH (b)
		Rivaroxaban	Placebo	pt-yrs	95% CI			
Efficacy	Non-bleeding CV death, MI or ischemic stroke	5.51	6.63	-112 *	( -197, -26)			-90
	Non-bleeding CV death	1.82	2.43	-60 *	( -111, -10)			-166
	MI excl CV death	3.29	3.81	-52	( -117, 13)			-193
	Ischemic stroke excl CV death	0.55	0.51	4	( -20, 29)			2277
	Non-CV death excl fatal bleed	0.17	0.17	-1	( -15, 14)			-18883
	Severe Recurrent Ischemia	3.93	4.13	-20	( -89, 49)			-502
Safety	TIMI life threatening bleeding + TIMI major bleeding	1.71	0.74	97 *	( 62, 132)			103
	TIMI life threatening bleeding	1.03	0.47	56 *	( 29, 84)			178
	Fatal Bleeding + symptomatic ICH	0.42	0.23	19	( -0, 37)			539
	Fatal Bleeding	0.24	0.19	5	( -12, 21)			2220
	Intracranial Bleeding (ICH)	0.30	0.12	18 *	( 3, 33)			548
	Fatal ICH	0.12	0.08	4	( -7, 15)			2385
	Non-fatal ICH	0.18	0.04	14 *	( 3, 25)			711
