Australian Government
Department of Health
Therapeutic Goods Administration

AusPAR Attachment 1

Extract from the Clinical Evaluation Report for Rivaroxaban

Proprietary Product Name: Xarelto

Sponsor: Bayer Australia Ltd

Date of first round CER: August 2012

Date of second round CER: October 2012

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

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About the Extract from the Clinical Evaluation Report

- This document provides a more detailed evaluation of the clinical findings, extracted from the Clinical Evaluation Report (CER) prepared by the TGA. This extract does not include sections from the CER regarding product documentation or post market activities.
- The words [Information redacted], where they appear in this document, indicate that confidential information has been deleted.
- For the most recent Product Information (PI), please refer to the TGA website <http://www.tga.gov.au/hp/information-medicines-pi.htm>.

Contents

1. Clinical rationale

The following clinical rationale was provided by the sponsor and was considered acceptable.

"Coronary heart disease (CHD) is a common clinical and pathological condition. The incidence and prevalence rates of CHD remain high throughout the world; it is a major cause of death in adults in most countries in Europe and in the US. Cardiovascular (CV) and coronary heart diseases are the chief contributors to the disease burden in Australia. The most severe clinical manifestation of CHD is referred to as ACS, a term which includes conditions of unstable angina (UA), non-ST-segment elevation myocardial infarction (NSTEMI) and ST-segment elevation myocardial infarction (STEMI). Following an ACS event, patients are at higher risk of another ACS event or stroke or dying from a CV cause. The current standard of 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. Despite the widespread use of antiplatelets in the acute and chronic setting, the incidence of CV events in the post-ACS population remains high.

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. Since many of the clinical events that occur in ACS patients are due to acute and subacute thrombosis, an additional management strategy is the use of an anticoagulant either instead of or in addition to antiplatelet (ASA and thienopyridine) therapy.

Because of difficulties inherent with warfarin monitoring, such as variations in dose response, the need for patient compliance in the monitoring of coagulation parameters and adjustment of dosing, 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 the development of safer, efficacious, and convenient oral anticoagulants that do not depend on vitamin K antagonism for the treatment of subjects with ACS. One such promising class of oral anticoagulants is the FXa inhibitors."

2. Contents of the clinical dossier

2.1. Scope of the clinical dossier

The clinical dossier documented a development program of pharmacokinetic (PK), population PK/pharmacodynamic (PD), dose-finding and pivotal trial(s) relating to the proposed extension of indication. The submission contained the following clinical information:

- 3 small, single-dose bioavailability studies in healthy subjects; Study 12361, 12570, and 12571
- 1 PK study in 36 healthy Japanese subjects (Study 14883) of the effects of switching from warfarin to rivaroxaban (≤ 5 mg warfarin taken for 6 days and 15 mg rivaroxaban taken for 4 days)
- 2 population PK/PD studies (Study R-8642 and R-8645). These 2 PK/PD studies are related. In Study R-8642 the population PK model for rivaroxaban in ACS was developed and used to investigate the relationship between rivaroxaban and prothrombin time (PT) and prothrombinase-induced clotting time (PiCT). In Study R-8645 the PK parameters estimated in R-8642 were used to predict steady state systemic rivaroxaban exposure, and to quantify its relationship with bleeding outcomes. These studies are based on data from the dose-finding study (below).
- 1 dose-finding study: the ATLAS ACS TIMI 46 trial (*A*nti-Xa *T*herapy to *L*ower cardiovascular events in addition to *A*spirin with or without thienopyridine therapy in *S*ubjects With *A*cute *C*oronary *S*yndrome) (hereafter referred to as TIMI 46), a Phase II, randomised, double-blind, double-dummy, parallel-group, placebo-controlled study over 6 months of the efficacy and safety of rivaroxaban in 3,491 subjects with a recent ACS (2,331 subjects on a range of rivaroxaban doses versus 1,160 on placebo).
- 1 pivotal efficacy/safety study: the ATLAS ACS 2 TIMI 51 trial (TIMI 51), a Phase III, randomised, double-blind, placebo-controlled, event-driven multicentre study to evaluate the efficacy and safety of rivaroxaban in 15,526 subjects with a recent ACS (5,174 on rivaroxaban 2.5 mg bd, 5,176 on rivaroxaban 5 mg bd and 5,176 on placebo).
- Literature references

Evaluator's comment

The dose-finding study (TIMI 46) has been previously evaluated (Trim reference R10/297673) as part of a specific condition of the original registration of Xarelto 10 mg (PM-2007-3400-3) to provide "all efficacy and safety information from any ongoing studies involving rivaroxaban". All issues raised with the Sponsor as a result of this evaluation were satisfactorily addressed. This study had only a small number of subjects on rivaroxaban 2.5 mg bd (n=153) or 5 mg bd (n=527) and only 6 and 14, respectively, subjects with the composite endpoint of all cause death, MI or stroke - sufficient to provide supportive data to the pivotal efficacy study at best. This study has not been re-evaluated, but extracts of the earlier evaluation have been reproduced here where appropriate.

2.2. Paediatric data

A paediatric development program for Xarelto has been agreed with the EMA for the conditions "*Prevention of thromboembolic events*" and *"Treatment of thromboembolic events*", not ACS. Therefore the sponsor did not include details of this program in the application.

2.3. Good clinical practice

The sponsor has stated that all studies included in this submission were conducted and reported in accordance with the ethical principles originating in the Declaration of Helsinki and in accordance with International Conference on Harmonisation Good Clinical Practice guidelines, applicable regulatory requirements and in compliance with the respective protocols.

3. Pharmacokinetics

3.1. Studies providing pharmacokinetic data

Summaries of the evaluated pharmacokinetic studies are presented in the clinical evaluation report (CER). Table 1 shows the studies relating to each pharmacokinetic topic and the location of each study summary.

Table 1. Studies providing PK data.

PK Topic	Subtopic	Study ID
PK in healthy adults	General PK – Single dose	12361
	Bioequivalence – single dose	12570
		12571
PK interactions	Warfarin	14883
PK in special populations	Target population – multi-dose	TIMI 46
Population PK analyses	Target population	R-8642

None of the pharmacokinetic studies had deficiencies that excluded their results from consideration.

3.2. Summary of pharmacokinetics

The information in the following summary is derived from conventional pharmacokinetic studies unless otherwise stated.

3.2.1. Dose proportionality

Study 12361 was a single-centre, randomised, non-blind, non-controlled, single dose, 3-way crossover study to evaluate dose proportionality and assess the pharmacokinetics, safety, and tolerability of the 2.5 mg and 5 mg doses of rivaroxaban in comparison to the registered 10 mg dose, under fasting conditions in healthy male subjects (n=24). There was a 7 day wash-out between treatments.

The the PK parameters are summarised below in Table 2. All doses were rapidly absorbed with a median t_{max} of 1.5 to 2.5 hr. The $t_{1/2}$ increased with rivaroxaban dose, ranging from 5 hr (2.5 mg) to 10.8 hr (10 mg).

C_{max} increased dose dependently, and the dose normalised C_{max}/D decreased over the dose range studied (0.021/L, 0.018/L, and 0.014/L for the 2.5, 5 and 10 mg dose, respectively).

Criteria for bioequivalence (0.80 – 1.25) were not met for the comparison 10 mg versus 5 mg (0.68 ‑ 0.87), 10 mg versus 2.5 mg (0.59 ‑ 0.75), or 5 mg versus 2.5 mg (0.76 ‑ 0.98).

AUC showed a dose dependent increase (321, 626 and 1114 µg.h/L after 2.5, 5 and 10 mg rivaroxaban, respectively), while dose normalised AUC/D values were relatively stable over the dose range studied (0.129 h/L, 0.125 h/L and 0.111 h/L for the 2.5, 5 and 10 mg dose, respectively). The point estimates and exploratory 95% CIs met the criteria for bioequivalence for all comparisons [10 mg versus 5 mg (0.83 ‑ 0.96), 10 mg versus 2.5 mg (0.80 ‑ 0.93), and 5 mg versus 2.5 mg (0.90 ‑ 1.04)].

Table 2. Study 12361 - PK parameters of 2.5, 5 and 10 mg rivaroxaban [geometric mean/%CV (range)], PK analysis set, n=23

Parameter	Unit	2.5 mg (n=23)	5 mg (n=23)	10 mg (n=23)
AUC	µg*h/L	321.4/28.82 (165.4 – 551.9)	626.1/18.79 (422.6 – 851.4)	1114/25.22 (685.3 – 1842)
AUC/D	h/L	0.1285/28.82 (0.06616 – 0.2208)	0.1252/18.79 (0.08451 – 0.1703)	0.1114/25.22 (0.06853 – 0.1842)
AUC(0-tn)	µg*h/L	313.6/28.92 (163.2 – 547.6)	617.5/19.07 (414.3 – 846.0)	1092/25.19 (679.7 – 1812)
C_{max}	µg/L	51.96/28.11 (28.60 – 103.0)	90.62/23.99 (56.20 – 145.0)	138.4/29.74 (77.40 – 251.0)
C_{max}/D	1/L	0.02078/28.11 (0.01144 – 0.04120)	0.01813/23.99 (0.01124 – 0.02900)	0.01384/29.74 (0.007740 – 0.02510)
$t_{1/2}$	h	4.985/28.78 (2.330 – 7.387)	6.785/33.36 (3.621 – 13.34)	10.77/42.22 (5.381 – 23.94)
MRT	h	6.558/20.79 (3.995 – 9.424)	7.282/20.05 (5.153 – 11.01)	10.17/28.29 (5.630 – 17.34)
t_{max} [a]	h	2.000 (0.7500 – 4.000)	1.500 (0.7500 – 6.000)	2.500 (1.000 – 4.000)

[a] Median (Range)

Evaluator's comment

Study 12361 was a good quality dose-proportionality study, with a satisfactory study design, conduct and analysis. Assay validation and within study performance was satisfactory, washout period was appropriate, sampling schedule was adequate for characterising C_{max} and t_{max}, and duration of sampling was appropriate to ensure the extrapolated AUC was less than 10% of the total.

The 2.5, 5 and 10 mg doses of rivaroxaban given as an IR tablet were safe and well tolerated, with comparable safety profiles. The increase in $t_{1/2}$ with increasing rivaroxaban dose was suggested by the sponsor to be a result of the poor aqueous solubility of the drug limiting the absorption rate at higher doses, rather than altered drug elimination. This is considered plausible.

The C_{max}/D did not meet the criteria for bioequivalence, with the C_{max} for the 2.5 mg dose being proportionally higher than the C_{max} for the 10 mg tablet. This is not considered to have safety implications as the absolute C_{max} for the 2.5 mg tablet is much lower than that seen for the 10 mg tablet and as the doses are used in different indications, it is not considered likely that they would be prescribed interchangeably. The AUC/D did meet the criteria for bioequivalence and on this basis the proposed 2.5 mg tablet can be considered dose proportional to the registered 10 mg tablet.

3.2.2. Bioequivalence of different dosage forms and strengths

Studies 12570 and 12571 do not relate to the rivaroxaban dosage and indication of the current submission. They compared two different 12 mg extended release (ER) formulations of rivaroxaban (E202 and GITS 329, respectively) with and without food to the standard 10 mg immediate release (IR) formulation in healthy male subjects. As the 10 mg dose is not the subject of this application, the 12 mg formulations are not proposed for registration at this time, and no proposed changes to the current PI are based on these studies, only a brief summary of the study results has been included in the body of the submission.

Safety and tolerability of the 12 mg E202 and GITS formulations in the fed or fasted state were comparable to the standard 10 mg IR tablet. In the fasted state both ER formulations had a reduced C_{max} in comparison to the IR tablet, whereas the AUCs were almost identical. In the fed state, AUC of rivaroxaban was increased after intake of both ER formulations as compared to the IR tablet; the C_{max} was only increased with the E202 formulation. As expected for an extended release formulation, absorption of rivaroxaban from the ER tablets was prolonged compared to the IR tablet in both the fed and fasted state (Table 3).

Table 3. Selected PK parameters of rivaroxaban in plasma, least squares mean ratios (90% CIs) of the ER formulation versus the IR formulation, all subjects valid for PK.

	C_{max} – ratio (90% CI)	AUC– ratio (90% CI)	C(24)h – ratio (90% CI)
E202 (N = 11)			
Fasted	0.8964 (0.8020 – 1.002)	1.043 (0.9339 – 1.166)	1.457 (1.115 – 1.905)
Fed	1.402 (1.254 – 1.567)	1.391 (1.245 – 1.554)	1.578 (1.207 – 2.063)
GITS 329 (N = 11)			
Fasted	0.6979 (0.6299 – 0.7732)	1.044 (0.9521 – 1.144)	1.860 (1.590 – 2.175)
Fed	1.054 (0.9516 – 1.168)	1.218 (1.111 – 1.335)	1.697 (1.451 – 1.985)

3.2.3. Pharmacokinetics in the target population

3.2.3.1. TIMI 46

TIMI 46 was a double blind, randomised, dose escalation and dose-confirmation study designed to evaluate the safety and efficacy of rivaroxaban in combination with ASA alone (Stratum 1) or with ASA and a thienopyridine (Stratum 2) in subjects with ACS. The total daily doses (TDD) of rivaroxaban studied were 5 mg, 10 mg, 15 mg and 20 mg, administered as either once-daily or twice-daily regimens.

During this trial both rich and sparse pharmacokinetic data were collected for use in population PK/PD studies to be discussed below. Discussed here are the results of the rich data obtained in a subset of subjects on Day 30 of treatment, used to calculate a number of steady state PK parameters for descriptive purposes only. These results are summarised below in Table 4. Dose and dosing regimen did not seem to affect clearance (CL/F) or t_{max}; median CL/F ranged between 8.4 and 17.4 hr, and median t_{max} varied between 0 and 2.5 hr.

Table 4. Median (min-max) PK parameters of rivaroxaban (study TIMI 46: PK analysis set)

Dose	n	$C_{predose}$ (ng/mL)	C_{max} (ng/mL)	$C_{max,norm}$ [a] (ng/mL)	t_{max} (h)	AUC_τ [b] (h.ng/mL)	$AUC_{\tau,norm}$ [a,b] (h.ng/mL)	CL/F (h)
5 mg od	8	2.08 (0.930-40.0)	64.8 (40.0-95.6)	130 (80.0-191)	2.01 (0.00-9.27)	484 (296-1014)	968 (592-2027)	10.7 (4.93-16.9)
2.5 mg bid	4	8.54 (4.12-39.3)	57.5 (25.7-84.2)	115 (51.4-168)	2.50 (1.02-3.00)	236 (156-534)	471 (313-1068)	11.0 (4.68-16.0)
10 mg od	18	10.8 (1.20-113)	117 (1.94-352)	117 (1.94-352)	2.00 (0.00-3.05)	972 (16-2988)	972 (16-2988)	10.3 (3.35-627)
5 mg bid	19	34.6 (BQL-140)	112 (30.3-229)	112 (30.3-229)	2.00 (0.00-12.0)	598 (117-1402)	598 (117-1402)	8.37 (3.57-28.3)
15 mg od	3	12.2 (3.69-78.6)	78.6 (3.69-172)	52.4 (2.46-115)	0.00 (0.00-4.00)	861 (60.4-1874)	574 (40.3-1250)	17.4 (8.00-248)
7.5 mg bid	3	29.7 (10.6-86.1)	122 (79.8-233)	81.3 (53.2-155)	2.00 (1.00-2.00)	855 (589-1263)	570 (393-842)	8.77 (5.94-12.7)
20 mg od	6	48.9 (17.4-308)	232 (45.4-437)	116 (22.7-219)	0.50 (0.00-2.00)	1947 (513-3126)	973 (256-1563)	10.6 (6.40-39.0)
10 mg bid	10	33.1 (5.70-340)	168 (96.8-395)	83.8 (48.4-198)	1.00 (0.00-4.08)	959 (570-2528)	479 (285-1264)	10.4 (3.96-17.5)

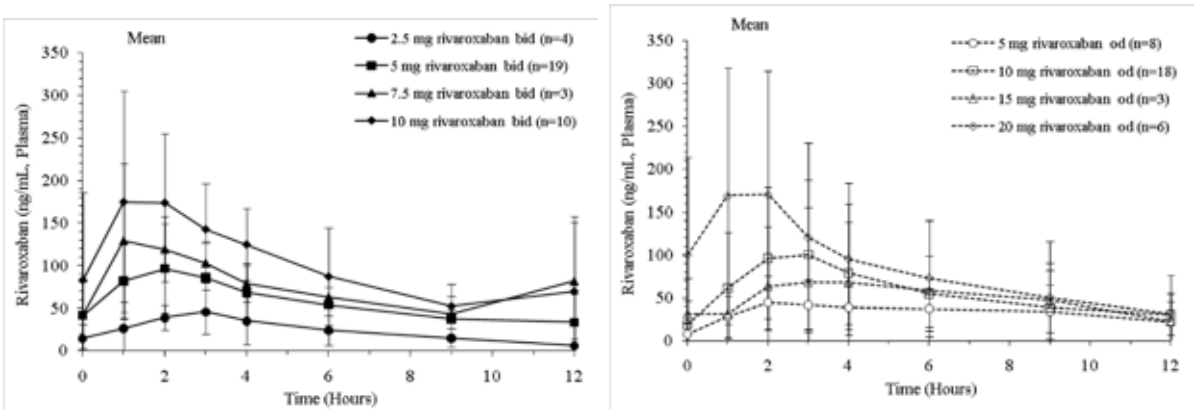
od= once-daily; bid=twice-daily

[a] Normalization was done to a rivaroxaban dose of 10 mg once-daily or 5 mg twice-daily

[b] τ= 24 hours for once-daily and 12 hours for twice-daily

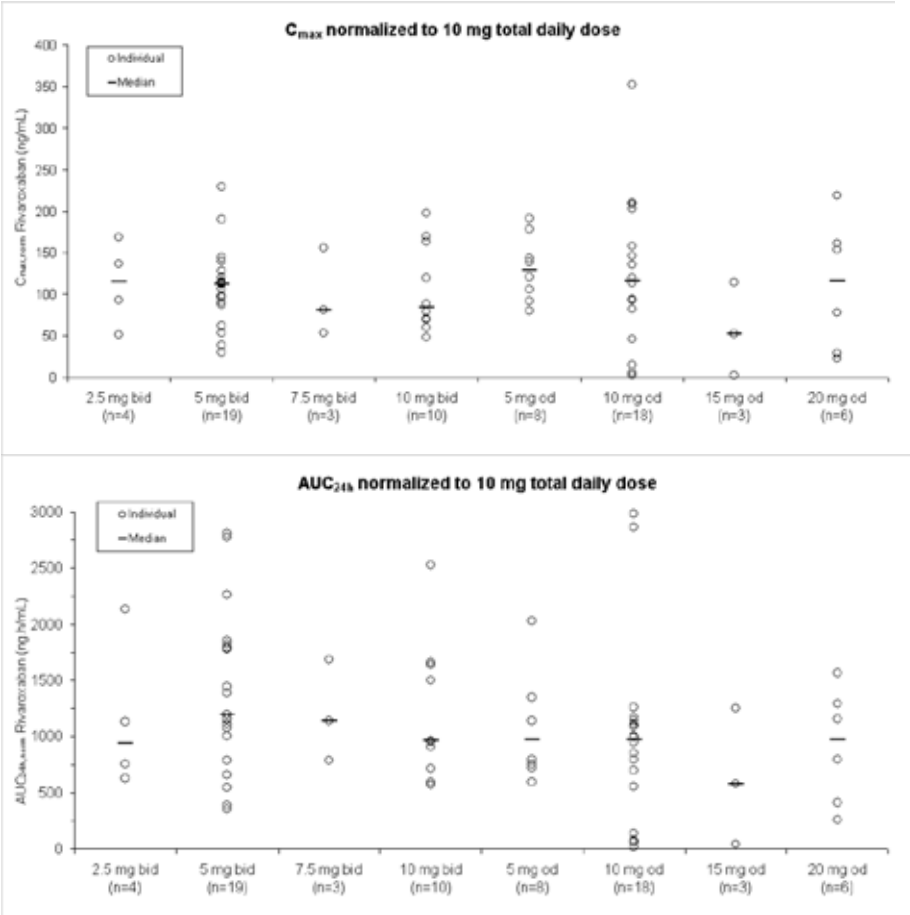
The mean plasma concentration time curves (Figure 1) and derived PK parameters generally increased with increasing dose within the dosing regimen (once daily or bd), however no formal statistical analysis was done.

Figure 1. Concentration-time profiles of rivaroxaban, per dosing group and regimen (study TIMI 46: PK analysis set)



Dose normalised C_{max} and AUC_{24} are presented in Figure 2. In order to compare AUC's between the different dosing regimens the AUC_{12h} values of the twice-daily regimens were multiplied by 2. The AUC_{24} was comparable for the once-daily and twice-daily dosing regimens.

Figure 2. Rich PK data: rivaroxaban steady-state C_{max} and AUC24 values normalised to 10 mg TDD (Day 30) (study TIMI 46: PK analysis set)



od = once daily; bd = twice daily

3.2.4. Population PK analyses

There were 2 related PK/PD studies included in the application. Study R-8642 (discussed below and under *Dose proportionality*) in which the population PK (POPPK) model for rivaroxaban in ACS was developed and used to investigate the relationship between rivaroxaban and prothrombin time (PT) and prothrombinase-induced clotting time (PiCT); and R-8645 which utilised the PK parameters estimated in R-8642 to predict steady state systemic rivaroxaban exposure and to quantify its relationship with bleeding outcomes.

3.2.4.1. Study R-8642

The main objective of Study R-8642 was to characterise the inter- and intra-individual variability in the derived PK parameters of rivaroxaban in patients with ACS, and to evaluate the influence of patient covariates on the PK of rivaroxaban in these patients..

All TIMI 46 patients randomised to rivaroxaban (n=2,331) had sparse PK and PD samples, with additional intensive PK samples obtained from between 3 and 19 patients at each rivaroxaban dose group. A total of 9,392 (92.7%) PK samples from 2,290 (99.8%) subjects were used to develop the POPPK model in ACS, which was derived from the non-linear mixed effects model previously developed for rivaroxaban in patients with DVT.