	Non-fatal, non-ICH TIMI life threatening bleeding	0.61	0.23	38 *	( 17, 58)			266
	Non-fatal, non-ICH bleeding requiring surgical intervention	0.13	0.12	1	( -11, 14)			7703
	Non-fatal, non-ICH bleeding requiring IV inotropic agents	0.06	0.04	2	( -7, 11)			4766
	Non-fatal, non-ICH bleeding requiring transfusion >=4 units	0.49	0.14	35 *	( 18, 53)			283
	TIMI Major Bleeding, non-life threatening	0.71	0.27	44 *	( 21, 66)			229
	TIMI Minor Bleeding	0.84	0.47	37 *	( 11, 64)			268

See footnotes on the first page of the table.



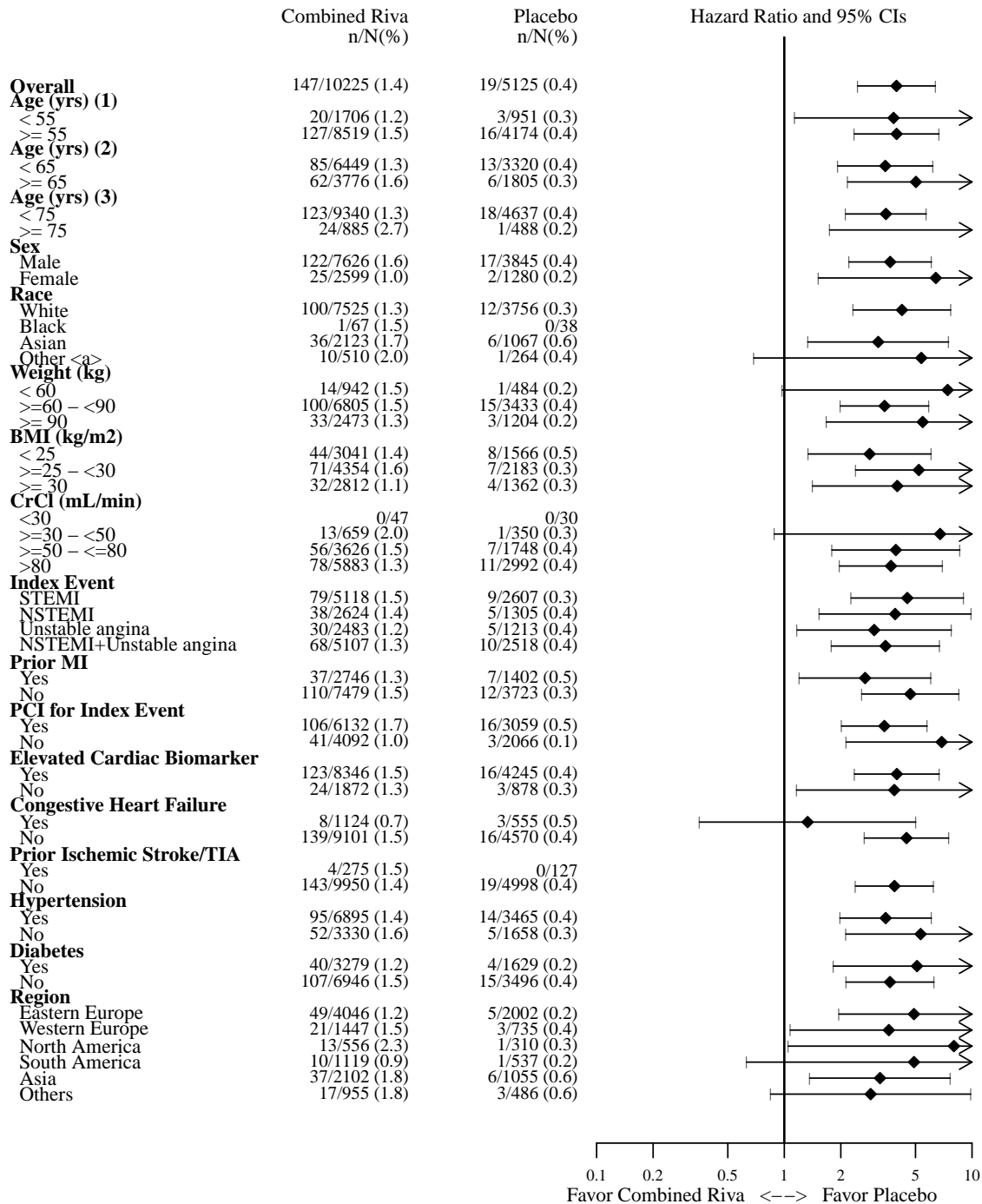
Figure FNCB1009a: Cumulative Excess Number of Events Based on Kaplan–Meier Method for Composite of Non-bleeding CV death, MI, Ischemic Stroke vs. Fatal Bleeding, Symptomatic ICH (Adjudicated by CEC), MITT, Rivaroxaban 2.5mg vs Placebo (Stratum = All Strata)

(Study 39039039ACS3001 Modified Intent–To–Treat (Excluding Sites 091001, 091019 and 091026))



**Figure FBL10A: Hazard Ratios and Rates of First Occurrence of Treatment–Emergent Non–CABG related TIMI Major Bleeding Events by Subgroups for Combined Rivaroxaban Dose Groups Compared with Placebo in All Stratum**

(Study RIVAROXACS3001: Treatment–Emergent Safety Analysis Set)



Note: Hazard Ratio and 95% confidence interval as compared to placebo arm is based on the stratified Cox proportional hazards model.

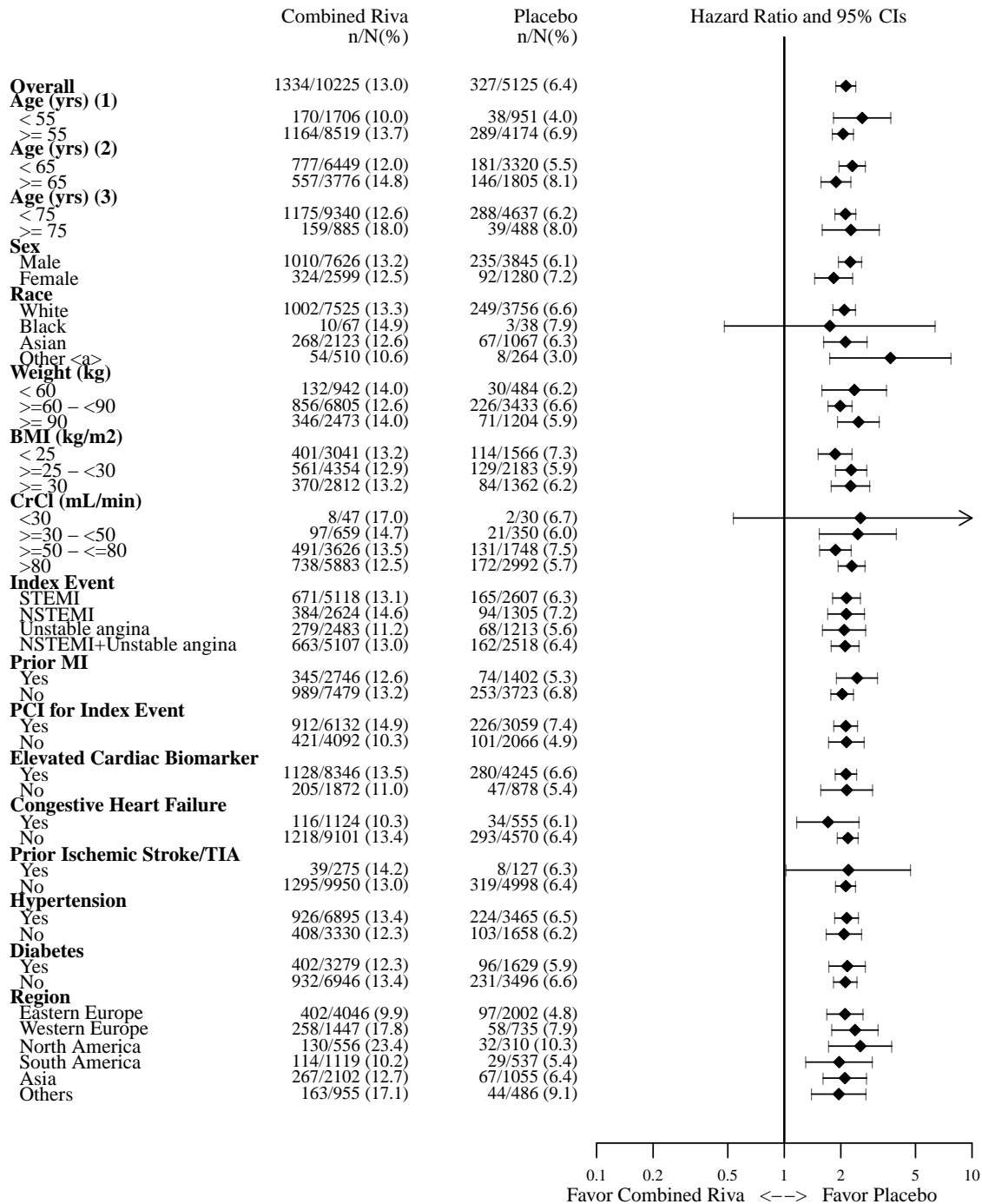
Note: Scale of X axis was based on log transformation of the ratio. Tick labels of X axis are in the original ratio scale.

Note: <a> Including 'American Indian or Alaska Native', 'Native Hawaiian or Other Pacific Islander' and 'Other' per CRF.

Note: Arrow (< or >) of a line indicates that the confidence interval limit exceeds the X-axis range.

**Figure FBL15A: Hazard Ratios and Rates of First Occurrence of Treatment–Emergent Clinically Significant Bleeding Events by Subgroups for Combined Rivaroxaban Dose Groups Compared with Placebo in All Stratum**

(Study RIVAROXACS3001: Treatment–Emergent Safety Analysis Set)



Note: Hazard Ratio and 95% confidence interval as compared to placebo arm is based on the stratified Cox proportional hazards model.