The PK data in ACS patients were adequately described by a one-compartment model with first-order absorption and first-order elimination. The parameter estimates for the final model showed moderate IIV and were comparable to those for VTE prevention patients, DVT treatment patients, and AF patients.

Both clearance (CL/F) and volume of distribution (V/F) for rivaroxaban decreased linearly with age by approximately 1.1% and 0.71%, respectively, per one year increase from the median age of 57 years. In addition, CL/F decreased by 1.5% per 0.1mg/dL increase from the median serum creatinine of 0.95 mg/dL, and V/F increased by 0.83% per one kg increase from the median lean body mass of 61 kg. These covariate estimates were consistent with findings in VTE, DVT, and AF patients.

Individual parameter estimates from the POPPK model were then used to predict steady-state rivaroxaban exposure parameters (AUC, C_{max}, and C_{min}). The simulated median AUC was 1.5 times higher in patients with moderate renal impairment (CRCL < 50 mL/min) than in patients with normal renal function, and about 43% higher in the elderly (> 75 yr) than in younger patients (< 50 yr). These findings were stated to be consistent with previous Phase I studies in renal impairment and age comparison populations. Lean body mass had only a small effect on rivaroxaban exposure.

3.2.5. Pharmacokinetic interactions

Study 14883 does not relate to the rivaroxaban dosage and indication of the current submission. It investigated the PK while switching from warfarin (dosed to steady state; INR 2.0 to 3.0) to rivaroxaban treatment (15 mg once daily) in 36 healthy Japanese men who have a higher sensitivity to the anticoagulation activity of warfarin than the Caucasian population. Only a brief summary of the study results has been included in the body of the submission.

No pharmacokinetic interaction was observed between warfarin and rivaroxaban. The PK characteristics of rivaroxaban ($AUC_{(0-24)}$ and C_{max}) were similar irrespective of whether treatment followed warfarin treatment or not. Although not statistically powered to demonstrate bioequivalence, the 95% CIs calculated for the ratios 'warfarin/rivaroxaban'/'rivaroxaban alone' of $AUC_{(0-24)}$ and C_{max} were 0.797 – 1.086 and 0.772 – 1.004, respectively, and thus almost met the criteria for bioequivalence (0.80 – 1.25) (Table 5, below).

Terminal half life was calculated for R- and S-warfarin after the last warfarin dose. Results were similar in subjects regardless of whether they received subsequent rivaroxaban or subsequent placebo. 95% CIs constructed for the ratio 'rivaroxaban'/'placebo' of $t_{1/2}$ were 0.847 to 1.463 and 0.966 to 1.189, respectively, and almost met the criteria for bioequivalence.

Table 5. Assessment of bioavailability of rivaroxaban and warfarin in plasma, PK/PD set, n=36

Analyte	Parameter	Test	Reference	Test/reference LS mean (95% CI)
Rivaroxaban	AUC(0-24)	Rivaroxaban (A)	Rivaroxaban (C)	0.930 (0.797, 1.086)
	C_{max}	Rivaroxaban (A)	Rivaroxaban (C)	0.880 (0.772, 1.004)
R-warfarin	$t_{1/2}$	Rivaroxaban (A)	Placebo (B)	1.114 (0.847, 1.463)
S-warfarin	$t_{1/2}$	Rivaroxaban (A)	Placebo (B)	1.072 (0.966, 1.189)

A = Rivaroxaban following warfarin
B = Placebo following warfarin
C = Rivaroxaban alone

Evaluator's comment

This study was designed to supplement a previous exploratory study (Study 12089, not known to be previously evaluated) which investigated the potential interaction between a single dose of 15 mg of warfarin and a single dose of 5 mg of rivaroxaban in 7 healthy male subjects. In Study 12089 no pharmacokinetic interaction was observed between the two compounds. The recently completed evaluation included a similar study (10849) which investigated the PK during the switching procedure from warfarin (≤ 5 mg dosed to steady state; INR 2.0 to 3.0) to rivaroxaban (20 mg once daily) in 84 healthy male subjects. The study found that warfarin had no significant effect on the PK of rivaroxaban, and rivaroxaban had no significant effect of on the

half-life of either s-warfarin or r-warfarin. The findings of Study 14883 in the Japanese population are consistent with these earlier studies.

3.3. Evaluator's overall conclusions on pharmacokinetics

Conventional PK studies

- In the fasted state, the $t_{1/2}$, C_{max} and AUC increased dose dependently for the 2.5 mg, 5 mg and 10 mg doses of rivaroxaban
- The dose normalised C_{max} and AUC increased dose dependently, but only the AUC/D met the criteria for bioequivalence. The lack of dose proportionality for C_{max}/D suggests that rivaroxaban may begin to exhibit solubility-limited absorption at 5 mg under fasting conditions
- The 2.5 mg tablet can be considered dose proportional to the 10 mg tablet based on the AUC/D

From TIMI 46:

- Dose (from 2.5 mg to 20 mg) and dosing regimen (once daily or bd) did not seem to affect CL/F or t_{max}
- The mean plasma concentration time curves and derived PK parameters generally increased with increasing dose within the dosing regimen
- The AUC_{24} was comparable for the once-daily and twice-daily dosing regimens.

Population PK study

- Rivaroxaban PK data in ACS patients can be adequately described by a one-compartment model with first-order absorption and first-order elimination
- Rivaroxaban PK parameter estimates and the IIV for ACS patients were comparable to those for VTE prevention patients, DVT treatment patients, and AF patients
- Rivaroxaban clearance decreases with age and increasing plasma creatinine. These are the same patient covariates previously found to influence rivaroxaban PK in VTE, DVT, and AF patients. The model estimates were consistent with findings from Phase I studies in renal impairment and age comparison populations.

The PK of rivaroxaban has been well characterised for higher dose tablets in other indications. The PK of the 2.5 mg tablet in patients with ACS is consistent with what is already known for the 10 mg, 15 mg and 20 mg rivaroxaban tablets. The only statement that has not been fully supported by data in this submission is whether the absolute bioavailability of the 2.5 mg dose is affected by food.

In the *Summary of Biopharmaceutic Studies* included with the application, the sponsor refers to a *"lack of a relevant food effect observed with the 10 mg rivaroxaban tablet (Study 11937), and similar results obtained from an exploratory pooled PK analysis across Phase 1 studies (PH-36318) which included dose strengths less than 10 mg"*, as the reason for not conducting a dedicated food effect study for the 2.5 mg tablet and supporting that rivaroxaban 2.5 mg tablets can be taken with or without food. The evaluator obtained a copy of the pooled PK analysis (PH-36318), but only found reference to the 2.5 mg dose in the fasted state and the following statement:

> *No pharmacokinetic and pharmacodynamic conclusions are presented in this report. After medical review of the table set provided, rivaroxaban pharmacokinetic and pharmacodynamic results and conclusions drawn from these results will be reported under separate cover.*

The sponsor was asked to provide the data to support the lack of food effect with the 2.5 mg tablet.

4. Pharmacodynamics

4.1. Studies providing pharmacodynamic data

Table 6 shows the studies relating to each pharmacodynamic topic.

Table 6. Studies providing pharmacodynamic data.

PK Topic	Subtopic	Study ID
Population PD and PK/PD analyses	Target population	R-8642 R-8645
PD interactions	Warfarin	14883

None of the pharmacodynamic studies had deficiencies that excluded their results from consideration.

4.2. Summary of pharmacodynamics

4.2.1. Study R-8642

The PK/PD analyses were conducted in a subgroup of 1,347 subjects with time matched PK and PD samples. The PD measurements included prothrombin time (PT; 6,644 observations available) and prothrombinase induced clotting time (PiCT; 5,433 observations available). The current analysis used the estimated PK parameter values presented under *Pharmacokinetics in the target population* above.

A close-to-linear relationship was shown between rivaroxaban plasma concentrations and both PT and PiCT, which could be described by linear intercept models with a declining exponent on plasma concentration. Both models suggested an adequate fit based on the residual and observed versus predicted plots.

The baseline PT in the study population was 14 s, and the estimated mean slope of the correlation between PT and rivaroxaban plasma concentrations (Cp) was 3.2 s/(100 ng/mL) in the ACS population. This correlation is consistent with the estimates in the DVT (3.6 s), AF (4.3 s), hip VTE (3.2 s) and knee VTE (4.2 s) studies. The IIV for the correlation between rivaroxaban plasma concentrations and PT was low overall (<10%). CrCl had a moderate effect on the model with an 8.9% variation in the PT at a concentration of 50 ng/mL for the creatinine clearance range in this study population.

In the PiCT model, the baseline PiCT was 13.1 s, and the slope of the correlation between PiCT and rivaroxaban plasma concentrations was 16.5 s/(100 ng/mL). In comparison, the baseline PiCT in an AF population was 7.97 s with a slope of 9.5 s/(100ng/mL). The IIV for the correlation between rivaroxaban plasma concentrations and PiCT was moderate overall (up to ~ 25%). CrCl had a small effect on the model, with a 3.3% variation in the PT at a concentration of 50 ng/mL for the creatinine clearance range in this study population.

Evaluator's comment

The significance of the higher baseline PiCT and other differences in the model in the ACS population compared with the AF population is not known. The sponsor suggested that it could

be due to "differences between the patient populations", and "*may not be of any statistical significance*". As PiCT is an assay for monitoring anticoagulants inhibiting factor Xa and it appears that for rivaroxaban PT is a better assay, it does not appear to be clinically relevant.

4.2.2. Study R-8645

Study R-8645 was an exploratory study to quantify the relationship between predicted rivaroxaban systemic exposure (separately for subjects in Stratum 1 and Stratum 2), clinical covariates, and bleeding outcomes using the PK parameter estimates from Study R-8642, and the dosing regimens and outcomes from TIMI 46.

- The measures of exposure used were: the area under the rivaroxaban concentration-time curve at steady state over 24 hr (AUC_{24}); the highest rivaroxaban concentration during a dosing interval (C_{max}); and the lowest rivaroxaban concentration during a dosing interval (C_{min}).
- The clinically relevant covariates included treatment stratum, age, creatinine clearance, systolic blood pressure, diabetes status, and prior history of MI.
- The bleeding outcome used was "clinically significant bleeding", a composite of TIMI major, TIMI minor or bleeding requiring medical attention.

Similar rivaroxaban exposure levels were seen in both strata for each rivaroxaban dose. When comparing the dosing regimens with the same TDD, the AUC_{24} were similar, but the C_{max} was approximately 35% lower, and the C_{min} approximately 150% higher for the bd regimen compared with the once daily regimen.

For all 3 measures of rivaroxaban exposure(grouped by whether exposure was < or ≥ the median value), rates of bleeding generally increased with exposure, and higher rates of bleeding were seen in subjects on ASA and thienopyridine (Stratum 2) than in subjects on ASA alone. However, the AUC_{24} was the best predictor of the exposure parameters evaluated. To quantify this relationship a Cox Proportional Hazards Model was developed to investigate the contribution of AUC_{24}, treatment (rivaroxaban versus placebo), TDD, and regimen (once daily versus bd), either individually or in combination. The final model included the clinical covariates, AUC_{24} and treatment indicating that both the magnitude of rivaroxaban exposure (continuous AUC_{24} values) and rivaroxaban treatment (dichotomous variable) was needed to explain the bleeding hazard. It estimated an increase in the hazard of clinically significant bleeding of ~38% for each 1 μg.hr/mL increase in AUC_{24} in subjects treated with rivaroxaban. A further model determined that there was no difference in the hazard of clinically significant bleeding between once daily and bd regimens, over and above that already contained within the AUC_{24}-clincially significant bleeding outcome relationship.

4.2.3. Pharmacodynamic interactions

Study 14883 evaluated the influences of warfarin and rivaroxaban on a wide variety of clotting tests during the switching period from warfarin (INR 2.0 to 3.0) to rivaroxaban 15 mg once daily in Japanese men. Most of the tests like Factor Xa activity inhibition, aPTT prolongation and ETP (decrease of AUC and peak height as well as prolongation of ETP lagtime and time to peak) showed additive effects during the switching period from warfarin to rivaroxaban. Relevant agonistic effects were observed for PT, which showed more than additive effects after the switch than expected from results of warfarin/placebo and rivaroxaban alone. Anti-Factor Xa activity appears the most suitable test for monitoring the effect of rivaroxaban, since it reliably demonstrated rivaroxaban effects but not warfarin effects.

4.2.3.1. Evaluator's comment

The results of Study 14883 were consistent with Study 12089 which investigated the potential interaction between a single dose of 15 mg of warfarin and a single dose of 5 mg of rivaroxaban in 7 healthy male subjects. In Study 12089 maximal effects on INR were higher after

concomitant administration of rivaroxaban and warfarin (INR 1.8 ± 0.5) compared to warfarin alone (INR 1.4 ± 0.3). Factor Xa activity, aPTT, HepTest, ETP AUC, and PiCT were not influenced by the concomitant administration of rivaroxaban and warfarin.

4.3. Evaluator's overall conclusions on pharmacodynamics

The pharmacodynamics of rivaroxaban has been well characterised for higher dose tablets (10, 15 and 20 mg) in other indications.

Data from R-8642 confirms the PD data in the approved PI, namely that rivaroxaban prolongs PT in a dose dependent way. PT (using the Neoplastin® assay) would therefore be suitable for estimating rivaroxaban exposure in patients, if this was thought clinically necessary.

Study R-8645 explored the relationship between estimates of rivaroxaban systemic exposure and bleeding outcomes and found that higher exposure was associated with more bleeding events, with the rate of clinically significant bleeding being generally lower in the subjects on ASA alone than in those on ASA plus thienopyridine. AUC_{24} was found to be the best predictor of the exposure parameters evaluated. When modelled, an increase of ~38% in the hazard of clinically significant bleeding was predicted for each 1 µg.hr/mL increase in AUC_{24} in subjects treated with rivaroxaban. The AUC_{24} was shown to be a better predictor of bleeding events than rivaroxaban dose alone, which is biologically plausible based on the variability in the PK of rivaroxaban.

5. Dosage selection for the pivotal studies

The dose selection for the pivotal Phase III TIMI 51 study was based on the review of safety, efficacy and the resulting net clinical outcome data from of the phase II TIMI 46 study (further discussed under *Study 11898 (ATLAS ACS TIMI 46)*). TIMI 46 was a double blind, randomised, dose escalation and dose-confirmation study designed to evaluate the safety and efficacy of rivaroxaban in combination with ASA alone (Stratum 1) or with ASA and a thienopyridine (Stratum 2) in subjects with ACS. The total daily doses (TDD) of rivaroxaban studied were 5 mg, 10 mg, 15 mg and 20 mg, administered as either once-daily or twice-daily regimens.

The 2 lowest rivaroxaban TDDs (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 to once-daily. Therefore, bd doses of 2.5 mg and 5 mg were chosen for the Phase III TIMI 51 trial. The rationale given by the sponsor for studying 2 doses of rivaroxaban was "to develop a better understanding of the efficacy and safety profile of rivaroxaban in a wider dose range".

Evaluator's comment

While it is clear why the 2.5 mg bd and 5 mg bd doses of rivaroxaban were chosen for the Phase III trial, there were no data supplied in the application or adequate explanation given for the original choice of 2.5 mg as the lowest dose in the Phase II trial. The only reference to the selection of the 2.5 mg dose the evaluator could find was in the TIMI 46 Clinical Protocol. Here the sponsor stated: "*In the VTE prophylaxis studies, the lowest effective twice-daily dose tested was demonstrated to be 2.5 mg twice daily*." The evaluator also identified a publication[1] that reported that the 1.25 mg dose of rivaroxaban showed no significant inhibition of factor Xa activity compared with placebo, but a 2.5 mg dose was not tested. While Factor Xa inhibition by the 2.5 mg dose of rivaroxaban can be assumed based on PT prolongation, no data was provided

[1] Kubitza D, Becka M, Voith B, Zuehlsdorf M and Wensing G. Safety, pharmacodynamics, and pharmacokinetics of single doses of BAY 59-7939, an oral, direct factor Xa inhibitor. Clin Pharmacol Ther 2005; 78:412-21

regarding this in the application. The sponsor is requested to provide the basis for the decision to use the 2.5 mg dose including data on Factor Xa inhibition.

6. Clinical efficacy

6.1. Acute coronary syndrome

6.1.1. Pivotal efficacy study

6.1.1.1. Study 13194 (ATLAS ACS 2 TIMI 51)

6.1.1.1.1. Study design, objectives, locations and dates

TIMI 51 was a multicentre, randomised, double-blind, placebo-controlled, event driven study 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 consisting of low dose ASA (Stratum 1) or low dose ASA plus thienopyridine (Stratum 2).

The *primary objective* of this study was to determine whether rivaroxaban is superior to placebo in addition to standard care[2] in reducing the risk of the composite of CV death, MI, or stroke in subjects with a recent ACS.

The *secondary objectives* of this study were to:

- determine whether rivaroxaban reduces the risk of the composite of all cause death, MI, or stroke;
- examine the effect of rivaroxaban on net clinical outcome, defined as the composite of CV death, MI, ischemic stroke, or a Thrombolysis in Myocardial Infarction (TIMI) major bleeding event not associated with coronary artery bypass graft (CABG) surgery;
- determine whether rivaroxaban reduces the risk of the composite of CV death, MI, stroke, or severe recurrent ischemia requiring revascularisation (SRIR); and
- determine whether rivaroxaban reduces the risk of the composite of CV death, MI, stroke, or severe recurrent ischemia leading to hospitalisation (SRIH).

The study was conducted at 766 sites in 44 countries worldwide between 26 November 2008 and 19 September 2011, including 62 sites in the USA, 17 sites in the UK, 17 sites in Canada, and 16 sites in Australia. It included 15,526 randomised patients, 1,053 in Stratum 1 and 14,473 in Stratum 2.

The study had 3 phases: a 6-day screening phase, a double-blind treatment phase, and a 30 day follow-up phase. Subjects who experienced a primary or secondary efficacy endpoint event (except for death and hemorrhagic stroke) continued to receive blinded study drug and completed all assessments at all scheduled visits, if possible. Subjects returned to the study centre every 12 weeks until the global treatment end date - the projected date of accrual of at least 983 primary efficacy endpoint events anticipated to be adjudicated as an evaluable event.

6.1.1.1.2. Inclusion and exclusion criteria

Eligible patients included men and women aged ≥18 years, currently receiving ASA therapy (75 to 100 mg/day) alone or in combination with a thienopyridine (clopidogrel or ticlopidine per national dosing recommendation), who had been hospitalised for symptoms suggestive of ACS that lasted at least 10 minutes at rest, and occurred 48 hr or less before hospital presentation, or who developed ACS while being hospitalised for an indication other than ACS and had a

[2] Throughout this evaluation, when "placebo" is used as the comparator it should be interpreted as "placebo added to standard care", where standard care is either ASA alone or ASA plus thienopyridine.

diagnosis of STEMI, NSTEMI or unstable angina. 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.

Evaluator's comment

These inclusion criteria are consistent with Australian ACS patients who would be considered at intermediate or high risk of short-term adverse outcomes (6-month risk of death or myocardial infarction)[3].

Key exclusion criteria were:

- Increased bleeding risk such as:
  - Active internal bleeding, clinically significant bleeding, bleeding at a noncompressible site, or bleeding diathesis within 30 days of randomisation
  - Platelet count <90,000/µL at screening
  - History of intracranial haemorrhage (ICH)
- Severe concomitant diseases such as:
  - Calculated creatinine clearance <30 mL/min at screening
  - Known significant liver disease (for example, acute hepatitis, chronic active hepatitis, cirrhosis), or liver function test (LFT) abnormalities (confirmed with repeat testing) which would require study drug discontinuation, that is, alanine aminotransferase (ALT) >5x upper limit of normal (ULN) or ALT >3x ULN plus total bilirubin >2x ULN
  - A prior ischemic stroke or transient ischemic attack (TIA) in subjects who the investigator planned to include in Stratum 2 (ASA plus thienopyridine)4. Subjects with a prior hemorrhagic stroke were excluded completely from the study.

In addition to specified inclusion and exclusion criteria the study also included criteria for temporary and permanent discontinuation and withdrawal from the study. These included: procedures or conditions increasing bleeding risk, major bleeding events, safety reasons, pregnancy, administration of prohibited medications, withdrawal of consent, and serious liver enzyme abnormalities.

Evaluator's comment

The patient population represents a broad ACS population with minimal exclusionary criteria, apart from conditions that may increase the risk of bleeding, which is appropriate. Stratum 1 included patients at higher risk of atherothrombotic outcomes (history of prior ischemic stroke or TIA allowed).

6.1.1.1.3. Study treatments

Rivaroxaban was supplied as 2.5 mg or 5 mg tablets with matching placebo tablets. Subjects were randomly assigned in a 1:1:1 ratio to one of 3 treatment groups: rivaroxaban 2.5 mg bd, rivaroxaban 5 mg bd, or placebo bd. All subjects also received standard care, including low-dose ASA therapy (75 to 100 mg/day) +/- a thienopyridine (clopidogrel or ticlopidine only). The 2 newer antiplatelet agents, prasugrel and ticagrelor were not approved for use at the outset of the TIMI 51 trial and were therefore not included in this trial. The duration of dual antiplatelet treatment was at the discretion of the investigator and could have varied depending on the subject's diagnosis or whether a bare metal stent or drug eluting stent was implanted. The

[3] Guidelines for the management of acute coronary syndromes 2006. Acute Coronary Syndrome Guidelines Working Group. Med J Aust 2006; 184 (8): 1-32.
[4] The decision to exclude these subjects was based on previous studies (TIMI 46 and a study of prasugrel4), which suggested no benefit with the addition of rivaroxaban or prasugrel, respectively.

thienopyridine dosage was to follow the national or local prescribing information. For clopidogrel, the daily maintenance dose was not to exceed 75 mg/day, and for ticlopidine, the daily maintenance dose was not to exceed 250 mg twice-daily. Where thienopyridine therapy was not considered appropriate, subjects received ASA therapy alone, which was to be maintained at a dose of 75 to 100 mg/day throughout the study.

Subjects were randomly assigned to study drug up to 7 calendar days after they had been hospitalised for the index ACS event, when parenteral anticoagulant therapy would normally be discontinued. Enrolment was to occur as soon as possible after the initial treatments for the index ACS event, including revascularisation procedures, but could not occur during the first 24 hr following hospitalisation.