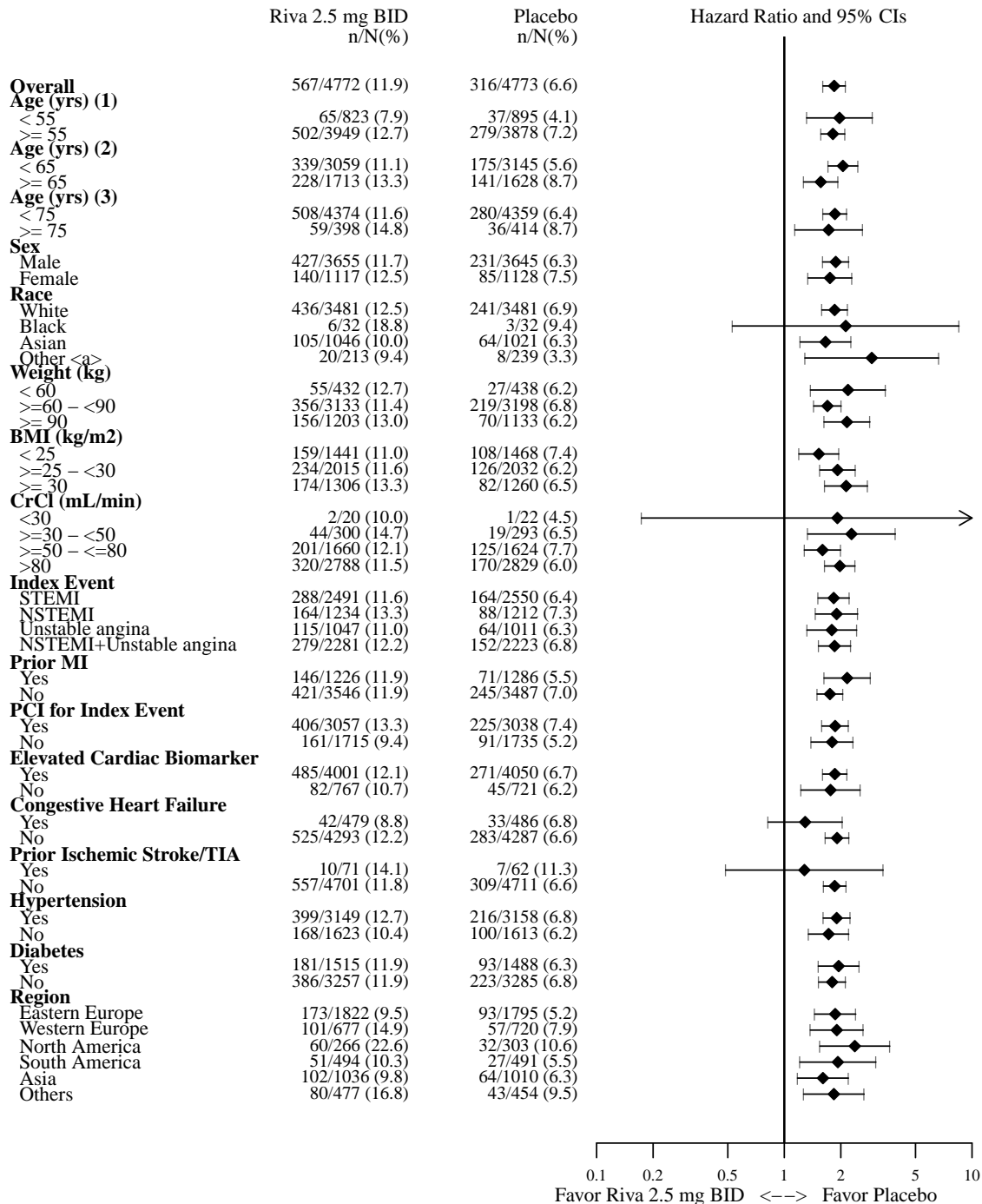
Note: Scale of X axis was based on log transformation of the ratio. Tick labels of X axis are in the original ratio scale.

Note: <a> Including 'American Indian or Alaska Native', 'Native Hawaiian or Other Pacific Islander' and 'Other' per CRF.

Note: Arrow (< or >) of a line indicates that the confidence interval limit exceeds the X-axis range.

**Figure FBL15H: Hazard Ratios and Rates of First Occurrence of Treatment–Emergent Clinically Significant Bleeding Events by Subgroups for Rivaroxaban 2.5 mg BID Group Compared with Placebo in ASA + Thieno Stratum**

(Study RIVAROXACS3001: Treatment–Emergent Safety Analysis Set)



Note: Hazard Ratio and 95% confidence interval as compared to placebo arm is based on the unstratified Cox proportional hazards model.