Subjects were to receive the first dose of study drug as soon as possible after randomisation, but no sooner than 4 hr after the final dose of intravenous unfractionated heparin (UFH), 2 hr after the final dose of bivalirudin, and 12 hr after the final dose of other intravenous or subcutaneous anticoagulants (for example, enoxaparin or fondaparinux).

All other concomitant medication use was at the discretion of the managing clinician. It was advised that the appropriate guideline recommendations be followed for all other concomitant medications. Chronic use of non-steroidal anti-inflammatory drugs was advised against, and medicines that reduce gastric acid (and may therefore reduce the incidence of gastrointestinal bleeding) were to be considered. Prohibited medications included ASA doses >100 mg/day, systemic treatment with strong CYP 3A4 and P-gp inhibitors, and chronic use of other antiplatelet medication or anticoagulant therapy. These therapies could be used on a temporary basis if the study drug was temporarily discontinued first.

Evaluator's comment

Aspirin and clopidogrel for STEMI, NSTEMI and ACS are considered standard care in Australia. Ticlopidine and prasugrel have little use based on PBS data, and ticagrelor is approved but not yet listed.

In the 2011 addendum to the ANZ guidelines for the management of acute coronary syndromes 2006[5], aspirin is recommended for all patients with STEMI (unless contraindicated), with the addition of clopidogrel for patients undergoing PCI with a stent or fibrinolytic therapy. Prasugrel or ticagrelor are considered as alternatives for clopidogrel in subgroups at high risk of recurrent ischaemic events. For patients with high risk NSTEMI or UA, aspirin and clopidogrel are recommended for all patients (unless contraindicated), but clopidogrel should be avoided if emergency CABGs are likely. Prasugrel or ticagrelor are suggested for patients at low risk of bleeding, while clopidogrel is preferred in those at high risk of bleeding.

Despite their low use at present, given that both ticagrelor and prasugrel are associated with higher rates of bleeding than clopidogrel, consideration should be given to advising against the concomitant use of rivaroxaban with these agents specifically in the *Precautions* and *Interactions with Other Medicines* sections of the PI.

6.1.1.1.4. Efficacy variables and outcomes

This was a clinical outcomes study with the following events used in composite efficacy endpoints:

- Death
- MI
- Stroke (ischaemic, haemorrhagic, uncertain)

[5] 2011 Addendum to the National Heart Foundation of Australia/Cardiac Society of Australia and New Zealand Guidelines for the Management of Acute Coronary Syndromes (ACS) 2006. Heart, Lung and Circulation Vol. 20, Issue 8, Pages 487-502

- Severe recurrent ischemia
- Bleeding events

Occurrences of these events post-randomisation were adjudicated and classified by the independent blinded Clinical Events Committee (CEC) according to definitions in the CEC charter. Members were board-eligible or board-certified cardiologists, and other specialist physicians (such as neurologists) as required. In addition, the CEC also confirmed and classified cases of coronary stent thrombosis according to the Academic Research Consortium (ARC) definitions. The adjudicated results were used for the efficacy analysis.

The primary efficacy endpoint was the composite of CV death, MI, or stroke.

The secondary efficacy endpoints were:

1. composite of all-cause death, MI, or stroke
2. Net Clinical Outcome (composite of CV death, MI, ischaemic stroke, or TIMI major bleeding event not associated with CABG surgery)
3. composite of CV death, MI, stroke, or severe recurrent ischemia requiring revascularisation (SRIR)
4. composite of CV death, MI, stroke, or severe recurrent ischemia leading to hospitalisation (SRIH)

Stent thrombosis was evaluated as a pre-specified standalone efficacy endpoint.

Evaluator's comment

The TGA adopted guideline relating to the investigation of medicines for the treatment of ACS without persistent STEMI, (CPMP/EWP/570/98) consider that a "*composite double efficacy endpoint consisting of all cause mortality and new MI*" to be the "*primary endpoint of choice*" although a "*triple endpoint could still be acceptable, if it includes all cause mortality and new MI as components with the third component defined very precise*". This trial has a primary triple endpoint that incorporates CV mortality, MI, or stroke. Stroke is defined in the CEC Charter and adjudicated by the CEC and a triple endpoint incorporating all cause mortality is a secondary endpoint, so this is considered acceptable.

Stent thrombosis was not considered a formal endpoint according to the TIMI 51 protocol, although it was adjudicated by the CEC. In Section 2.2.10.4.2 "*Analysis Methods*" of the Rivaroxaban Statistical Analysis Plan RIVAROXACS3001-Amendment 2 it states: *"Stent thrombosis and its sub-categories will be summarized by treatment group since this endpoint is not a formal study endpoint in the study protocol (even though it's adjudicated), thus it's expected only few of these events to warrant more involved analyses."* However stent thrombosis contributed to individual components of the primary or secondary composite endpoints as a potential underlying cause of death, MI, SRIR or SRIH (as a subset of those endpoints). It is therefore acting as another composite endpoint, but not one that was formalised with respect to the study analysis (see also *Statistical methods* and *Results for other efficacy outcomes*).

6.1.1.1.5. Randomisation and blinding methods

Subjects were stratified by the intention to use thienopyridine (clopidogrel or ticlopidine only as per the national or local indicated dosage) as standard care (Stratum 1 = no, Stratum 2 = yes) in addition to low-dose ASA.

Central randomisation was based on a computer generated randomisation schedule prepared before the study. The randomisation was balanced by using randomly permuted blocks and subject stratification. Within each stratum, subjects were assigned to treatment via an Interactive Voice Response System (IVRS) or Interactive Web Response System (IWRS).

Study subjects, study personnel, the Clinical Events Committee (CEC) and the sponsor were to remain blinded to treatment assignment until all subjects had completed the study and the database was finalised with the following exception: if specific emergency treatment would be dictated by knowing the treatment status of the subject.

6.1.1.2. Evaluator's comment

Randomisation and blinding were satisfactory.

6.1.1.2.1. Analysis populations

There were six analysis sets defined for this study:

i. Modified Intent-to-Treat (mITT), [**primary efficacy analysis set**]

ii. Intent-to-Treat (ITT)

iii. Intent-to-Treat Total (ITT-Total)

iv. Treatment-Emergent Safety, [**primary safety analysis set**]

v. mITT Approach for Safety, and

vi. Safety Observational Period (including all post baseline events)

The first three of the 6 analysis sets (that is, mITT, ITT, and ITT-Total) are based on the efficacy population (that is, all randomised subjects excluding sites 091001, 091019 and 091026 [see *Evaluator's comment* below]) and differ from one another only in the censoring rules for determining evaluable events. The other 3 analysis sets are based on the safety population (that is, all randomised subjects who received at least one dose of study drug) and differ from one another only in the censoring rules for determining evaluable events.

The mITT analysis set included endpoint events that occurred:

- from randomisation 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 randomisation (for subjects who were randomised but never treated).

The treatment emergent safety set included all events from first dose up to the date of last dose of study drug plus 2 days. This was also used as a sensitivity analysis set for efficacy.

An additional supplementary analysis set was defined in the SAP for exploratory analyses of potential off-treatment CV effects. The off-treatment analysis set included all study drug-treated subjects who had at least 1 day of follow up after the last dose of study drug administration (i.e., a subset of the safety population) and the endpoint events that occurred after the last dose of study drug administration.

6.1.1.3. Evaluator's comment

The preferred analysis set for efficacy is the ITT or ITT-Total which have the advantage of including all endpoints from randomisation until either the global treatment end date or date of last contact with subject, respectively, rather than for a maximum of 30 days after the last dose of study drug for those subjects who discontinued early or 30 days after randomisation for those subjects who were randomised but never treated. However both the ITT and ITT-Total analysis sets were included as sensitivity analyses, so this is acceptable.

Some 184 subjects from sites 091001, 091019 and 091026 were excluded from the efficacy analyses due to potential trial misconduct. Based on a sponsor's audit of these sites misconduct included use of the same ECG for multiple patients on multiple dates, missing ECGs and laboratory reports to confirm subject eligibility, date discrepancies on informed consents, and missing drug product. The number of excluded subjects was approximately the same across

treatment groups; there were proportionally fewer subjects excluded from Stratum 1 compared with Stratum 2. While not used in the mITT analysis, the data from the subjects enrolled at these sites was stated to be included in sensitivity and other analyses, including safety analyses. However, the evaluator was unable to find efficacy analyses containing the excluded sites in the dossier (see also R*esults for the primary efficacy outcome*).

6.1.1.3.1. Sample size

This was an event-driven study. A total of 983 primary efficacy endpoint events were estimated to have approximately 96% power to detect a 22.5% relative reduction (that is, hazard ratio=0.775) between pooled doses of rivaroxaban and placebo arms pooled across Stratum 1 and 2, with a 2-sided type I error rate of 0.05. The total 983 events was estimated based on the sum of the events required at approximately 90% power in each stratum, to detect a 35% relative reduction in Stratum 1 (255 primary efficacy endpoint events required) and a 22.5% relative reduction in Stratum 2 (728 primary efficacy endpoint events required) comparing combined rivaroxaban doses (2.5 mg bd and 5 mg bd) and placebo arms within each strata. The number of primary efficacy endpoint events available to compare each rivaroxaban dose with the placebo treatment group was estimated to be 2/3 of the total events required for the 3-arm study. Each individual dose arm, pooled across Stratum 1 and 2, was powered at approximately 90% for an overall relative risk reduction (RRR) of 22.5% (based on 655 primary efficacy endpoint events), within each individual dose arm, and within each individual stratum the study was powered at approximately 80% for the assumed RRR of 35% in Stratum 1 and 22.5% in Stratum 2.

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 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, the final sample size was increased (as allowed in the protocol) to approximately 15,500, in order to allow for accrual of a total of 983 clinical endpoint events, and maintain the originally planned power of the study.

Evaluator's comment

The assumptions on which the calculation of sample size is based are acceptable. Sample size was reached for the primary analysis of the pooled strata with 1,002 evaluable events (mITT analysis set; 87 in Stratum 1 and 915 in Stratum 2). It should be noted that the study was not powered to detect a reduction in individual components of the composite primary efficacy endpoint.

During the course of the study use of thienopyridine became more widespread in clinical practice resulting in a lower than expected recruitment in Stratum 1 and increasing the number of patients eligible for recruitment into Stratum 2. This coupled with the small number of endpoint events in Stratum 1 means that it didn't reach the targeted study power to detect the estimated efficacy improvement, and limits interpretation of the data. Consideration should be given to limiting the approved indication for rivaroxaban in ACS to those patients receiving both ASA and thienopyridine.

6.1.1.3.2. Statistical methods

Interim analysis

The study protocol specified an interim analysis of efficacy and safety data 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 conservative 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 versus placebo

primary efficacy analyses. This corresponds to a nominal critical point of rejection of H_0 when the hazard ratio (HR) ≤ 0.7402 (pooled rivaroxaban doses, combined strata) or HR ≤ 0.7046 (pooled rivaroxaban doses, stratum 2 only). The data cut-off for the interim analysis was November 29, 2010, based on 704 primary efficacy events. The Independent Data Monitoring Committee (IDMC) met on January 12, 2011 to review the data. The study continued unaltered following the analysis.

The performance of the interim analysis required small adjustments for the final primary efficacy analysis, with evaluation using a two-sided a=0.0499982 instead of 0.05.

Evaluator's comment

The methodology adopted for the planned interim analysis is well-known, commonly used, and considered acceptable. The stopping boundary was predefined, it was interpreted by the IDMC, a conservative p value was chosen, and a sufficient number of outcome events had occurred. Justification for the change in α was given and appears acceptable.

General analysis

Two simultaneous evaluation strategies were employed for the primary endpoint analyses based on differing regulatory requirements. The primary evaluation strategy analysed the data combined across both strata (that is, "All Strata") as recommended by the EMA, while the second evaluation strategy was based on the FDA recommended approach of combined analyses across both dose regimens in subjects in Stratum 2 (ASA plus thienopyridine) only (as this is the standard of care for ACS patients in the US).

Time from randomisation to the first occurrence of the primary efficacy endpoint was analysed and tested in the primary mITT analysis set. The primary efficacy analysis was a stratified log-rank test between the combined rivaroxaban groups and the placebo group. If the combined rivaroxaban groups were found to be superior to placebo, then a similar stratified log-rank test using the same stratum variable was performed for each rivaroxaban individual dose at a 2-sided significance level of 0.050. The same testing strategy was used for Stratum 2, except with an unstratified model.

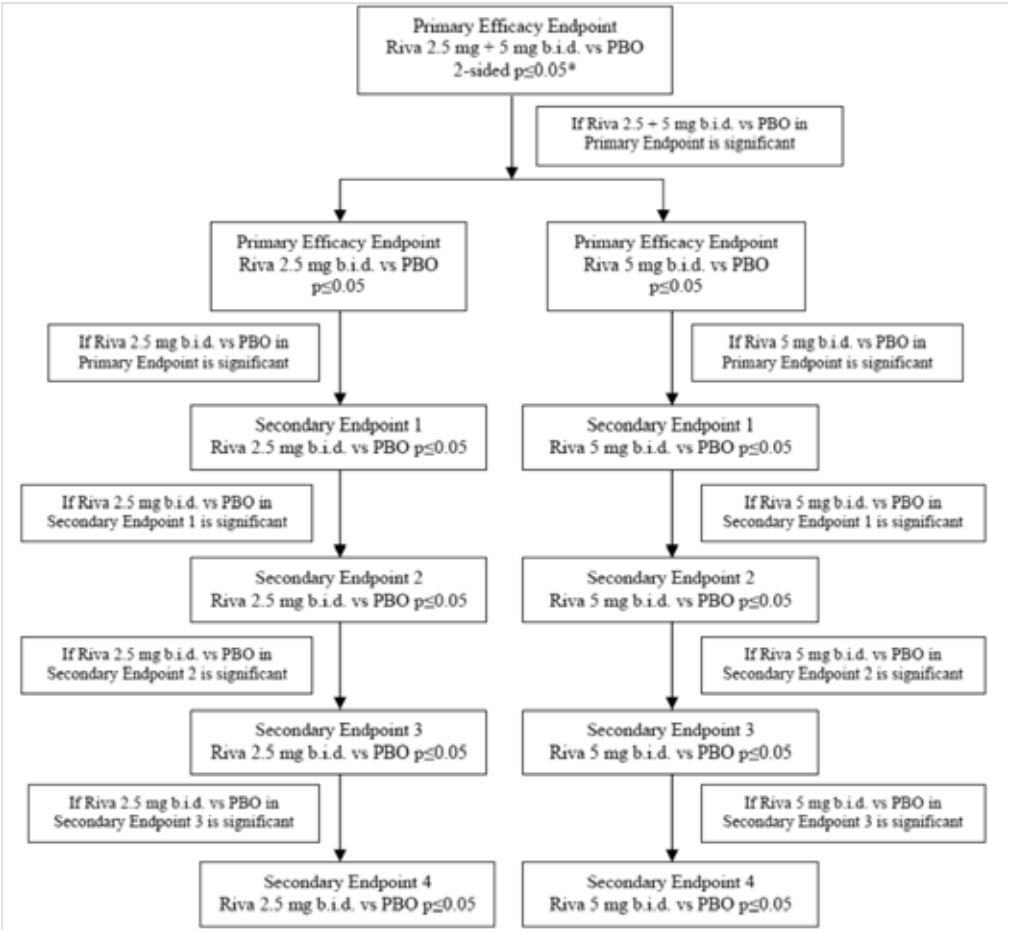
A stratified (by the intention to use a thienopyridine [yes or no]) or unstratified (Stratum 2 alone) Cox proportional hazards regression model was used with treatment group (rivaroxaban versus placebo) as the covariate to provide a point estimate and 95% confidence interval (CI) for the treatment effect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

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

These same methods were used for the secondary efficacy endpoints. If superiority of rivaroxaban compared with placebo for the primary efficacy endpoint was declared within a dose group, then the secondary efficacy endpoints were tested sequentially within that dose group in an hierarchical testing strategy (All Strata, and Stratum 2 only), with further testing continuing only if a statistically significant result was found for the previous endpoint (Figure 3).

For stent thrombosis, the HR and 95% CI based on Cox proportional hazards (stratified for All Strata only) model were provided for time to first occurrence of stent thrombosis as a post-hoc analysis.

Figure 3. Hierarchical statistical testing procedure



Subgroup analyses

Pre-specified subgroup analyses by demographics and baseline characteristics were performed with respect to the efficacy endpoints.

Sensitivity analyses

The same analysis approach used in the mITT analysis set was also used in the ITT, Treatment-Emergent Safety, and ITT-Total analysis sets for sensitivity analyses. Two additional Treatment-Emergent Safety sensitivity analyses were performed on the primary efficacy endpoint, censoring events 7 days or 30 days after last dose of study drug (as compared with 2 days after last dose in the original Treatment-Emergent Safety analysis set). A per protocol analysis was also performed on the primary efficacy endpoint using the mITT analysis set, excluding subjects who had selected major protocol deviations (that is, received the wrong medication kit, randomised but never received study drug, or not withdrawn as per protocol). A sensitivity analysis of the primary efficacy endpoint was also performed using investigator-reported events instead of adjudicated events. The analysis methods replicated that used for the primary efficacy analysis.

Components of composite endpoints

The components of the various composite endpoints were also evaluated to gain a better understanding about what contributed to the composite treatment effect.

6.1.1.4. Evaluator's comment

The statistical methods are conventional and appropriate and are considered to be acceptable.

According to the SAP, stent thrombosis was initially only to be summarised by treatment group as it was not a formal study endpoint, yet a full post-hoc analysis was performed and based on these results prevention of stent thrombosis is now sought in the indication. This is not considered appropriate and an alternative wording for the indication was proposed by the evaluator.

6.1.1.4.1. Participant flow

The study screened 15,932 subjects for eligibility; 15,526 (97.5%) subjects were randomised 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%]).

Of the 15,526 subjects randomised, 15,342 (98.8%) subjects (5,114 in the 2.5 mg bd group, 5,115 in the 5 mg bd group, and 5,113 in the placebo group) were included in the efficacy population, and 15,350 (98.9%) subjects (5,115 in the 2.5 mg bd group, 5,110 in the 5 mg bd group, and 5,125 in the placebo group) received at least 1 dose of study drug and were included in the safety population (Table 7, below).

Table 7. Number of randomised subjects (study TIMI 51; all randomised subjects)

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

Note: All randomized subjects constitute the Intent-to-Treat population.
Note: The safety population includes all subjects who received at least one dose of study drug.
Note: * excluding sites 091001, 091019 and 091026.
Note: Percentages calculated with the number of subjects in each subject stratum and treatment group as denominator.
Note: ASA = Acetylsalicylic acid; Thieno = Thienopyridine.

Subject disposition in the efficacy analysis set was summarised in the study report. The vast majority of subjects (14,473/15,526, 93.2%) were randomised to Stratum 2 (ASA + thienopyridine). Approximately 85% of subjects completed the study in each treatment group. There were some differences among treatment groups in the reasons for premature discontinuation from the study (for example, more subjects treated with rivaroxaban (8.6%) withdrew consent compared with subjects on placebo (7.8%). As previously mentioned, 184 subjects from 3 sites were excluded from all efficacy analyses due to potential trial misconduct. The number of excluded subjects was approximately the same across treatment groups; there were proportionally fewer subjects excluded from Stratum 1 compared with Stratum 2.

Premature discontinuations for adverse events (AEs) were reported for the safety analysis set. More rivaroxaban-treated subjects prematurely discontinued study drug due to an AE than placebo subjects in All Strata (9.8% and 7.3%, respectively) and Stratum 2 (10.0% and 7.3%,

respectively), with a higher percentage in the 5 mg bd group than in the 2.5 mg bd group. Stratum 1 had a similar pattern, but the percentage of subjects who prematurely discontinued study drug due to an AE was lower in all treatment groups, was similar in the 2.5 mg bd rivaroxaban (7.0%) and placebo (6.8%) groups, but was numerically higher in the 5 mg bd (7.9%) group. The higher discontinuation rate in the rivaroxaban groups was due, at least in part, to a higher percentage of bleeding-related treatment-emergent AEs leading to discontinuation observed in the 5 mg bd group (5.0%) compared with the 2.5 mg bd (3.6%) and placebo (1.8%) groups.

Evaluator's comment

Within each stratum, the randomisation to each of 3 treatment groups was well balanced. However, the percentage of subjects who discontinued prematurely from the study was relatively high at ~15%, with about half of this due to withdrawal of consent. While the percentages were similar across treatment groups and strata, there is the potential for this to introduce bias and to limit the validity of the results. This is a key issue identified in the EU Guideline "*Points to Consider on Application with: 1. Meta-Analyses; 2. One Pivotal Study*". The FDA considered this in their Briefing Document for the Cardiovascular and Renal Drugs Advisory Committee (CRDAC) on May 23 2012[6], and the reviewer decided that while not acceptable, it could be overlooked in the absence of additional information adversely affecting "*overall trial interpretability*". The CDRAC subsequently voted against approval of rivaroxaban for ACS.

Information will be requested from the sponsor comparing the demographic and baseline disease characteristics of those subjects who discontinued prematurely to those who completed the study (by Stratum) to better understand the potential bias this may have introduced.

6.1.1.4.2. Major protocol violations/deviations

Of the 15,526 randomised subjects in All Strata, 992 (6.4%) subjects had prospectively defined major protocol deviations, which was comparable across the treatment groups. The most common protocol deviation was not meeting the protocol-specified inclusion and exclusion criteria, affecting 639 (4.4%) of 14,473 subjects in Stratum 2 and 27 (2.6%) of 1,053 subjects in Stratum 1.

The most frequent protocol inclusion/exclusion criteria not met in All Strata were subjects 18 to 54 years old who did not have either diabetes mellitus or a prior MI (81 [0.8%] rivaroxaban subjects, 34 [0.7%] placebo subjects), prior ischemic stroke or TIA in subjects who the investigator planned to include in Stratum 2 (64 [0.6%] rivaroxaban subjects, 29 [0.6%] placebo subjects), and subjects not currently receiving ASA therapy (75 to 100 mg/day) at randomisation (57 [0.6%] rivaroxaban subjects, 24 [0.5%] placebo subjects).

In Stratum 1, 19 (1.8%) of 1,053 subjects were randomised into the wrong stratum compared with 23 (0.2%) of 14,473 subjects in Stratum 2. In All Strata, 176 (1.1%) subjects were randomised and never treated with study drug (summarised as "*Other*"), 78 (0.5%) subjects received the incorrect medication kit, and 70 (0.5%) subjects did not withdraw as per protocol.

Evaluator's comment

The distribution of protocol deviations was generally similar across treatment groups and / or the absolute numbers were small, and it is therefore considered unlikely to have affected the conclusions of the study.

[6] FDA Briefing Document for the Cardiovascular and Renal Drugs Advisory Committee (CRDAC). <http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/CardiovascularandRenalDrugsAdvisoryCommittee/UCM304755.pdf. Accessed 30/05/2012>

6.1.1.4.3. Baseline data

The baseline demographics and disease characteristics were generally well balanced across the treatment groups although some between strata differences were noted. Overall, approximately 75% of subjects were male, the mean age was 62 years (36.5% aged 65 years or older and 9.0% aged 75 years or older) and ~73% were White. There were relatively few subjects enrolled with moderate to severe renal impairment (7.1% subjects with baseline CrCl <50 mL/min), and the majority of subjects had at least one CV risk factor, such as hypertension (67%), DM (32%), history of MI (27%), or hypercholesterolemia (49%).

The admitting diagnosis was STEMI in approximately half of the subjects randomised, with NSTEMI and UA each comprising about 25% of the ACS index events. For subjects with unstable angina, more than 75% of subjects had a TIMI risk score of 3 or 4. On average, subjects were randomised 4.7 days following the index event. There were 9,387 (60.5%) subjects who had a revascularisation procedure for the index event, predominantly PCI (99%). Among subjects with a STEMI index event, 2,003 (25.6%) subjects were given fibrinolytic therapy. There was a low incidence of subjects with prior stroke and prior TIA consistent with the protocol.

The demographic and baseline characteristics in Stratum 2 were similar to those for All Strata; however there were some notable differences in Stratum 1. Compared with Stratum 2, subjects in Stratum 1 were older (mean age 61.6 versus 64.1 years) with a higher proportion aged 65 years or older (35.7 versus 47.5%) and 75 years or older (8.6 versus 16%) and there were proportionally more women (23.8 versus 45.4%). Compared with Stratum 2, a higher percentage of subjects in Stratum 1 had a history of prior MI (26.2 versus 37.5%), diabetes (31.4 versus 39.7%), hypertension (66.1 versus 85.3%) and moderate to severe renal impairment (6.5 versus 14% subjects with baseline CrCl <50 mL/min). The majority of the 1,053 subjects in Stratum 1 had an index event of unstable angina (59.0%), while 23.7% subjects had NSTEMI and 17.3% subjects had STEMI. Substantially fewer subjects (6.6%) had revascularisation procedures for the index event, and higher percentages of subjects underwent CABG as part of their revascularisation. As would be expected based on the protocol exclusion criteria, very few subjects in Stratum 2 had a history of prior ischemic stroke (0.9%) or TIA (0.6%) compared with Stratum 1 (15.1% and 4.5%, respectively).

Evaluator's comment

The baseline demographics and disease characteristics of Stratum 1 generally identify the participants as being at higher risk of the efficacy endpoints compared with Stratum 2.

Prior therapies

Medications received prior to the randomisation date were considered prior medications, even if the subject continued on the medication concomitantly with the study drug. Overall, the most common medications taken prior to randomisation were: ASA (98.6%), beta-blockers (66.1%), ACE inhibitors or angiotensin receptor blockers (39.0%), and calcium channel blockers (15.0%). As expected, the vast majority (98.0%) of subjects in Stratum 2 were receiving a thienopyridine prior to randomisation compared with only 22.0% of 1,053 randomised subjects in Stratum 1. Prior use of statins was also more common among subjects in Stratum 2 (84.6%) than in Stratum 1 (69.2%). Within each stratum, the use of these prior medications of interest was similar across treatment groups.

Concomitant ASA and thienopyridine

Concomitant use of ASA and thienopyridine during the double-blind treatment period was summarised in the study report. Of 15,350 subjects who received at least one dose of study drug, only 10 subjects (all in Stratum 2) did not receive ASA therapy during the double-blind treatment period. In Stratum 2, 99.4% of subjects received a thienopyridine and the majority received clopidogrel (98.8%); the use of ticlopidine (0.9%) and other thienopyridines (0.4%) was minimal. Thienopyridine use in Stratum 1 overall was expectedly lower (13.6%) than in

Stratum 2 and, based on median exposure, transient in nature; use of a concomitant thienopyridine in Stratum 1 was lowest in the 5 mg bd group (11.7%), followed by 2.5 mg bd (14.0%) and placebo (15.1%).

Since this was an event-driven study, subjects were exposed to concomitant ASA and thienopyridine for varying lengths of time, depending on when they were randomised. In All Strata, across all treatment groups, more than 75% of subjects were exposed to concomitant ASA for ≥ 6 months, more than half for ≥ 12 months, and almost one-third were exposed for ≥ 18 months. For thienopyridine the cumulative duration of exposure was ≥ 6 months in 72.9%, ≥ 12 months in 45.4%, and ≥ 18 months in 19.4% subjects. Total and median exposure for both drugs was generally lower in the 5 mg bd rivaroxaban group than either the 2.5 mg bd or placebo group, suggested by the sponsor to be due to the higher rate of premature discontinuation from double-blind treatment observed in the 5 mg bd group.

Other concomitant medications

Concomitant medication use other than ASA and thienopyridines was at the discretion of the managing clinician. The most common classes of concomitant medications taken at or after randomisation by ≥10% of subjects in any treatment group were: platelet aggregation inhibitors (excluding heparin) (>99.9%), HMG CoA reductase inhibitors (61.8%), selective beta-blocking agents (51.3%), ACE inhibitors (48.3%), organic nitrates (32.1%), proton pump inhibitors (PPIs) (25.7%), dihydropyridine derivatives (15.4%), sulfonamides (14.4%), heparins (13.0%), benzodiazepine derivatives (12.7%), angiotensin II antagonists (12.1%), H2 ⊣receptor antagonists (11.4%) and biguanides (10.3%). Use of these concomitant medications was broadly similar across the treatment groups.

Evaluator's comment

Baseline demographics, disease characteristics and concomitant medication usage were generally representative of a moderate-to-high-risk population of subjects with ACS who would be eligible to receive rivaroxaban if the submission is approved, and were generally well balanced across the treatment groups. There were some between strata differences and more variability in Stratum 1 due to the smaller number of subjects. This further highlights issues with interpretation of the results in Stratum 1.

6.1.1.4.4. Results for the primary efficacy outcome

The results for the composite primary efficacy endpoint of CV death, MI, or stroke are summarised below in Table 8 and Figure 4 (All Strata only).

For subjects in All Strata, the combined rivaroxaban group was superior to placebo in reducing the occurrence of the composite primary efficacy endpoint of CV death, MI, or stroke (6.1% versus 7.4%; HR: 0.84; 95% CI: 0.74-0.96; p=0.008). Further, the individual rivaroxaban doses each achieved superiority to placebo for the primary efficacy endpoint: 2.5 mg bd - 6.1% versus 7.4%; HR: 0.84; 95% CI: 0.72-0.97; p=0.020 and 5 mg bd - 6.1% versus 7.4%; HR: 0.85; 95% CI: 0.73-0.98; p=0.028.

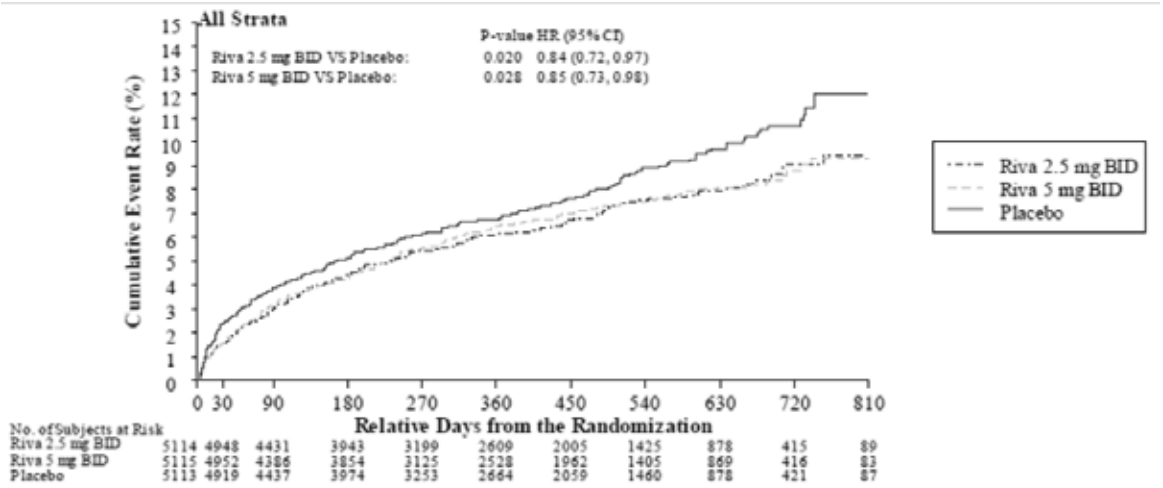
The effect of rivaroxaban 2.5 mg bd on the primary efficacy endpoint was largely driven by the reduction in CV deaths (HR: 0.66, 95% CI: 0.51 - 0.86, p= 0.002); whereas the effect in the 5 mg bd group was largely driven by the reduction in MIs (HR: 0.79, 95% CI: 0.65 - 0.97, p= 0.020), although with a higher proportion of fatal MIs.

Rivaroxaban was also superior to placebo in Stratum 2 for subjects in the combined rivaroxaban group (6.0% versus 7.1%; HR: 0.86; 95% CI 0.75-0.98; p=0.024) and in the 2.5 mg bd group (6.0% versus 7.1%; HR: 0.85; 95% CI: 0.72-0.99; p=0.039); in the 5 mg bd group the favourable HR did not reach statistical significance for superiority (6.1% versus 7.1%; HR: 0.87; 95% CI: 0.74-1.01; p=0.075).

Similar to All Strata, in Stratum 2 the effect of rivaroxaban 2.5 mg bd on the primary efficacy endpoint was largely driven by the reduction in CV deaths (HR: 0.62, 95% CI: 0.47 - 0.82, p=<0.001), whereas in the 5 mg bd group there was a numerically larger reduction in MIs (HR: 0.83, 95% CI: 0.68-1.02, p=0.077).

In Stratum 1, although the HR point estimates were the most favourable (7.3% versus 10.2%; HR: 0.69, 95% CI: 0.45 - 1.05; p=0.084, for combined rivaroxaban versus placebo, respectively) they were not statistically significant. The effect of rivaroxaban 2.5 mg bd was driven by the numerical reduction in MIs (HR: 0.72, 95% CI: 0.38 - 1.37) and strokes (HR: 0.28, 95% CI: 0.06 - 1.37), while the 5 mg bd group was driven by the reduction in MIs alone (HR: 0.44, 95% CI: 0.21 - 0.93).

Figure 4. Kaplan-Meier estimates of the primary efficacy endpoint for all strata (study TIMI 51: mITT analysis set)



The primary efficacy endpoint results were robust, with sensitivity analyses generally consistent with the results of the primary efficacy analysis (mITT). In particular, the superiority of the combined, 2.5 mg bd and 5 mg bd rivaroxaban treatment groups compared to placebo was confirmed in the ITT and ITT-Total analysis sets for All Strata. However in Stratum 2, the favourable but non-significant risk reduction seen with the 5 mg bd rivaroxaban group in the mITT analysis set was statistically significant when based on the ITT or ITT-Total analysis set. Sensitivity analyses including those sites excluded from the study for misconduct were not found in the dossier. However in the FDA Briefing Document for the Cardiovascular and Renal Drugs Advisory Committee (CRDAC) on May 23 2012[7], sensitivity analyses were conducted with these sites included and were consistent with the mITT results.

The results for each of the individual components of the primary composite endpoint will be discussed under *Results for other efficacy outcomes*.

Subgroup analyses

In general, the HR favoured rivaroxaban across the majority of subgroups for the combined rivaroxaban group compared with placebo. A similar pattern of improved outcomes was seen for the 2.5 mg and 5 mg rivaroxaban groups, and in Stratum 2. Due to the small number of subjects and events in Stratum 1 and the resulting wide confidence intervals, these subgroup analyses are difficult to interpret.

[7] FDA Briefing Document for the Cardiovascular and Renal Drugs Advisory Committee (CRDAC). <http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/CardiovascularandRenalDrugsAdvisoryCommittee/UCM304755.pdf. Accessed 30/05/2012>

There was a nominally significant interaction for history of CHF, with these subjects appearing to derive a greater benefit from rivaroxaban treatment (All Strata/rivaroxaban combined doses: HR: 0.59, 95% CI: 0.45 - 0.78) compared with subjects who did not have prior CHF (HR: 0.92, 95% CI: 0.79 - 1.06) across both rivaroxaban doses in All Strata and Stratum 2. Conversely, subjects with a history of ischemic stroke or TIA derived no benefit when treated with rivaroxaban (HR: 1.57, 95% CI: 0.75 – 3.31) compared with subjects who did not have prior ischemic stroke or TIA (HR: 0.82 95% CI: 0.72 - 0.94); the interaction was nominally significant for the 2.5 mg bd rivaroxaban group compared with placebo in All Strata.

Evaluator's comment

While rivaroxaban was statistically superior to placebo in reducing the occurrence of the composite primary efficacy endpoint, it should be noted that it did not reach the 22.5% relative reduction (hazard ratio=0.775) used by the sponsor when calculating the number of primary efficacy endpoint events required in the study. It could be assumed that this relative reduction was considered the minimal clinically important difference, in which case rivaroxaban has not delivered this benefit (although the HR of 0.775 was included in the 95% CIs of the results). The sponsor will be asked to provide the reasons behind the choice of relative risk reduction used to calculate the number of primary efficacy endpoints required for the study.

While not statistically significant, study participants aged ≥ 75 years appeared to derive less benefit than younger subjects. For example, in All Strata/2.5 mg bd rivaroxaban, the HR for subjects aged ≥ 75 years was 0.90 (95% CI: 0.62 - 1.30) compared with HR: 0.77, 95% CI: 0.53 - 1.13) in those aged < 55 years. This is important in light of the higher rate of Non−CABG related TIMI Major Bleeding Events in older subjects (discussed under *All adverse events* below).

Table 8. Effect of rivaroxaban compared with placebo on the primary and selected secondary efficacy endpoints (study TIMI 51; mITT analysis set)

Subject Stratum	Rivaroxaban									
	2.5 mg bd	5 mg bd	Combined	Placebo	2.5 mg bd versus Placebo		5 mg bd versus Placebo		Combined versus Placebo	
	n (%)	n (%)	n (%)	n (%)	HR (95% CI)	Log-Rank P-value	HR (95% CI)	Log-Rank P-value	HR (95% CI)	Log-Rank P-value
All Strata (N)	5114	5115	10229	5113						
CV Dth/	31	31	626 (6.1	376	0.84 (0.72	0.	0.85	0.0	0.84 (0.7	0.

Subject Stratum	Rivaroxaban									
	2.5 mg bd	5 mg bd	Combined	Placebo	2.5 mg bd versus Placebo		5 mg bd versus Placebo		Combined versus Placebo	
	n (%)	n (%)	n (%)	n (%)	HR (95% CI)	Log-Rank P-value	HR (95% CI)	Log-Rank P-value	HR (95% CI)	Log-Rank P-value
MI/St	3 (6.1)	3 (6.1)	)	(7.4)	, 0.97)	020	(0.73, 0.98)	28	4, 0.96)	008
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
ASA (N)	349	348	697	353						
CV Dth/	27	24	51 (7.3	36 (1	0.74 (0.45	0.	0.64	0.0	0.69 (0.4	0.

Subject Stratum	Rivaroxaban									
	2.5 mg bd	5 mg bd	Combined	Placebo	2.5 mg bd versus Placebo		5 mg bd versus Placebo		Combined versus Placebo	
	n (%)	n (%)	n (%)	n (%)	HR (95% CI)	Log-Rank P-value	HR (95% CI)	Log-Rank P-value	HR (95% CI)	Log-Rank P-value
MI/St	(7.7)	(6.9)	)	0.2)	,1.22)	234	(0.38, 1.07)	89	5, 1.05)	084
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
ASA + Thieno (N)	4765	4767	9532	4760						
CV Dth/MI/S	286	289	575 (6.0)	340 (7.	0.85 (0.72,	0.0	0.87 (0.	0.07	0.86 (0.75,	0.0

Subject Stratum	Rivaroxaban									
	2.5 mg bd	5 mg bd	Combined	Placebo	2.5 mg bd versus Placebo		5 mg bd versus Placebo		Combined versus Placebo	
	n (%)	n (%)	n (%)	n (%)	HR (95% CI)	Log-Rank P-value	HR (95% CI)	Log-Rank P-value	HR (95% CI)	Log-Rank P-value
t	(6.0)	(6.1)		1)	0.99)	39	74, 1.01)	5	0.98)	24
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

Note: The data shown are for all randomised subjects and the endpoint events occurring at or after randomisation and the earliest date of the global treatment end date, 30 days after study drug was prematurely discontinued and 30 days after randomisation for those subjects who were randomised 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/MI/St: first occurrence of cardiovascular death, MI or stroke; 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; 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.

6.1.1.4.5. Results for other efficacy outcomes

Secondary efficacy endpoints

As per the hierarchical testing strategy (discussed above), analysis of the first secondary endpoint only occurred for those rivaroxaban doses in the strata with significant results for the primary endpoint, and likewise for each subsequent secondary endpoint. Therefore, the combined rivaroxaban and the 2 individual dose groups were tested in the 1st secondary efficacy endpoint analyses for All Strata, but only the 2.5 mg bd dose in Stratum 2.

The results of the 1st and 2nd secondary efficacy endpoint analyses are summarised in Table 8. All 4 secondary efficacy endpoints and the individual components of the composite secondary endpoints were summarised the study report but not shown here.

Secondary efficacy endpoint 1: composite of all-cause death, MI, or stroke

As this endpoint was very similar to the primary efficacy endpoint (CV deaths replaced by all cause death, and 92% of all-cause deaths adjudicated as having CV causes), the results of secondary efficacy endpoint 1 were consistent with those of primary efficacy endpoint. In All Strata, rivaroxaban significantly reduced the occurrence of secondary efficacy endpoint 1 events compared with placebo in the combined doses group (HR: 0.84; 95% CI: 0.74-0.95; p=0.006) and the 2 individual dose groups - 2.5 mg bd (HR: 0.83; 95% CI: 0.72-0.97; p=0.016) and 5 mg bd (HR: 0.84; 95% CI: 0.73-0.98; p=0.025).

In Stratum 2, a statistically significant reduction in the occurrence of secondary efficacy endpoint 1 was observed in the rivaroxaban 2.5 mg bd group compared with the placebo group (HR: 0.84; 95% CI: 0.72 - 0.98; p = 0.028).

In All Strata, Stratum 2 and Stratum 1, the Kaplan-Meier plot closely mirrored those in the primary efficacy endpoint analyses.

Secondary efficacy endpoint 2: net clinical outcome (composite of CV death, MI, ischemic stroke and non-CABG TIMI major bleeding events)

As a result of the analyses in secondary endpoint 1, the combined rivaroxaban and the 2 individual dose groups were tested in secondary efficacy endpoint 2 analyses for All Strata, and for the 2.5 mg bd dose in Stratum 2.

Neither the combined rivaroxaban doses nor each individual dose demonstrated a statistically significant reduction compared with placebo in secondary efficacy endpoint 2 for All Strata or Stratum 2; therefore hierarchical testing for the remaining secondary endpoints was stopped.

Individual components of the composite efficacy endpoints

Results for the individual components of the composite primary and composite secondary endpoints were summarised in the study report.

Cardiovascular-related deaths

In All Strata and Strata 2, both the 2.5 mg bd and combined rivaroxaban groups were superior to placebo in reducing the incidence of CV deaths, and this largely drove the effect of rivaroxaban 2.5 mg bd on the primary efficacy endpoint. In All Strata the 2.5 mg bd versus placebo result was: 1.8% versus 2.8%; HR: 0.66; 95% CI 0.51-0.86; p=0.002.

All-cause deaths

The results for all-cause deaths mirror those of CV deaths, as CV deaths comprised the majority of all-cause deaths

Myocardial infarctions

Rivaroxaban 5 mg bd was the only individual dose that demonstrated a significant reduction in MIs, both in All Strata (3.5% versus 4.5%; HR: 0.79; 95% CI 0.65-0.97; p=0.020) and Stratum 1 (2.9% versus 6.2%; HR: 0.44; 95% CI 0.21-0.93; p=0.026), with the combined dose being significant in All Strata only. This largely drove the effect of rivaroxaban 5 mg bd on the primary efficacy endpoint. Of note, the percentage of fatal MIs was higher with the 5 mg rivaroxaban dose compared with the 2.5 mg dose, and this contributed to the higher CV deaths in the 5 mg group.

Stroke

With the exception of the 2.5 mg and combined rivaroxaban groups in Stratum 1, strokes (including ischaemic, hemorrhagic, and uncertain types) were numerically higher in the rivaroxaban groups compared with the placebo groups (such as All Strata: 0.9%, 1.1% and 0.8% for the 2.5 mg, 5 mg and placebo groups respectively). This was largely due to a higher incidence of haemorrhagic strokes in the rivaroxaban treatment groups. Fatal strokes were slightly higher in the 5 mg rivaroxaban group compared to the 2.5 mg rivaroxaban and placebo groups.

Ischaemic stroke

The incidence of ischaemic stroke was similar across the rivaroxaban and placebo groups with the exception of Stratum 1 where they were numerically lower in those subjects on rivaroxaban (particularly the 2.5 mg group), but overall numbers were also very small in this Stratum.