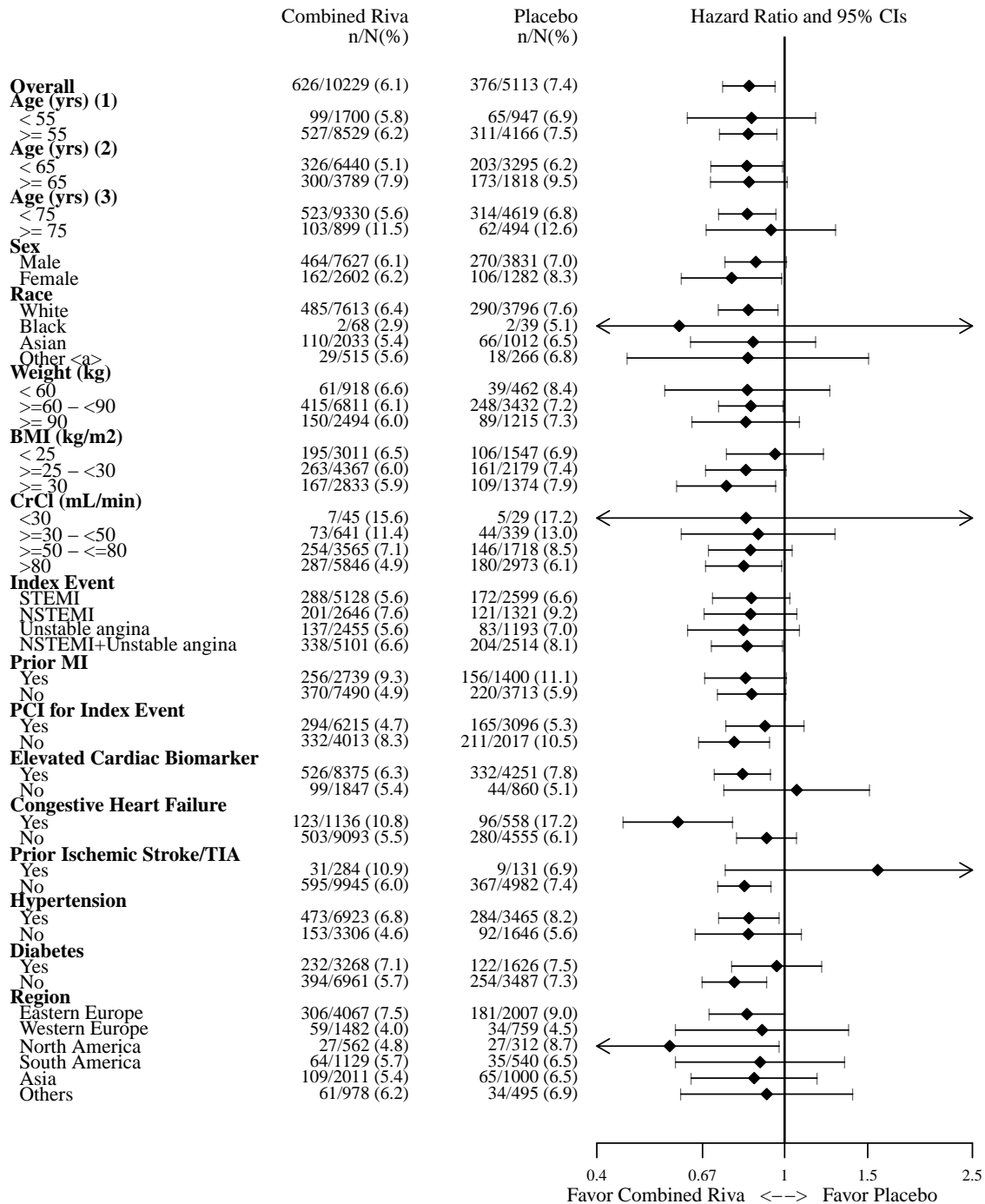
Note: Scale of X axis was based on log transformation of the ratio. Tick labels of X axis are in the original ratio scale.

Note: <a> Including 'American Indian or Alaska Native', 'Native Hawaiian or Other Pacific Islander' and 'Other' per CRF.

Note: Arrow (< or >) of a line indicates that the confidence interval limit exceeds the X-axis range.

**Figure FEF20A: Hazard Ratios and Rates of the Primary Efficacy Endpoint (First Occurrence Cardiovascular Death, MI, Stroke) by Subgroup for Combined Rivaroxaban Dose Groups Compared with Placebo in All Strata**

(Study RIVAROXACS3001: Modified Intent-to-Treat (Excluding Sites 091001, 091019 and 091026) Analysis Set)



Note: Hazard Ratio and 95% confidence interval as compared to placebo arm is based on the stratified Cox proportional hazards model.

Note: Scale of X axis was based on log transformation of the ratio. Tick labels of X axis are in the original ratio scale.

Note: <a> Including 'American Indian or Alaska Native', 'Native Hawaiian or Other Pacific Islander' and 'Other' per CRF.

Note: Arrow (< or >) of a line indicates that the confidence interval limit exceeds the X-axis range.