Severe recurrent ischemia

Severe recurrent ischemia requiring revascularisation (SRIR) and severe recurrent ischemia requiring hospitalisation (SRIH) were components of secondary efficacy endpoints 3 and 4, respectively. Incidence of SRIR was comparable across the rivaroxaban and placebo groups in All Strata, while the incidence of SRIH was numerically lower in the rivaroxaban compared to the placebo group but the differences were not statistically significant.

Stent thrombosis

In a post-hoc analysis of "*definite*", "*probable*" or "*possible*" stent thromboses, there was a nominally significant reduction in incidence in the combined, 2.5 mg and 5 mg rivaroxaban groups (all 1.2%) compared with placebo (1.7%) in All Strata, with similar results in Stratum 2. When only cases that were "*definite*" or "*probable*" are considered, the rates were 0.7% and 0.8% for the 2.5 mg bd and 5 mg bd groups, respectively, and 1.2% for the placebo group.

Off-treatment endpoint events

The following endpoints were included in off-treatment analyses: composite of CV Death, MI, Stroke; composite of Death, MI, Stroke; and their component endpoints. In general, endpoint events after the last dose of rivaroxaban were well-balanced across the combined rivaroxaban and placebo groups. There was no evidence of increased risk for off-treatment endpoint events up to 30 days following the last dose of rivaroxaban. Rivaroxaban 2.5 mg bd generally had a lower incidence of events compared with placebo, while a higher incidence of events was generally observed in the 5 mg bd group compared with both the 2.5 mg bd group and placebo. This was consistent across subjects who discontinued at any time during the trial and those who completed the double blind treatment period. The exception to this was the incidence of MI up to ~10 days after the last dose of rivaroxaban, which was higher in the rivaroxaban groups [for example, at 1 to 10 days from the last dose, combined rivaroxaban 62/9,864 (0.6%), 2.5 mg bd 26/4,940 (0.5%), 5 mg bd 36/4924 (0.7%), versus placebo 17/4910 (0.3%)].

Evaluator's comment

It is unclear why rivaroxaban has inconsistent results on the individual components of the composite efficacy endpoints depending on the dose and strata, and whether these differences are biologically plausible. The lack of similar findings on all important endpoints is a key issue identified in *the EU Guideline* "Points to Consider on Application with: 1. Meta-Analyses; 2. One Pivotal Study". Because the study was not powered to look at these endpoints it is not known whether these differences are a chance finding.

According to the SAP, stent thrombosis was initially only to be summarised by treatment group as it was not a formal study endpoint, yet a full post-hoc analysis was performed and based on these results prevention of stent thrombosis is now sought in the indication. This is not considered appropriate. The primary and secondary endpoints were all composite endpoints and subject to hierarchical testing. If stent thrombosis were to be considered it should have been subject to these same criteria.

The increased incidence of MI 1 to 30 days after the last dose of rivaroxaban, may be a chance finding as it was not reflected in the other endpoints.

6.1.2. Other efficacy studies

6.1.2.1. Study 11898 (ATLAS ACS TIMI 46)

This study has previously been evaluated as part of a specific condition of the original registration of Xarelto 10 mg. Therefore only a brief summary of the methods will be presented here, followed by the key findings as reported in the earlier evaluation.

TIMI 46 was a randomised, multicentre, double-blind, placebo-controlled Phase II study designed to evaluate the safety and efficacy of rivaroxaban in subjects with recent ACS who received standard of care background ASA therapy without the intention to use thienopyridine therapy (Stratum 1, ASA only) or with the intention to use thienopyridine therapy (Stratum 2, ASA plus thienopyridine).

A total of 3,576 subjects were screened for study eligibility and 3,491 subjects were randomly assigned to treatment. Of the 3,491 randomised subjects, 761 subjects were included in Stratum 1, and 2,730 subjects were included in Stratum 2. Patients were randomised to 8 treatment groups: rivaroxaban at 2.5, 5, or 10 mg bd (5, 10, or 20 mg total daily dose [TDD]), rivaroxaban at 5, 10, or 20 mg once daily in the evening (with a placebo dose in the morning), or placebo. In Stratum 2, an additional 2 treatment groups (rivaroxaban 7.5 bd or 15 mg once daily) were included. Study drug was taken with or without food. Planned duration of treatment was 6 months. There were 2,331 subjects randomly assigned to the rivaroxaban groups and 1,160 subjects were randomly assigned to placebo.

The primary efficacy endpoint was the composite of all cause death, MI (or repeat MI [reMI]), stroke (ischemic, hemorrhagic, or unknown), or SRI requiring revascularisation (not an endpoint in TIMI 51) and the key secondary efficacy endpoint was the composite of death, MI (or reMI) or stroke (the primary efficacy endpoint in TIMI 51).

The analysis methods were similar to those used in TIMI 51 [stratified log-rank test of combined rivaroxaban versus placebo, cumulative risk over time estimated using the Kaplan-Meier method by treatment group and strata, and a Cox proportional-hazards regression model to estimate the hazard ratio of a rivaroxaban group compared with the placebo group and its associated 95% confidence interval (CI)].

The evaluator's conclusions on the efficacy of rivaroxaban have been reproduced below, and a summary of the key results provided below in Table 9:

> *Overall, the number of efficacy events was relatively small, making it difficult to accurately estimate effect size. The results of the efficacy analyses demonstrated that:*

- *Rivaroxaban appeared to demonstrate some efficacy with a relative reduction in the risk of firstly the composite endpoints of* (all cause) *death, MI, stroke or severe recurrent ischaemia requiring revascularisation of 16% and of secondly the composite endpoint of* (all cause) *death, MI or stroke of 24%. However, at this stage these results are indicative of a trend only since they were not statistically significant. They need to be replicated in a larger, Phase 3 trial which was always the primary objective of this study.*
- *The efficacy results were more favourable for subjects in Stratum I (aspirin alone). It was noted, in Stratum 2, that rivaroxaban at doses of 2.5 mg and 5 mg twice daily resulted in 71 % and 37% relative risk reductions, respectively, in the composite endpoint of death, MI or stroke. However, these results must be interpreted very cautiously since, as has been pointed out earlier, the study was not powered to assess treatment effects by particular dose regimens. Furthermore, the group with the most outstanding result, namely those who took 2.5 mg bd only had a relatively small number of subjects in comparison with the other groups.*
- *The twice daily rivaroxaban dosing regimen showed a trend to a numerically greater effect on the primary and key secondary efficacy endpoints than the once daily regimen.*
- *The rivaroxaban 2.5 mg and 5 mg twice daily dosing regimens appeared to be the most promising. Across both strata, rivaroxaban at doses of 2.5 mg and 5 mg twice daily resulted in 35% and 14% reductions, respectively, in relative risk of the pre-specified net clinical benefit endpoint. Once again the same caveats apply to the interpretation of these results.*

Table 9. Treatment effect of primary and key secondary efficacy endpoints for the combined rivaroxaban dose groups* as adjudicated by the CEC (study TIMI 46: ITT analysis set)

Endpoints	Rivaroxaban K/N (%)	Placebo K/N (%)	Hazard Ratio (95% CI)
Combined strata			
Primary	141/2331 (6.0)	83/1160 (7.2)	0.84 (0.64,1.10)
Key 2nd	101/2331 (4.3)	66/1160 (5.7)	0.76 (0.55,1.03)
Stratum 1			
Primary	40/508 (7.9)	34/253 (13.4)	0.57 (0.36,0.90)
Key 2nd	35/508 (6.9)	29/253 (11.5)	0.59 (0.36,0.96)
Stratum 2			
Primary	101/1823 (5.5)	49/907 (5.4)	1.03 (0.73,1.45)
Key 2nd	66/1823 (3.6)	37/907 (4.1)	0.89 (0.59,1.33)

K/N: # of events / # of randomized subjects
Intention to treat analysis based on adiudicated events

*Rivaroxaban doses included: 2.5 mg, 5 mg, 7.5 mg, or 10 mg twice daily; and 5 mg, 10 mg, 15 mg, and 20 mg once daily

Evaluator's comment

The current evaluator agreed with the previous evaluator's efficacy conclusions. TIMI 46 identified rivaroxaban 2.5 mg and 5 mg bd as the most promising dosing regimens based on safety and efficacy, to be taken forward into the Phase III (TIMI 51) trial. The higher relative risk reductions (compared with TIMI 51) noted for the 2.5 mg and 5 mg bd doses in the composite endpoint of death, MI or stroke are likely due to chance as the study was not powered to assess treatment effects by particular dose regimens and the number of subjects and endpoints in these dose groups was small.

As the appendices had not been submitted with the TIMI 46 CSR at the time of its evaluation, the current evaluator reviewed the appendices supplied with this submission but found no data necessitating further evaluation, or altering the conclusions reached.

6.1.3. Analyses performed across trials (pooled analyses and meta-analyses)

No efficacy analyses have been performed across trials.

6.2. Evaluator's conclusions on clinical efficacy

The pivotal efficacy study (TIMI 51) compared 2 doses of rivaroxaban, 2.5 mg bd and 5 mg bd, with placebo, in addition to standard care (ASA alone [Stratum 1] or ASA plus thienopyridine [Stratum 2]) on the ability to reduce CV events in subjects with ACS. The overall results were driven by the results of Stratum 2, which recruited in excess of 92% of the study subjects. The study had some methodological limitations including: the small size of Stratum 1 (based on a change in clinical practice), and use of an mITT analysis rather than ITT, but the major concern is the large number of subjects who discontinued treatment (~15%) as this may have introduced bias and compromised the internal validity of the results. Internal validity has been identified by the CPMP as a critical issue "where the confirmatory evidence is provided by one pivotal study only".

The key efficacy findings were:

- In All Strata, the combined, 2.5 mg bd and 5 mg bd rivaroxaban doses were all superior to placebo in reducing the thrombotic events of the composite primary efficacy endpoint (CV death, MI, or stroke); (HR: 0.84; 95% CI: 0.74-0.96; p=0.008; HR: 0.84; 95% CI: 0.72-0.97; p=0.020 and HR: 0.85; 95% CI: 0.73-0.9; p=0.028, respectively). This was true for both the mITT and ITT analyses. The degree of statistical significance is "considerably stronger than p<0.05" as required when a single pivotal study is the source of evidence. The efficacy benefit would appear to be clinically relevant although the16% reduction in the primary efficacy endpoint did not reach the 22.5% reduction used by the sponsor when determining the number of primary efficacy endpoint events required in the study. It could be assumed that this relative reduction was considered the minimal clinically important difference, in which case rivaroxaban has not delivered this benefit.
- In Stratum 2, the combined and 2.5 mg bd doses were superior to placebo for the primary efficacy endpoint (HR: 0.86; 95% CI 0.75-0.98; p=0.024; HR: 0.85; 95% CI: 0.72-0.99; p=0.039).
- These primary efficacy results were largely driven by a reduction in CV deaths for rivaroxaban 2.5 mg bd, and by a reduction in non-fatal MIs for rivaroxaban 5 mg bd (fatal MIs were higher in the 5 mg bd group).
- Sensitivity analyses generally confirmed the results, although in the ITT analysis rivaroxaban 5 mg bd was also superior to placebo in Stratum 2.
- Stratum 1 failed to recruit the required subject numbers to reach the expected number of primary efficacy endpoints and hence the targeted study power for this stratum. Therefore, despite the most favourable HR point estimates, none of the rivaroxaban dose groups were superior to placebo for the primary efficacy endpoint. Patients in this stratum also had different baseline demographics and disease characteristics, and it could therefore be argued that rivaroxaban should not be recommended for use in patients intended to be treated with ASA alone.
- There was no clear dose-effect with respect to efficacy.
- While subgroup analyses generally showed an internally consistent benefit with rivaroxaban, of note was the apparent greater benefit derived from rivaroxaban in those subjects with a history of CHF, while conversely those subjects with a history of ischemic stroke or TIA derived no benefit when treated with rivaroxaban. Subjects aged ≥ 75 years appeared to derive less benefit than younger subjects.

- Results for the secondary efficacy endpoint (All cause death, MI, or stroke) mirrored those of the primary efficacy endpoint as the majority of deaths (92%) were CV in origin.
- In a post-hoc analysis fewer cases of definite or probable stent thrombosis were observed in both the rivaroxaban 2.5 mg bd and 5 mg bd rivaroxaban groups compared with placebo.
- Despite the shorter duration (6 months) of the dose-finding study (TIMI 46) and the small number of both subjects and endpoints in the 2.5 mg bd and 5 mg bd individual dose groups, it provided supportive, directionally consistent results to those of TIMI 51. The greater apparent reduction in death, MI and stroke (71%) with 2.5 mg bd rivaroxaban in TIMI 46 and in Stratum 1 compared with Stratum 2, is likely due to chance.

Based on the key efficacy findings, the 2.5 mg bd rivaroxaban dose is preferred to the 5 mg bd dose.

NB: only approval for the 2.5 mg bd dose is being sought by the sponsor for the ACS indication.

7. Clinical safety

The sponsor provided a side-by-side comparison of bleeding adverse events from the TIMI 46 and TIMI 51 studies, but the evaluator has used the results as presented in the original CSR for TIMI 51 and the previous evaluation for TIMI 46.

7.1. Studies providing evaluable safety data

The following studies provided evaluable safety data:

7.1.1. Pivotal efficacy study

In the pivotal efficacy study (TIMI 51), the following safety data were collected:

- TIMI major bleeding events not associated with CABG surgery (that is, non-CABG TIMI Major bleeding) as the primary safety endpoint
- other bleeding events
- serious adverse events
- adverse events leading to discontinuation of study drug
- adverse events of special interest

Adverse events were reported by the subject at each study visit throughout the study. Serious adverse events, adverse events leading to discontinuation of study drug, and adverse events of special interest were recorded in the CRF; other non-serious adverse events were not routinely recorded in the CRF (with the exception of Japan).

Adverse events of special interest were defined as:

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

Three bleeding event scales were used to classify bleeding events in the study: the *T*hrombolysis *I*n *M*yocardial *I*nfarction (TIMI) scale, the International Society on Thrombosis and Haemostasis (ISTH) major bleeding event classification, and the Global Strategies for Opening Occluded Coronary Arteries (GUSTO) scale. Similar to the efficacy endpoints, the same

independent CEC adjudicated and classified the bleeding events according to definitions in the CEC charter.

An Hepatic Event Assessment Committee (HEAC) reviewed all liver cases meeting predefined criteria. The HEAC was composed of 3 clinical reviewers and 2 pathology reviewers. The evaluations by the HEAC were performed in a blinded fashion for individual cases on an ongoing basis during clinical study conduct. Cases meeting any of the selection criteria listed below were assessed by the HEAC:

- Any ALT > 8xULN (includes symptomatic and asymptomatic cases)
- All deaths with ALT >3x ULN within 30 days of death
- Combined ALT >3xULN with total bilirubin >2x ULN
  - Concurrent elevations (concurrent refers to laboratory analyses drawn from the same sample)
  - Non-concurrent elevations if the ALT elevation is followed by a Total bilirubin elevation within 30 days,
- Other (includes cases of possible concern not meeting any of the 3 categories listed above).
- Cases under 'Other' were identified using 28 hepatic disorder adverse event terms that might indicate acute liver injury.

Laboratory tests (including haematology and serum chemistry) and clinical status were collected as per the study schedule.

7.1.2. Dose-response and non-pivotal efficacy studies

7.1.2.1. TIMI 46

Adverse events were reported by the subject at each study visit throughout the study and were documented in the CRF.

Adverse events of special interest included:

- Bleeding events
- Hepatic events

Bleeding events were classified into the following categories:

- Clinically Significant Bleeding, consisting of:
  - TIMI Major Bleeding: defined as any intracranial bleeding or clinically overt bleeding that was associated with a decrease in Hb of ≥5 g/dL or an absolute drop in haematocrit of ≥15%;
  - TIMI Minor Bleeding: defined as any clinically overt bleeding, including bleeding that is evident on imaging studies, that was associated with a decrease in Hb by ≥ 3 g/dL but <5 g/dL from baseline Hb value;
  - Bleeding Requiring Medical Attention: defined as any bleeding that required medical treatment, surgical treatment, or laboratory evaluation and did not meet criteria for major or minor bleeding, as defined above.
- Clinically insignificant bleeding: was defined as a reported blood loss or bleeding episode not meeting criteria for clinically significant bleeding.

All cases of bleeding were reviewed in a blinded fashion by an independent CEC.

Liver function was assessed during the conduct of the study by monitoring clinical hepatic adverse events and laboratory hepatic adverse events, detected by regular, scheduled, laboratory testing throughout the study.

Blood samples for serum chemistry, haematology, coagulation testing, and a urine sample for pregnancy test were also taken.

7.1.3. Other studies evaluable for safety only

Clinical pharmacology studies

- *Study 12361* recorded adverse events, vital signs (pulse rate, blood pressure, and body temperature), safety laboratory including coagulation parameters, and ECGs.
- *Study 12570* recorded adverse events, physical examination, vital signs (pulse rate, blood pressure), safety laboratory including coagulation parameters, ECG.
- *Study 12571* recorded adverse events, physical examination, vital signs (pulse rate, blood pressure), safety laboratory including coagulation parameters, ECG.
- *Study 14883* recorded adverse events, vital signs, 12-lead ECG, and clinical laboratory tests.

7.2. Pivotal studies that assessed safety as a primary outcome

Not applicable.

7.3. Patient exposure

7.3.1. Pivotal efficacy study

The All Strata treatment exposure data for TIMI 51 are summarised below in Table 10. The median total duration of treatment was 397.0 days (range: 1, 927) and 376.5 days (range: 1, 929) in the rivaroxaban 2.5 mg bd and 5 mg bd groups, respectively, and 399.0 days (range: 1, 932) 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, 30.9% for ≥ 18 months and 9.9% for ≥ 24 months, with rates similar for each treatment group.

Table 10. Total duration of treatment (including any study drug interruption) (study TIMI 51; 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
Cumulative duration of treatment, n (%)					
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)

7.3.2. Dose-response and non-pivotal efficacy studies

The exposure data for TIMI 46 are summarised below in Table 11. The median total duration of treatment was 182.0 days (range: 1, 204) in the rivaroxaban 5 mg TDD group, 181.0 days (range: 1, 219) for the 10 mg TDD group, and 181.0 days (range: 1, 243) in the placebo group for subjects in the safety population. Across the rivaroxaban groups, ≥80% had cumulative durations of exposure ≥ 6 months.

Table 11. Total duration of treatment (study TIMI 46; safety analysis set)

	Placebo	Rivaroxaban				
	(N=1153)	5 mg TDD (N=307)	10 mg TDD (N=1046)	15 mg TDD (N=353)	20 mg TDD (N=603)	Total (N=2309)
Total treatment duration[a], n (%)						
N	1153	307	1046	353	603	2309
<1 week	30 (2.6)	7 (2.3)	34 (3.3)	6 (1.7)	12 (2.0)	59 (2.6)
≥ 1 week - 1 month (<30 days)	27 (2.3)	8 (2.6)	38 (3.6)	16 (4.5)	26 (4.3)	88 (3.8)
≥ 1 month (30 days) - 3 months (<75 days)[b]	53 (4.6)	14 (4.6)	62 (5.9)	18 (5.1)	39 (6.5)	133 (5.8)
≥ 3 months (75 days) - 6 months (<165 days)[b]	73 (6.3)	17 (5.5)	74 (7.1)	34 (9.6)	41 (6.8)	166 (7.2)
≥ 6 months (≥165 days)[b]	970 (84.1)	261 (85.0)	838 (80.1)	279 (79.0)	485 (80.4)	1863 (80.7)
Total treatment duration (days)						
N	1153	307	1046	353	603	2309
Mean (SD)	163.58 (48.103)	164.47 (47.121)	157.93 (53.790)	159.05 (51.398)	158.22 (53.084)	159.05 (52.412)
Median	181.00	182.00	181.00	181.00	181.00	181.00
Range	(1.0; 243.0)	(1.0; 204.0)	(1.0; 219.0)	(2.0; 228.0)	(1.0; 219.0)	(1.0; 228.0)

TDD=Total Daily Dose.
[a] Duration of treatment is from first dose to last dose.
[b] Two-week (15 days) window to include early scheduled visit.
Missing date of last dose is imputed as the minimum of date of premature termination from study drug, death, and day 199.

7.3.2.1. Study 12361

Of the 24 subjects included, 23 completed the study according to protocol and received single doses of 2.5, 5 and 10 mg rivaroxaban according to protocol. Overall, each subject was exposed to 17.5 mg rivaroxaban. The subject who terminated the study prematurely after the second study period received single doses of 2.5 and 10 mg rivaroxaban.

7.3.2.2. Study 12570

Eleven subjects received a single rivaroxaban ER 12 mg tablet fasted (at least 10 hr fast) as well as with a high calorie, high fat breakfast and a single dose of rivaroxaban IR 10 mg tablet fasted (34 mg rivaroxaban). One subject received a single dose rivaroxaban ER 12 mg tablet with a high calorie, high fat breakfast (12 mg rivaroxaban).

7.3.2.3. Study 12571

Eleven subjects received a single rivaroxaban GITS 12 mg tablet fasted (at least 10 hr fast) as well as with a high calorie, high fat breakfast. In addition, all subjects received a single dose as a rivaroxaban IR 10 mg single dose tablet fasted.

7.3.2.4. Study 14883

Twenty-four subjects received rivaroxaban 15 mg once daily for 4 days, 12 had 6 days prior warfarin therapy.

7.4. Adverse events

7.4.1. All adverse events (irrespective of relationship to study treatment)

7.4.1.1. Pivotal study

As mentioned above, the TIMI 51 study did not routinely record non-serious adverse events (AEs), but focused on TIMI major bleeding events not associated with CABG surgery (that is, non-CABG TIMI major bleeding), other bleeding events, serious adverse events (SAEs), AEs leading to discontinuation of study drug, AEs of special interest and clinical laboratory tests. In addition, SAEs identified during the clinical development program of rivaroxaban and the post marketing surveillance (acute pancreatitis, thrombocytopenia, acute renal failure,

agranulocytosis, and hypersensitivity reaction) were also scrutinised. Bleeding events will be discussed in detail in below.

Overall, AEs were reported by 55 - 59% of subjects across all treatment groups, with the majority of these being treatment-emergent. The proportion of subjects with non-bleeding treatment-emergent adverse events (TEAEs) was similar across the rivaroxaban and placebo groups, affecting 47 – 49% of subjects. Treatment-emergent bleeding AEs were higher in the combined rivaroxaban groups (22.0%) than in the placebo group (12.5%), with more events in the 5 mg bd group (25.0%) than in the 2.5 mg bd group (19.0%). In All Strata, deaths occurred at similar rates in the rivaroxaban 5 mg bd (3.8%) and placebo groups (3.8%), and were numerically lower in the rivaroxaban 2.5 mg bd group (2.8%). A similar proportion and pattern of AEs was seen in Stratum 2.

In Stratum 1 the proportion of subjects with non-bleeding treatment-emergent adverse events (TEAEs) was lower than in All Strata or Stratum 2, but remained similar across the rivaroxaban and placebo groups, affecting 41 – 44% of subjects. Bleeding AEs were higher in the rivaroxaban groups (10.1%) than the placebo group (7.7%), and higher in the 5 mg bd group (12.6%) than in the 2.5 mg bd group (7.6%), but occurred less frequently than in All Strata and Stratum 2. The proportion of deaths was higher in Stratum 1, with more deaths occurring in the rivaroxaban 5 mg bd (4.7%) and 2.5 mg bd groups (5.5%), than in the placebo group (3.4%).

A total of 5,667 (55.4%) subjects in the combined rivaroxaban groups and 2,694 (52.6%) subjects in the placebo group reported TEAEs. The most frequently reported TEAEs in the pooled rivaroxaban group in All Strata were: angina (10.9%), epistaxis (6.0%), PCI (4.9%) and gingival bleeding (2.9%), with the bleeding TEAEs occurring more frequently in the 5 mg bd group than in the 2.5 mg bd group. The most frequently reported TEAEs in the placebo group were: angina (11.4%), PCI (4.7%) and epistaxis (2.8%). Stratum 2 was similar, but in Stratum 1 acute MI was also reported in at least 3% of subjects: rivaroxaban 2.5 mg bd (3.2%), rivaroxaban 5 mg bd (2.0%) and placebo (2.8%).

7.4.1.2. Other studies

7.4.1.2.1. TIMI 46

The AE comments from the earlier evaluation were:

Overall, the percentages of subjects who reported adverse events were comparable between the pooled rivaroxaban and placebo groups, 70.6% and 69.6%, respectively.

The overall incidences of the following adverse events were higher in the pooled rivaroxaban group compared with the placebo group:

- *Drug-related adverse events*
- *Drug-related treatment-emergent adverse events*
- *Drug-related serious adverse events*
- *Drug-related treatment-emergent adverse events*
- *Treatment-emergent bleeding adverse events*
- *Drug-related treatment-emergent bleeding adverse events*
- *Treatment-emergent bleeding serious adverse events*
- *Bleeding adverse events resulting in permanent discontinuation of study drug.*

After exclusion of all bleeding events, the incidences of all the foregoing types of adverse events were similar between the pooled rivaroxaban and placebo groups.

Overall, the percentages of subjects who reported treatment-emergent adverse events were comparable among the treatment groups. Other than for bleeding-related adverse events, there

were no notable differences in the incidences of treatment-emergent adverse events among placebo and rivaroxaban groups.

The most frequently reported treatment-emergent adverse events, i.e. those reported by at least 5% of subjects, in the pooled rivaroxaban group were chest pain (9.9%), epistaxis (8.6%), angina pectoris (5.2%) and gingival bleeding (5.1 %). The most frequently reported treatment-emergent adverse events in the placebo group were chest pain (9.5%) and angina pectoris (5.6%). The incidences of the following treatment-emergent bleeding adverse events were higher in the pooled rivaroxaban group compared with the placebo group: epistaxis (8.6% versus 2.3%), gingival bleeding (5.I % versus 1.1 %) and haematoma (3.0% versus 1.1 %).

7.4.1.2.2. Study 12361

TEAES were reported by 11/24 (46%) subjects -5/24 (21%) after 2.5 mg, 7/23 (30%) after 5 mg and 5/24 (21%) after 10 mg rivaroxaban. Of the 22 events, 14 were of mild, 7 of moderate, and one of severe intensity. The most common events were: increased lipase (n=5), headache (n=5), rhinitis (n=2), nasopharyngitis (n=2), and injection site haematoma (n=2). The moderate events were 5 episodes of headache, one case of thrombophlebitis and one case injection site haematoma. The severe event was an occurrence of CK elevation observed prior to dosing in Period 3 (5 mg) and 7 days after 2.5 mg rivaroxaban. CK values were increased to 13.9 times ULN. The elevation was explained by physical exercise during the wash-out phase. The 5 mg rivaroxaban dose was given and the CK declined and returned to normal limits within 7 days.

7.4.1.2.3. Study 12570

Some 5/12 healthy subjects (42%) reported 7 TEAEs, all of mild intensity. Incidence rates were 1/11 subjects (9%) after 12 mg ER fasted, 2/12 subjects (17%) after 12 mg ER fed and 3/11 subjects (27%) after 10 mg IR fasted. The events included nasopharyngitis (n=5), headache (n=1) and dyspnoea (n=1). All resolved.

7.4.1.2.4. Study 12571

No adverse events were reported in this study.

7.4.1.2.5. Study 14883

A total of 18 TEAEs were reported by 14 of the 36 subjects (38.9%). TEAEs occurred in 41.7% of the subjects during treatment with warfarin, in 16.7% of the subjects during or after rivaroxaban following warfarin, in 16.7% of the subject during or after placebo following warfarin and in 16.7% of the subjects during or after rivaroxaban alone. All AEs were of mild intensity. No TEAEs were reported in more than 2 subjects in any treatment group. Treatment-emergent bleeding events were reported in 4 subjects during treatment with warfarin; epistaxis (n=2) and gingival bleeding (n=2). All the bleeding events were transient.

7.4.2. Treatment-related adverse events (adverse drug reactions)

7.4.2.1. Pivotal studies

In All Strata, the incidence rate of drug-related adverse events was higher in the combined rivaroxaban group than in the placebo group (19.3% versus 11.6%). This was largely due to the higher rate of drug-related bleeding events in the rivaroxaban groups compared with the placebo groups (16.0% versus 8.0%), with incidence higher in the rivaroxaban 5 mg bd group (18.4%) compared with the 2.5 mg bd group (13.7%). By contrast, the number of subjects with at least 1 non-bleeding drug-related adverse event was similar between the 2.5 mg bd, 5 mg bd, and placebo groups (4.6%,. 5.3%, and 4.3%, respectively).

7.4.2.1.1. Bleeding events

All bleeding events, independent of severity or location, were adjudicated by the CEC members on 3 different bleeding scales, with the TIMI bleeding scale being the primary classification (as described above).

Table 12 below summarises the incidence of treatment-emergent bleeding events (TEBEs) in the treatment-emergent safety analysis set for All Strata, including the primary safety endpoint (non-CABG TIMI major bleeding). Rivaroxaban significantly increased the incidence of non-CABG TIMI major bleeding events compared with placebo, with rates of 1.4% (combined rivaroxaban), 1.3% (2.5 mg bd) and 1.6% (5 mg bd) versus 0.4% (placebo). This translates into: HR: 3.96 (95% CI: 2.46-6.38; p<0.001) for combined rivaroxaban; HR: 3.46 (95% CI: 2.08-5.77; p<0.001) for the 2.5 mg bd group, and HR: 4.47 (95% CI: 2.71-7.36; p<0.001) for the 5 mg bd group (

Figure 5, below). A very similar pattern was seen for Stratum 2, and was reflected in Stratum 1 but at much lower rates which did not reach statistical significance. Sensitivity analyses of the primary safety endpoint revealed similar results. The most frequently reported sites of TIMI major bleeding were gastrointestinal (0.9% versus 0.3%) and intracranial (0.3% versus 0.1%) in the combined rivaroxaban and placebo groups, respectively.

In All Strata, combined rivaroxaban also significantly increased the rates (2 to 3 fold) of clinically significant bleeding (13% versus 6.4%, p<0.001), TIMI bleeding requiring medical attention (11.0% versus 5.5%, p<0.001), TIMI minor bleeding (0.8% versus 0.4%, p=0.003), intracranial bleeding (0.3% versus 0.1%, p=0.009) and haemorrhagic stroke (0.3% versus 0.1%, p=0.006) compared with placebo. Rates were invariably higher in the rivaroxaban 5 mg bd group than in the 2.5 mg bd group. No difference in the rate of fatal bleeds was seen between combined rivaroxaban (0.2%) and placebo (0.2%) but was higher in the 5 mg bd group (0.3%) than in the 2.5 mg bd group (0.1%). The majority of fatal bleeds were intracranial (17/30) or gastrointestinal (7/30). Results were similar in Stratum 2, with a similar pattern but fewer events in Stratum 1. The vast majority of subjects had only 1 bleeding event.

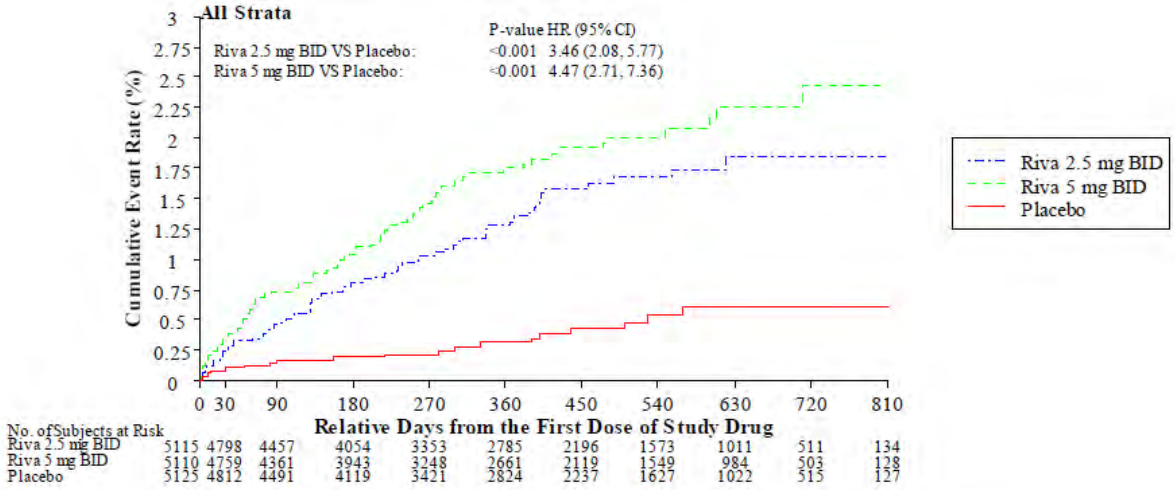
Table 12. Incidence of treatment–emergent bleeding events as adjudicated by the CEC (study TIMI 51; treatment-emergent safety analysis set)

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 (%)
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.

Figure 5. Kaplan-Meier estimates of the first occurrence of treatment-emergent non-CABG TIMI major bleeding events (study TIMI 51, 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% of that at the starting time point whichever is less.

7.4.2.1.2. TIMI life-threatening bleeding events

Within the TIMI bleeding classification, the CEC further categorised bleeding events as life-threatening. Overall 117 events met the life-threatening criteria, with 112 of these events occurring in Stratum 2. The incidence of life-threatening bleeding in All Strata was significantly higher in subjects on rivaroxaban 2.5 mg bd (0.8%) and 5 mg bd (1.1%), compared with subjects on placebo (0.4%) (HR 2.18, 95%CI 1.26 – 3.75, p = 0.004 and HR 3.09, 95% CI 1.84 – 5.20, p<0.001, respectively). The incidence of fatal bleeds was similar across the treatment groups: 6 (0.1%) in the 2.5 mg bd group, 15 (0.3%) in the 5 mg bd group and 9 (0.2%) on placebo.

Symptomatic intracranial bleeding was significantly higher in subjects on combined rivaroxaban (0.3%) than placebo (0.1%) as was the need for transfusion of 4 or more units of blood (0.5% versus 0.1%, respectively). Requirement for intravenous inotropic support or surgical intervention was similar across the rivaroxaban and placebo groups.

The pattern of treatment-emergent bleeding seen for most categories with the TIMI scale was similarly reflected in the GUSTO and ISTH scales - incidence rates were generally higher in the combined rivaroxaban group compared with placebo, generally higher in rivaroxaban 5 mg bd compared with rivaroxaban 2.5 mg bd, and were usually statistically significant versus placebo in All Strata and Stratum 2, but not in Stratum 1.

7.4.2.1.3. Subgroup analyses

The results of the subgroup analyses for the primary safety endpoint were generally comparable with the results of the overall 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 or region, and all interaction p values were ≥0.05.

Evaluator's comment

While not statistically significant, it should be noted that there was a trend to increased bleeding risk with age, particularly in subjects ≥75 years (All Strata/combined rivaroxaban HR: 12.90 (95% CI 1.74 - 95.40) in subjects ≥ 75 years; HR: 3.82 (95% CI 1.14 - 12.85) in subjects < 55 years).

7.4.2.2. Other studies

7.4.2.2.1. TIMI 46

The drug-related AE comments from the earlier evaluation were:

Overall, the incidence rate of treatment-emergent drug-related adverse events was higher in the pooled rivaroxaban group than it was for the placebo group (22.3% versus 11.4%). The difference was driven by the greater rate of treatment-emergent drug-related bleeding events in the rivaroxaban groups compared with the placebo groups. The majority of treatment-emergent adverse events (excluding bleeding events) in the rivaroxaban and placebo groups were assessed by the investigator as not related to study drug. By contrast, the majority of the bleeding events in all treatment groups were assessed by the investigator as related to study drug.

7.4.2.2.2. Study 12361

Three drug-related AEs were reported: 2 injection site haematomas (1 mild, 1 moderate) and 1 mild lipase elevation. Both haematomas (and all non drug-related AEs) resolved. The subject with the elevated lipase refused a follow-up examination, so the outcome was unresolved.

7.4.2.2.3. Study 12570

There were no drug related AEs reported.

7.4.2.2.4. Study 12571

There were no drug related AEs reported.

7.4.2.2.5. Study 14883

Drug-related TEAEs occurred in 7 of 24 subjects (29.2%) during treatment with warfarin, in 1 of 12 subjects (8.3%) after rivaroxaban following warfarin, in 2 of 12 subjects (16.7%) after placebo following warfarin and in 2 of 12 subjects (16.7%) after rivaroxaban alone. There were 4 bleeding events (gingival bleeding [n=2], and epistaxis [n=2]) which all occurred during warfarin pre-treatment. They were of mild intensity and transient, requiring no treatment.

7.4.3. Deaths and other serious adverse events

7.4.3.1. Pivotal study

7.4.3.1.1. Deaths

All deaths occurring post-randomisation were adjudicated by the CEC. Table 13, below, summarises all deaths by primary cause for the safety analysis set. In All Strata, 145 (2.8%) subjects in the 2.5 mg bd group, 194 (3.8%) subjects in the 5 mg bd group, and 193 (3.8%) subjects in the placebo group died from all causes[8].

Cardiovascular deaths accounted for the majority of deaths, as would be expected in an ACS population, with sudden or unwitnessed death, MI, and congestive heart failure/cardiogenic shock being the most common causes. There were fewer CV deaths in the combined rivaroxaban group (2.7%) compared with the placebo group (3.2%), largely due to a lower percentage of sudden or unwitnessed deaths (1.4% versus 1.9%, respectively). CV deaths generally occurred

[8] Note that there are more deaths recorded in the safety analysis population than in the efficacy population, because of the different subject composition.

at lower rates in the 2.5 mg than in the 5 mg rivaroxaban group. A similar pattern was seen for Stratum 2. In Stratum 1, the numbers of CV deaths were small, but the rates were higher in the combined rivaroxaban groups (4.4%) versus the placebo group (3.1%). This was largely due to an excess of sudden or unwitnessed death and MI in the rivaroxaban groups.

Of the non-cardiovascular deaths, malignancy and infection were the most common, and rates were generally similar between the treatment groups, and across the strata.

Table 13. Summary of all-cause deaths by primary cause as adjudicated by CEC (study TIMI 51: 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.

7.4.3.1.2. Serious adverse events

Overall, 2,116 (20.7%) subjects in the combined rivaroxaban groups and 1,018 (19.9%) subjects in the placebo group had treatment-emergent SAEs in All Strata, with a similar incidence of events in the rivaroxaban 2.5 mg bd and 5 mg bd groups (20.2% and 21.2%, respectively). In general, results in Stratum 2 were similar to those in All Strata. Table 14, below, summarises treatment-emergent SAEs in at least 1% of subjects in any treatment group in the safety analysis set; all SAEs were cardiac disorders (angina pectoris, unstable angina, and cardiac failure) which is consistent with an ACS population. The individual SAEs occurred at similar rates across the treatment groups, and were numerically lower in the 2.5 mg rivaroxaban group than in the 5 mg group, with the exception of cardiac failure which was higher in rivaroxaban 2.5 mg group (1.1%) than in 5 mg group (0.5%).

Table 14. Treatment–emergent SAEs in at least 1% of subjects in any treatment group by system organ class and preferred term (study TIMI 51; safety analysis set)

Subject Stratum: All Strata

	Rivaroxaban			
	2.5 mg BID	5 mg BID	Combined	Placebo
Body System Or Organ Class	(N=5115)	(N=5110)	(N=10225)	(N=5125)
Preferred Term	n (%)	n (%)	n (%)	n (%)
Total no. subjects with treatment-emergent serious adverse events	1033 (20.2)	1083 (21.2)	2116 (20.7)	1018 (19.9)
Cardiac disorders	402 (7.9)	426 (8.3)	828 (8.1)	437 (8.5)
Angina unstable	105 (2.1)	123 (2.4)	228 (2.2)	100 (2.0)
Angina pectoris	93 (1.8)	106 (2.1)	199 (1.9)	118 (2.3)
Cardiac failure	56 (1.1)	27 (0.5)	83 (0.8)	41 (0.8)

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: AE is sorted in descending order by percentage in Combined Rivaroxaban group.
Note: ASA = Acetylsalicylic acid; Thieno = Thienopyridine.

7.4.3.1.3. SAEs of special interest

During the clinical development program of rivaroxaban and the post marketing surveillance, safety observations emerged which were categorised as adverse events of special interest. AEs of special interest (in addition to bleeding and hepatic events) included acute pancreatitis, thrombocytopenia, acute renal failure, agranulocytosis, hypersensitivity reactions, and pseudoaneurysm. Standardised MedDRA Queries (SMQ) was used to identify and review cases of interest. While a small number of these events did occur, the frequency was similar between the rivaroxaban and placebo groups with the exception of pseudoaneurysm, where more subjects in the rivaroxaban 2.5 mg bd group (n=8) and the 5 mg bd group (n=7) experienced pseudoaneurysm than in the placebo group (n=3) (Table 15, below).

Table 15. Summary of SAEs of special interest in all strata (study TIMI 51: safety analysis set)

	Rivaroxaban			
Subject Stratum Adverse Event	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
Pancreatitis (category a (narrow term))	10 (0.2)	4 (0.1)	14 (0.1)	10 (0.2)
Thrombocytopenia	1 (<0.1)	0	1 (<0.1)	2 (<0.1)
Hypersensitivity	3 (0.1)	2 (<0.1)	5 (<0.1)	2 (<0.1)
Acute renal failure	12 (0.2)	8 (0.2)	20 (0.2)	14 (0.3)
Agranulocytosis	7 (0.1)	16 (0.3)	23 (0.2)	14 (0.3)
Pseudoaneurysm	8 (0.2)	7 (0.1)	15 (0.1)	3 (0.1)

Note: Percentages calculated with the number of subjects in each subject stratum and 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 categories.
Note: AEs as identified through a search of the AE database using the preferred term contained within the Standardized MedDRA Query (SMQ):
a.Pancreatitis (category A (narrow term)): main SMQ term="ACUTE PANCREATITIS (SMQ) " with term in narrow category A and without broad B and C category.
b.Thrombocytopenia: main SMQ term = "HAEMATOPOIETIC CYTOPENIAS (SMQ)" and sub SMQ term = "HAEMATOPOIETIC THROMBOCYTOPENIA (SMQ)".
c.Hypersensitivity : main SMQ term = "ANAPHYLACTIC REACTION (SMQ)" with term in narrow scope or main SMQ term = "SEVERE CUTANEOUS ADVERSE REACTIONS (SMQ)" with term in narrow scope.
d.Acute renal failure: main SMQ term = "ACUTE RENAL FAILURE (SMQ)".
e.Agranulocytosis: main SMQ term = "AGRANULOCYTOSIS (SMQ)".
Note: Pseudoaneurysm is identified by preferred terms "Vascular pseudoaneurysm" and "Cardiac pseudoaneurysm".
Note: ASA = Acetylsalicylic acid; Thieno = Thienopyridine.

7.4.3.2. Other studies

7.4.3.2.1. TIMI 46

The deaths and SAE comments from the earlier evaluation were:

Deaths

A summary of the subjects who died during the study for the safety analysis set was shown. There were 5I deaths during the study, 33 in subjects randomised to rivaroxaban (33/2309, 1.4%) and 18 in subjects randomised to placebo (18/1153, 1.6%). Thirty-eight subjects died while on study treatment. Consistent with the disease of subjects enrolled in the study, almost all of the deaths were classified as cardiovascular. One subject in the placebo group died of liver failure and for this subject there was a detailed narrative provided.

Serious adverse events

Treatment-emergent serious adverse events reported in at least 1 % of the subjects in any treatment group were summarised by preferred term and organ class. Overall, the percentages of subjects who reported treatment-emergent serious adverse events were comparable across the treatment groups. The most frequently reported treatment-emergent serious adverse events, i.e. those reported by more than 1% of subjects, in the rivaroxaban group were unstable angina (2.9%), angina pectoris (1.5%) acute MI (1.4%). The most frequently reported treatment-emergent serious adverse events in the placebo group were unstable angina (3.6%), acute MI (2.4%), chest pain (2.1 %) and angina pectoris (1.9%). All these data are consistent with the subjects' underlying ischaemic heart disease.

SAEs of special interest

A small number of these events did occur (acute pancreatitis, thrombocytopenia, acute renal failure, agranulocytosis, hypersensitivity reactions, and pseudoaneurysm), however the

frequency was similar between the rivaroxaban and placebo groups with the exception of pseudoaneurysm, where more subjects in the rivaroxaban 10 mg TDD group (n=5) and the 15 mg TDD group (n=6) experienced pseudoaneurysm than in the placebo group (n=0).

7.4.3.2.2. Study 12361

No deaths or SAEs occurred.

7.4.3.2.3. Study 12570

No deaths or SAEs occurred.

7.4.3.2.4. Study 12571

No deaths or SAEs occurred.

7.4.3.2.5. Study 14883

No deaths or SAEs occurred.

7.4.4. Discontinuation due to adverse events

7.4.4.1. Pivotal study

Table 16, below, summarises TEAEs resulting in permanent discontinuation of study drug in at least 0.25% of subjects in any treatment group in the safety analysis set, by System Organ Class and Preferred Term. In All Strata, TEAEs resulting in permanent discontinuation of study drug were more common in the combined rivaroxaban group (9.7%) than in the placebo group (7.6%). Gastrointestinal disorders and Cardiac disorders were the most commonly reported TEAEs resulting in discontinuation of study drug, and were generally higher in the rivaroxaban 5 mg bd group than the rivaroxaban 2.5 mg bd group. The majority of TEAEs leading to permanent discontinuation of study drug were bleeding-related. Results in Stratum 2 were similar to those in All Strata.

In Stratum 1, the most commonly reported TEAEs resulting in discontinuation of study drug were cardiac disorders.

Table 16. TEAEs resulting in permanent discontinuation of study drug in at least 0.25% of subjects in any treatment group by system organ class and preferred term (study TIMI 51; safety analysis set)

Subject Stratum: All Strata

Body System Or Organ Class Preferred Term	Rivaroxaban 2.5 mg BID (N=5115) n (%)	Rivaroxaban 5 mg BID (N=5110) n (%)	Rivaroxaban Combined (N=10225) n (%)	Placebo (N=5125) n (%)
Total no. subjects with treatment-emergent adverse events resulting in permanent discontinuation of study drug	443 (8.7)	548 (10.7)	991 (9.7)	389 (7.6)
Gastrointestinal disorders	89 (1.7)	140 (2.7)	229 (2.2)	78 (1.5)
Gingival bleeding	13 (0.3)	33 (0.6)	46 (0.4)	6 (0.1)
Gastrointestinal haemorrhage	10 (0.2)	23 (0.5)	33 (0.3)	6 (0.1)
Rectal haemorrhage	11 (0.2)	12 (0.2)	23 (0.2)	13 (0.3)
Cardiac disorders	55 (1.1)	87 (1.7)	142 (1.4)	80 (1.6)
Atrial fibrillation	21 (0.4)	20 (0.4)	41 (0.4)	21 (0.4)
Myocardial infarction	2 (<0.1)	15 (0.3)	17 (0.2)	5 (0.1)
Respiratory, thoracic and mediastinal disorders	51 (1.0)	58 (1.1)	109 (1.1)	25 (0.5)
Epistaxis	33 (0.6)	43 (0.8)	76 (0.7)	11 (0.2)
Investigations	41 (0.8)	28 (0.5)	69 (0.7)	24 (0.5)
Alanine aminotransferase increased	16 (0.3)	11 (0.2)	27 (0.3)	9 (0.2)
Renal and urinary disorders	21 (0.4)	42 (0.8)	63 (0.6)	9 (0.2)
Haematuria	19 (0.4)	36 (0.7)	55 (0.5)	4 (0.1)
Vascular disorders	22 (0.4)	25 (0.5)	47 (0.5)	20 (0.4)
Haematoma	10 (0.2)	14 (0.3)	24 (0.2)	9 (0.2)
General disorders and administration site conditions	19 (0.4)	23 (0.5)	42 (0.4)	33 (0.6)
Sudden death	8 (0.2)	8 (0.2)	16 (0.2)	13 (0.3)

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: AE is sorted in descending order by percentage in Combined Rivaroxaban group.
Note: ASA = Acetylsalicylic acid; Thieno = Thienopyridine.

7.4.4.2. Other studies

7.4.4.2.1. TIMI 46

The discontinuation due to AE comments from the earlier evaluation were:

Treatment-emergent adverse events which resulted in the permanent discontinuation of treatment with the study drug in at least 1 % of subjects in any treatment group were summarised by preferred term and system organ class.

The percentages of subjects who were discontinued from treatment with study drug due to adverse events were comparable between the rivaroxaban 5 mg dose group and the placebo (5.9% and 6.9%, respectively) and higher in the rivaroxaban dose groups taking a total daily dose of at least 10 mg (rivaroxaban 10 mg, 10.3%, rivaroxaban 15 and 20 mg, each 11.9%). The most frequently reported adverse events which led to discontinuation of treatment with study drug were epistaxis and gingival bleeding.

7.4.4.2.2. Study 12361

No discontinuations due to AEs occurred.

7.4.4.2.3. Study 12570

No discontinuations due to AEs occurred.

7.4.4.2.4. Study 12571

No discontinuations due to AEs occurred.

7.4.4.2.5. Study 14883

No discontinuations due to AEs occurred.

7.5. Laboratory tests

7.5.1. Liver function

7.5.1.1. Pivotal study

In All Strata, ALT, AST and total bilirubin (TB) post-baseline and treatment emergent values >3x ULN were balanced across the 2.5 mg bd and 5 mg bd rivaroxaban and placebo groups. Balance between treatment groups was also seen at higher levels of >5x and 8x ULN.

The sponsor used an eDISH plot of maximal ALT levels by maximal total bilirubin levels to assess for potentially serious liver injury ("Hy's Law"). In total, 24/10,209 (0.24%) rivaroxaban-treated and 13/5,114 (0.25%) placebo-treated subjects had elevations in ALT and total bilirubin that met the thresholds of >3xULN and >2xULN, respectively (irrespective of the pattern of liver injury, timing or order of the elevations). Incidence of combined concurrent cases where laboratory levels of AST >3xULN and total bilirubin >2xULN were met at any time, was low and balanced between treatment groups.

The sponsor also conducted a hepatic disorder SMQ search of the database and found no notable differences between the treatment groups for the outcome of any category of non-serious or serious hepatic disorder adverse events. No liver-related deaths associated with study drug were observed in the study.

7.5.1.1.1. HEAC assessments

A total of 92 liver events in 90 subjects were identified and sent for HEAC review. The most frequent criteria met was ALT >8x ULN (61/92 (66%) of the total cases), followed by ALT>3xULN and TB>2xULN on the same calendar day (33/92 (36%) of the total cases). There were no cases considered definitely related to study drug by any reviewer, and no cases with majority probable causality assessment.

Evaluator's comment

The sponsor does not state whether the subjects with both an ALT >3xULN and total bilirubin >2xULN also had an elevated ALP or other underlying cause for the abnormal LFTs, so it is not possible to determine whether there were any Hy's Law cases. This information will be sought from the sponsor.

7.5.1.1.2. Other studies

7.5.1.1.3. TIMI 46

The laboratory AE comments from the earlier evaluation were:

The incidence rates of hepatic disorder adverse events were similar between the rivaroxaban and placebo groups and these were summarised. The incidence rates of treatment-emergent hepatic disorders (defined as adverse events that occurred after the first dose and up to 2 days after the last dose) were similar between the pooled rivaroxaban (3.5%) and placebo (3.9%) groups. The most frequently reported treatment -emergent hepatic disorder adverse event was elevated ALT in both the rivaroxaban and placebo groups (2.3% [54/2309] versus 2.9% [33/1153], respectively).

Five (0.4%) subjects in the placebo group and 4 subjects (0.2%) in the pooled rivaroxaban group (2 subjects in the 5 mg group and 1 subject each in the 10 and 20 mg groups) had treatment-emergent serious hepatic disorder adverse events. Fourteen (1.2%) subjects in the placebo group and 13 (0.6%) subjects in the pooled rivaroxaban group discontinued treatment permanently due to hepatic adverse events.

Analysis of liver function test results

Figure 31[9] shows the relationship between maximal ALT and maximal total bilirubin concentrations observed after baseline in all subjects with non-missing values in the safety analysis set excluding one site [10]. The right upper quadrant of this figure represents those subjects who had both a serum ALT > 3 x ULN and a serum bilirubin> 2 x ULN, a combination recognised to be a reliable indicator of the potential for serious drug-induced hepatic injury. In order to capture as many cases as possible both central and local laboratory data were included in the analysis, as well as ALT and bilirubin elevations occurring concurrently and those not occurring concurrently (the particular data for concurrent elevations of both parameters and for non-concurrent elevations of both parameters are shown in the first and last rows, respectively of Table 87[11]).

The distribution of subjects in this right upper quadrant was similar between the rivaroxaban (2/2270, 0.1 %) and placebo (4/1134, 0.35%) groups. In fact, the ALT and bilirubin elevations which did occur concurrently were all in subjects in the placebo group. Results for the right lower quadrant also reinforce the lack of a hepatic signal for rivaroxaban. The right lower quadrant represents those subjects who experienced an elevation of ALT greater than 3 x ULN with normal or slightly elevated « 2 x ULN) values of total bilirubin. All drugs which have been associated with serious liver injury have had an imbalance in this quadrant. One can observe that the distribution of subjects in this quadrant was balanced between rivaroxaban (84/2270, 3.7%) and placebo (51/1134, 4.5%). It would also appear that the distribution of subjects between active and placebo was balanced in the left upper quadrant, i.e. for subjects with an elevation in total bilirubin but not in ALT. By the clinical evaluator's calculations (from Table 30 on page 150 of the CSR), there were 5 (5/2270, 0.22%) such subjects in the rivaroxaban group and 3 (3/1134, 0.26%) such subjects in the placebo group.

The incidence rates of abnormally elevated ALT and total bilirubin (both treatment-emergent and post-baseline) were low and comparable across all doses of rivaroxaban and placebo. Kaplan-Meier curves of the first occurrence of ALT > 3 x ULN show similar cumulative event rates in both the rivaroxaban and placebo groups (HR: (95% CI), 0.82 (0.58, 1.I6), p-value = 0.26) during the double-blind and follow-up phases.

7.5.1.1.4. Study 12361

No LFT abnormalities were reported apart from a mild, self-limiting elevation of glutamate dehydrogenase in 1 subject.

7.5.1.1.5. Study 12570

No LFT abnormalities >2xULN were reported.

7.5.1.1.6. Study 12571

No LFT abnormalities >2xULN were reported.

7.5.1.1.7. Study 14883

No LFT abnormalities >2xULN were reported.

[9] Not shown in this AusPAR.
[10] This was site 922009 and the sponsor has provided the reasons for exclusion of this one site.
[11] Not shown in this AusPAR.

7.5.2. Other clinical chemistry

7.5.2.1. Pivotal study

Overall there were no clinically relevant changes in mean or median change from baseline in the clinical laboratory test results (for example, haemoglobin, WBCs, platelets, creatinine), and they were comparable across the treatment groups.

7.5.2.2. Other studies

7.5.2.2.1. TIMI 46

The clinical chemistry AE comments from the earlier evaluation were:

Mean and mean changes from baseline in clinical chemistry and haematology variables, apart from liver function tests, were also collected and analysed. Comparison between the pooled rivaroxaban and placebo groups showed that the difference in the mean changes from baseline were small and not considered to be clinically relevant.

7.5.2.2.2. Study 12361

One episode of self-limiting CK elevation was reported, and was explained by physical exercise during the wash-out phase.

7.5.2.2.3. Study 12570

Two episodes of self-limiting CRP elevation were reported, both associated with the common cold. Both occurred whilst on the IR formulation.

7.5.2.2.4. Study 12571

One subject had elevated triglycerides throughout the study (including screening) and a second subject had elevated lipase and amylase which return to normal by the final examination. These elevations all occurred during the ER formulation treatment periods.

7.5.2.2.5. Study 14883

One episode each of self-limiting CRP and CK elevation was reported.

7.6. Postmarketing experience

Rivaroxaban is not marketed for the targeted indication. Postmarketing exposure to Xarelto (rivaroxaban) 10 mg for prevention of VTE following elective hip or knee replacement surgery since the approval of rivaroxaban in Canada on 15 September 2008 until a cut-off date of 15 September 2011 was estimated at 1,147,750 patients, excluding clinical and observational studies. Safety data were collected from spontaneous reports Bayer's Global Pharmacovigilance (GPV) database and included 2,799 spontaneous case reports (including 114 consumer reports), of which 5,158 were AEs, with 2,915 being SAEs. In total, 76 deaths were reported, with the most frequent single underlying event being pulmonary embolism (n=31). Bleeding events with fatal outcome (n=17) included GI (n=7) and intracranial (n=6). The most common SAEs reported were: pulmonary embolism (n=268), DVT (n= 253), haematoma (161) and wound secretion (n=95).

Of the 1,246 bleeding-related AEs identified, 867 were considered serious. The most common were: haematoma (n=161), post-procedural haemorrhage (n=88), haemorrhage (n=77), GI haemorrhage (n=70) and post-procedural haematoma (n=58).

A total of 112 cases with at least 1 hepatic AE (95 SAEs, 2 deaths) were identified. Thirty-six met the criteria for assessment by the HEAC, with only 6 cases assessed as having a probable relationship to rivaroxaban. Five of these cases were confounded by other potential causes.

A further 113 AEs (86 SAEs, 1 death) were identified in non-Bayer post-marketing studies. The most frequent serious adverse events were wound secretion (15), haematoma (11), staphylococcal wound infection (6), haemorrhage (5), wound infection (4), and transfusion (4). The most frequent bleeding-related serious adverse events were hematoma (11), haemorrhage (5), and decreased haemoglobin (3). One case was reviewed by the HEAC and the relationship to rivaroxaban was assessed as possible.

Overall, the safety profile of rivaroxaban from these postmarketing surveillance data appears consistent with the underlying disease being treated and/or with that seen in the clinical studies (known safety profile). No new or unexpected safety information has been identified.

7.7. Safety issues with the potential for major regulatory impact

7.7.1. Liver toxicity

Please see *Liver function* above.

7.7.2. Haematological toxicity

Please see section "*SAEs of Special Interest*" for information on thrombocytopenia and agranulocytosis.

7.7.3. Cardiovascular safety

Please see section "*SAEs of Special Interest*" for information on pseudoaneurysm.

Study 12361

One subject had QTcB (Bazett) values above 450 ms on 2 occasions after 2.5 mg rivaroxaban (451 and 459 ms, predose 446 ms), on one occasion after 5 mg rivaroxaban (451 ms, predose 434 ms) and on 1 occasion after 10 mg rivaroxaban (454 ms, predose 449 ms). They were reported as mild and non-drug related. No QTcB or QTcF (Fridericia) prolongations ≥ 60msec above baseline occurred.

7.7.4. Unwanted immunological events

Please see section "*SAEs of Special Interest*" for information on hypersensitivity reactions.

7.8. Other safety issues

7.8.1. Safety in special populations

The results of the subgroup analyses were generally consistent with the results of the overall primary safety endpoint analysis, with an increase of 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 or region; all interaction p values were ≥0.05.

Paediatric use: The TIMI 46 and TIMI 51 studies excluded subjects under the age of 18 years; therefore no safety data are available.

Geriatric use: In TIMI 51, subgroup analyses were conducted for 4 specified age groups (<55, 55 - <65, 65 - 74, and ≥75 years). Non-bleeding and bleeding adverse events in general increased with age, especially in the 5 mg bd rivaroxaban group. In TIMI 46, only 9 subject >75 years of age were enrolled in the rivaroxaban group and 4 in the placebo. Incidence of the TEAEs was similar for all age groups across the study, although clinically significant bleeding increased with age, particularly in those aged ≥ 75 years.

Gender: Incidence of bleeding adverse events tended to be lower in both the placebo and rivaroxaban groups in females compared with males in TIMI 51, but higher in TIMI 46 (not statistically significant).

Body weight: For the primary safety endpoints, no difference was noted between the combined rivaroxaban group and placebo group for all weight categories (<60 kg, ≥ 60 kg - <90 kg and ≥ 90 kg) or BMI in either study.

Race: no difference was noted among racial groups (White, Black, Asian, and Other) for the primary safety endpoint for either study.

Patients with Hepatic Impairment: Subjects with known significant liver disease or LFT abnormalities were excluded from the TIMI 51 and TIMI 46.

Patients with Renal Impairment: Subjects with CrCl values <30 mL/min at screening were excluded from both TIMI 51 and TIMI 46. 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.

7.9. Evaluator's overall conclusions on clinical safety

The pivotal efficacy study (TIMI 51) compared 2 doses of rivaroxaban, 2.5 mg bd and 5 mg bd, with placebo, in addition to standard care (ASA alone or ASA plus thienopyridine) on the ability to reduce CV events in subjects with ACS.

The key safety findings were:

- In All Strata, the combined, 2.5 mg bd and 5 mg bd rivaroxaban doses all significantly increased the incidence of the primary safety endpoint (non-CABG TIMI major bleeding) compared with placebo:
  - combined rivaroxaban: 1.4% versus 0.4%, HR: 3.96; 95% CI: 2.46-6.38; p<0.001
  - 2.5 mg bd rivaroxaban: 1.3% versus 0.4%, HR: 3.46; 95% CI: 2.08-5.77; p<0.001
  - 5 mg bd rivaroxaban: 1.6% versus 0.4%, HR: 4.47; 95% CI: 2.71-7.36; p<0.001

Results in Stratum 2 mirrored these results and were directionally consistent but not statistically significant in Stratum 1.

- In All Strata and Stratum 2 each of the rivaroxaban dose groups also increased the risk of:
  - Clinically significant bleeding
    - TIMI major bleeding
    - TIMI minor bleeding
    - Bleeding requiring medical attention
  - Intracranial bleeding
  - Haemorrhagic stroke
  - Life-threatening bleeding

Results were similar in Stratum 1, with numerically higher incidence rates in both rivaroxaban groups compared with placebo in most of the bleeding categories.

In all bleeding categories but haemorrhagic stroke there was a clear dose response with the 5 mg bd dose of rivaroxaban associated with higher event rates than the 2.5 mg bd dose.

- Fatal bleeding events were low overall and generally comparable between the 2.5 mg bd rivaroxaban dose and placebo. Rates were numerically higher in the rivaroxaban 5 mg bd group.
- Sensitivity analyses generally confirmed these results.

- A similar proportion of rivaroxaban-treated (0.24%) and placebo-treated (0.25%) subjects had elevations in ALT and total bilirubin that met the thresholds of >3xULN and >2xULN, respectively. However, it was not possible to determine whether these represented potential Hy's Law cases.

Bearing in mind the shorter duration of the dose-finding study (TIMI 46), the safety data for the rivaroxaban 5 mg and 10 mg TDDs were consistent with those of TIMI 51.

Based on the key safety findings, the 2.5 mg bd rivaroxaban dose is preferred to the 5 mg bd dose.

NB: only approval for the 2.5 mg bd dose is being sought by the sponsor for the ACS indication.

8. First round benefit-risk assessment

8.1. First round assessment of benefits

Based on the key efficacy and safety findings, the 2.5 mg bd rivaroxaban dose is preferred to the 5 mg bd dose. As the 2.5 mg bd dose is the only dose for which approval is being sought by the sponsor for the ACS indication, only the 2.5 mg bd dose will be discussed hereafter. The benefits listed below have to be considered in the context of a study with a high discontinuation rate. While discontinuation was similar across treatment groups and strata, it is important to ascertain both the baseline characteristics and status of these individuals where possible, to rule out bias which may affect the validity of the results. (NNT/NNH will be discussed below).

The benefits of rivaroxaban 2.5 mg bd in the proposed usage are:

- A relative risk reduction of 16% in the combined primary efficacy endpoint of CV death, MI and stroke (HR: 0.84; 95% CI: 0.72 – 0.97; p = 0.020) in All Strata. This result was largely driven by a reduction in CV deaths. This result was robust, being confirmed in a number of sensitivity analyses. A similar reduction of 15% was seen in Stratum 2 (HR: 0.85; 95% CI: 0.72 – 0.99; p = 0.039), but failed to reach statistical significance in Stratum 1 (HR: 0.74; 95% CI: 0.45 - 1.22; p = 0.234).
- Subjects aged ≥ 75 years appeared to derive less benefit than younger subjects (Primary Efficacy Endpoint, All Strata, HR: 0.90 (95% CI 0.62 - 1.30) in subjects ≥ 75 years; HR: 0.77 (95% CI 0.53 – 1.13) in subjects < 55 years).
- Subjects with a history of CHF appeared to derive greater benefit than subjects without a history of CHF (Primary Efficacy Endpoint, All Strata, HR 0.58 (95% CI 0.42 - 0.81) versus HR 0.92 (95% CI 0.77 – 1.09), respectively).
- Subjects with a history of ischemic stroke or TIA appeared to derive no benefit/be at increased risk (All Strata, HR 1.84 (95% CI 0.82 - 4.10)) compared with subjects without a history of ischemic stroke or TIA (All Strata, HR 0.81 (95% CI 0.69 - 0.94)).
- A relative risk reduction of 17% in the combined secondary efficacy endpoint of All-Cause death, MI and stroke (HR: 0.83; 95% CI: 0.72-0.97; p=0.016) in All Strata. A similar reduction of 15% was seen in Stratum 2 (HR: 0.84; 95% CI: 0.72 - 0.98; p = 0.028).
- In a post-hoc analysis, a nominally significant reduction in stent thrombosis was found for All Strata (HR: 0.70, 95% CI: 0.51 - 0.97; p = 0.033) and Stratum 2 (HR: 0.68; 95% CI 0.49 - 0.95; p = 0.024), but not Stratum 1 (HR: 1.50; 95% CI 0.25 - 8.99; p = 0.653).

8.2. First round assessment of risks

As expected with an anticoagulant, the major risks associated with the use of rivaroxaban 2.5 mg bd in ACS relate to bleeding and include:

- A significant increase in the incidence of the primary safety endpoint (non-CABG TIMI major bleeding) in All Strata (HR: 3.46; 95% CI: 2.08-5.77; p<0.001). Results in Stratum 2 mirrored these results (HR: 3.35; 95% CI: 2.01 - 5.60; p <0.001), and were directionally consistent but not statistically significant in Stratum 1.
- In All Strata and Stratum 2 rivaroxaban 2.5 mg bd also increased the risk of:
  - Clinically significant bleeding
    - TIMI major bleeding
    - TIMI minor bleeding
    - Bleeding Requiring Medical Attention
  - Intracranial bleeding
  - Haemorrhagic stroke
  - Life-threatening bleeding
- The incidence of fatal bleeds was low, and similar in the rivaroxaban 2.5 mg bd group (0.1%) and placebo group (0.2%).
- Subjects aged ≥ 75 years appeared to be more at risk of bleeding events than younger subjects (Non−CABG related TIMI Major Bleeding Events, All Strata HR 6.21 (95% CI 0.75 - 51.61) in subjects ≥ 75 years; HR 2.98 (95% CI 0.79 – 11.23) in subjects < 55 years).

8.3. First round assessment of benefit-risk balance

The benefit-risk balance of rivaroxaban 2.5 mg bd is unfavourable given the proposed usage, but may become favourable if the changes recommended below are adopted and satisfactory answers are received to the questions raised below.

The sponsor attempted to quantify the benefit-risk balance using "Net Clinical Outcome" as Secondary Efficacy Endpoint 2 (defined as the composite of CV death, MI, ischemic stroke, or non-CABG TIMI major bleeding event). While treatment with rivaroxaban 2.5 mg bd was numerically superior to placebo on this composite endpoint (HR 0.93; 95% CI 0.81 – 1.07), it was not statistically significant because the reductions in CV death, MI and ischemic stroke were largely offset by the increase in non-CABG TIMI major bleeding. This was a simplistic approach which was complicated by the fact that some events were included in both of the primary efficacy and safety endpoints (fatal bleed and haemorrhagic stroke). In addition there were increases in many other bleeding categories that, while not fitting the definition of a major event, could result in significant morbidity, require investigation and treatment, or otherwise negatively impact the health and/or quality of life of the patient.

The sponsor therefore provided an alternative post-hoc assessment of benefit-risk analysis based on number needed to treat (NNT) and number needed to harm (NNH). Endpoints were re-categorised to show ischemic events as efficacy and haemorrhagic events as safety (Table 17, below, Stratum 2 only).

In Stratum 2, rivaroxaban 2.5 mg bd prevented 115.18 (95% CI: 18.40, 211.96) non-haemorrhagic CV death, MI and ischemic stroke events per 10,000 patient-years compared with placebo, while causing an additional 10.16 (95% CI:-11.25, 31.57) fatal bleeding or ICH events. These results suggest that approximately 11 non-hemorrhagic events were prevented for 1 hemorrhagic event caused (that is, a favourable "benefit-risk ratio" of ~11 to 1). This equates to

1 less non-haemorrhage CV death, MI and ischemic stroke event per 87 years, and 1 more fatal bleeding or ICH event every 984 years.

When comparing the efficacy benefits with fatal bleeding and less severe but still clinically relevant bleeding outcomes such as TIMI major bleeding (72.22 excess events per 10,000 patient-years, 95% CI: 32.17, 112.27), a reduced but still favourable benefit-risk ratio remains of approximately 1.6 to 1, with 1 less non-haemorrhage CV death, MI and ischemic stroke event per 87 years, and 1 more fatal bleeding and TIMI major bleeding event every 138 years.

If fatal bleeding, TIMI major bleeding and TIMI minor bleeding (which includes bleeding events associated with a fall in Hb of 3 to <5g/dL) are all taken into consideration, the number of excess bleeding events reaches 86 and the NNH 116 – reducing the favourable benefit-risk ratio to approximately 1.3 to 1, with 1 less non-haemorrhage CV death, MI and ischemic stroke event per 87 years, and 1 more fatal bleeding, TIMI major bleeding and TIMI minor bleeding event every 116 years. Thus the benefit-risk balance very much depends on the decision about what constitutes a clinically significant bleeding event, and how much weight is put on events which cause irreversible harm versus temporary morbidity. However, on balance the benefit-risk ratio remains in favour of rivaroxaban compared with placebo.

Table 17. Ischemic and haemorrhagic events for 2.5 mg bd dose in stratum 2 (TIMI 51: mITT (excluding sites 091001, 091019 and 091026) analysis set)

Time to Event Category	Endpoints	Event Rate(a) (/100 Pt-yrs) Rivaroxaban	Event Rate(a) (/100 Pt-yrs) Placebo	Excess Number of Events (Rivaroxaban - Placebo) Excess # events for 10,000 pt-yrs	95% CI	NNT/NNH(b)
Efficacy	Non-hemorrhage CV death + MI + ischemic stroke	5.48	6.63	-115.18 *	(-211.96, -18.40)	-87
	Non-hemorrhage CV death	1.48	2.43	-95.05 *	(-149.41, -40.69)	-105
	MI excl CV death	3.59	3.81	-21.65	(-97.36, 54.07)	-462
	Ischemic stroke excl CV death	0.55	0.51	4.65	(-24.08, 33.39)	2150
	Non-CV death excl fatal bleed	0.16	0.17	-1.73	(-18.54, 15.08)	-5790
	Severe Recurrent Ischemia	3.84	4.13	-28.55	(-107.33, 50.23)	-350
Safety	TIMI life threatening bleeding	0.87	0.47	40.14 *	(7.95, 72.34)	249
	Fatal Bleeding + symptomatic ICH	0.33	0.23	10.16	(-11.25, 31.57)	984
	Fatal Bleeding	0.16	0.19	-3.67	(-20.90, 13.56)	-2726
	Non-fatal symptomatic ICH	0.18	0.04	13.83	(-0.61, 28.27)	723
	Non-fatal, non-ICH TIMI life threatening bleeding	0.53	0.23	29.93 *	(5.25, 54.61)	334
	Non-fatal, non-ICH bleeding requiring surgical intervention	0.12	0.12	0.15	(-14.40, 14.70)	66806
	Non-fatal, non-ICH bleeding requiring IV inotropic agents	0.04	0.04	0.06	(-10.78, 10.89)	181756
	Non-fatal, non-ICH bleeding requiring transfusion ≥ 4 units	0.39	0.14	25.82 *	(5.03, 46.62)	387
	Fatal Bleeding + TIMI Major Bleeding	1.40	0.68	72.22 *	(32.17, 112.27)	138
	Fatal bleeding + ICH	0.33	0.23	10.16	(-11.25, 31.57)	984
	Intracranial Bleeding (ICH)	0.28	0.12	15.91	(-2.22, 34.04)	629
	Fatal ICH	0.10	0.08	2.07	(-10.97, 15.12)	4819
	Non-fatal ICH	0.18	0.04	13.83	(-0.61, 28.27)	723
	TIMI Major Bleeding Excluding Fatal Bleeding and ICH	1.07	0.45	61.96 *	(27.69, 96.23)	161
	TIMI Major Bleeding Excluding Fatal Bleeding and ICH, Life threatening	0.45	0.17	27.86 *	(5.36, 50.36)	359
	TIMI Major Bleeding, non-life threatening	0.65	0.27	37.88 *	(10.92, 64.84)	264
	TIMI Minor Bleeding	0.61	0.47	14.47	(-14.55, 43.50)	691

(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-hemorrhage 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.

Benefit-risk balance with rivaroxaban is also influenced by individual patient characteristics. Individuals aged over 75 years appeared to derive less benefit and be at higher risk of bleeding events, individuals with a history of CHF appeared to derive greater benefit than subjects without a history of CHF, and individuals with a history of ischemic stroke or TIA appeared to derive no benefit compared with subjects without a history of ischemic stroke or TIA. Each of these factors potentially changes the point at which risk exceeds benefit. It is therefore critical that if rivaroxaban is approved in ACS, these issues are adequately communicated to prescribers

and addressed in the PI. It will also be important to monitor usage with other platelet inhibitors (such as prasugrel) as the risk-benefit balance may be different with these agents.

9. First round recommendation regarding authorisation

At this stage the clinical evaluator was unable to recommend approval of rivaroxaban 2.5 mg bd in acute coronary syndrome. However, the submission may become approvable if the PI is modified as recommended and satisfactory answers are received to the questions raised in below.

10. Clinical questions

10.1. Pharmacokinetics

1. In the Summary of Biopharmaceutic Studies, the Sponsor refers to a "lack of a relevant food effect observed with the 10 mg rivaroxaban tablet (Study 11937), and similar results obtained from an exploratory pooled PK analysis across Phase 1 studies [PH-36318]which included dose strengths less than 10 mg", as the reason for not conducting a dedicated food effect study for the 2.5 mg tablet and supporting the proposed label, that rivaroxaban 2.5 mg tablets can be taken with or without food. The evaluator obtained a copy of the pooled PK analysis but only found reference to the 2.5 mg dose in the fasted state, and the following statement:

   No pharmacokinetic and pharmacodynamic conclusions are presented in this report. After medical review of the table set provided, rivaroxaban pharmacokinetic and pharmacodynamic results and conclusions drawn from these results will be reported under separate cover.

   The sponsor was asked to provide the results and conclusions to support the lack of food effect with the 2.5 mg tablet.

10.2. Efficacy

Please see Questions 2-6 with sponsor's answers under *Section 11. Second Round evaluation of clinical data submitted in response to questions.*

10.3. Safety

Please see Question 7 with sponsor's answer under *Section 11. Second Round evaluation of clinical data submitted in response to questions.*

11. Second round evaluation of clinical data submitted in response to questions

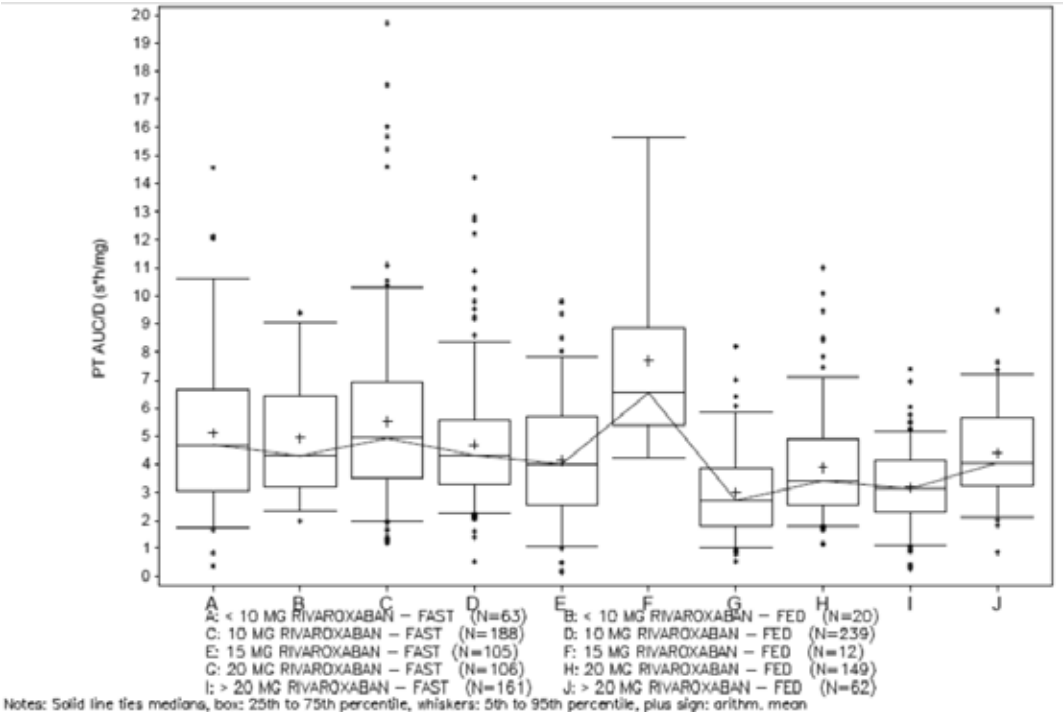
The clinical evaluator's questions (Q1-10) and the sponsor's responses were as follows:

Q1. The sponsor was asked to provide the results and conclusions to support the lack of food effect with the 2.5 mg tablet.

Sponsor's response

The sponsor referred to the PK study submitted with a previous evaluation that demonstrated a lack of food effect with a 10 mg dose of rivaroxaban (Study 11937). The sponsor also advised that contrary to the statement made in the synopsis of the exploratory pooled PK analysis (Study PH-36318), there is no separate report on the "*rivaroxaban pharmacokinetic and pharmacodynamic results and conclusions drawn from these results".* However, the sponsor stated that the pooled analysis supports the lack of a food effect at lower rivaroxaban tablet doses, and this appears to be confirmed by the pooled AUC/D (Figure 6, below).

Figure 6. Box-Whisker plot by group (dose categories and fasted versus fed state) parameter: PT AUC/D



Evaluator's comment

This request was made in order to obtain the report of the pooled PK analysis to confirm consistency with the results of Study 11937. Study 11937 was a confirmatory food effect study that was conducted because previous pilot trials of food effect with 10 mg doses of rivaroxaban showed an increase of AUC by 25% with a high-calorie/high-fat meal, which had also been seen with a 20 mg dose of rivaroxaban. Despite the lack of a pooled PK analysis report, Figure 6 is consistent with the results of Study 11937 and supports the lack of a food-effect with doses of rivaroxaban ≤ 10 mg.

Q2. A 22.5% relative reduction (hazard ratio=0.775) between pooled doses of rivaroxaban and placebo arms pooled across Stratum 1 and 2 was used to estimate the number of primary efficacy endpoint events required in the TIMI 51 study, and a 35% relative reduction in Stratum 1. The sponsor was requested to explain the basis for the choice of these figures.

Sponsor's response

The sponsor advised that the estimates of relative risk reduction (RRR) used to calculate the sample size for the TIMI 51 study were based on the clinical judgement of the TIMI group and the study Executive Steering Committee, using the following information:

In Stratum 1 (ASA alone) the proposed 35% RRR was based on 2 studies: (i) an open-label, randomised trial of warfarin plus ASA versus ASA alone in ACS[5] which showed a 29% RRR on the composite outcome of death, nonfatal reinfarction, or thromboembolic stroke with the combined treatment; and (ii) TIMI 46 which showed a RRR of 40% for the combined 2.5, 5, 7.5, or 10 mg bd rivaroxaban doses in stratum 1 for the endpoint of CV death/MI/stroke, and 45% for the combined 2.5 mg and 5 mg bd doses.

In Stratum 2 the only data available for anticoagulation on top of dual antiplatelet (DAP) therapy in ACS was the TIMI 46 study. The TIMI 46 results for Stratum 2 showed a RRR of 18% for the composite endpoint of CV death/MI/stroke for all bd doses combined and 41% for the combined 2.5 mg and 5 mg bd doses.

Across both strata there was a 28% RRR for all bd doses combined and 44% for the combined 2.5 mg bd and 5 mg bd doses.

Evaluator's comment

The sponsor's choice of percentage RRR for Stratum 1, Stratum 2 and All Strata based on findings from the literature and/or earlier studies is acceptable.

Q3. While it is clear why the 2.5 mg bd and 5 mg once daily doses of rivaroxaban were chosen for the Phase III trial, there were no data supplied in the submission or adequate explanation given for the original choice of 2.5 mg as the lowest dose in the Phase II trial. The only reference to the selection of the 2.5 mg dose the evaluator could find was in the TIMI 46 Clinical Protocol. Here it was stated: "*In the VTE prophylaxis studies, the lowest effective twice-daily dose tested was demonstrated to be 2.5 mg twice daily*." The evaluator also identified a publication[12] that reported that the 1.25 mg dose of rivaroxaban showed no significant inhibition of factor Xa activity compared with placebo, but a 2.5 mg dose was not tested. The sponsor was requested to provide the basis for the decision to use the 2.5 mg dose, including data on Factor Xa inhibition.

Sponsor's response

The sponsor referred to the results of the VTE prophylaxis dose-ranging studies, which indicated that 2.5 mg bd was "*the lowest effective twice-daily dose tested*". They also referred to the original study that was the basis of the Kubitza et al. (2005) publication (Study10842) in which the 1.25 mg dose of rivaroxaban was found to have no effect on Factor Xa inhibition or the HepTest and only small but clinically irrelevant effects on PT and aPTT. No information was provided on doses between 1.25 mg and 2.5 mg, or on Factor Xa inhibition with the 2.5 mg dose.

[12]Kubitza D, Becka M, Voith B, Zuehlsdorf M and Wensing G. Safety, pharmacodynamics, and pharmacokinetics of single doses of BAY 59-7939, an oral, direct factor Xa inhibitor. Clin Pharmacol Ther 2005; 78:412-21

Evaluator's comment

No new information was provided by the sponsor in this response. While it is understood that the 2.5 mg bd dose was the lowest effective dose tested in the VTE prophylaxis studies, because there is no information on the factor Xa inhibition of doses between the 1.25 mg "no effect" dose and the 5 mg dose tested in Study 10842, it remains unclear whether a dose lower than 2.5 mg bd may have been clinically effective with fewer adverse events.

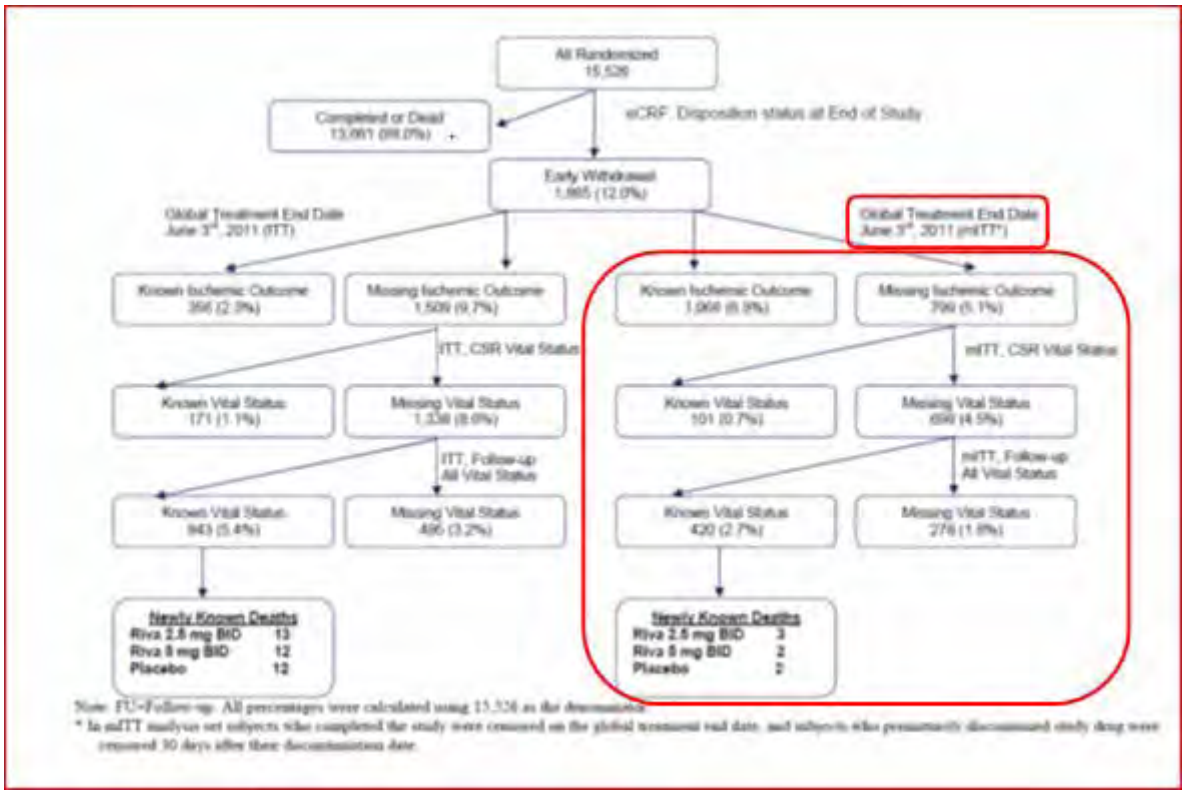
Q4. The percentage of subjects who discontinued prematurely from the TIMI 51 study was relatively high at ~15%, with about half of this due to withdrawal of consent. While the percentages were similar across treatment groups and strata, there is the potential for this to introduce bias and to limit the validity of the results. The Sponsor is requested to provide tables comparing the demographic and baseline characteristics of those subjects who discontinued prematurely to those who completed the study (by Stratum). Please also indicate what measures were undertaken to contact these individuals, and what further efforts will be undertaken to improve follow-up.

Sponsor's response

[information redacted].

As requested, the sponsor provided numerous tables showing the demographic and baseline characteristics of those subjects who discontinued prematurely (N=2,402, includes 537 subjects who died) and separately for those subjects who withdrew consent (N=1,294). They also clarified that of the 1,865 living subjects who discontinued prematurely, 1,066 (using the primary efficacy mITT analysis set) had experienced a primary efficacy event prior to discontinuation from the study, or had either endpoint follow-up or vital status information collected by the Global Treatment End Date (GTED) (Figure 7, below). More subjects had missing data in the ITT analysis set as it included subjects who dropped out of the study more than 30 days after study drug had been discontinued, who were considered completers (censored at 30 days post study drug discontinuation) for the mITT analysis.

Figure 7. Subjects completion/withdrawal and follow-up vital status in TIMI 51 (mITT and ITT analysis sets).



While the distribution of some demographic characteristics was different in the discontinued subjects compared with all randomised subjects (for example, in All Strata - lower proportion of white subjects [61.4% versus 73.5%, respectively], higher percentage of subjects ≥ 75 years [14.1% versus 9.0%, respectively], higher proportion with CrCl <30 mL/min [1.5% versus 0.5%, respectively]), the distribution was either balanced across the treatment groups, or showed a similar variation to that seen in all randomised subjects. This was observed in Stratum 1, Stratum 2 and All Strata. Admitting diagnosis and time from index event to randomisation were similar between the discontinued subjects compared with all randomised subjects. These findings were mirrored in the subjects who withdrew consent.

In addition, the sponsor provided a comparison of baseline characteristics in subjects who withdrew consent with those subjects included in the efficacy analysis (Table 18 below). This showed that subjects who withdrew consent more closely resembled subjects who survived and subjects without a primary endpoint event in terms of prior MI and baseline PCI for index event, which are recognised risk factors for adverse outcome in ACS patients.

Table 18. Baseline characteristics for all randomised subjects, subjects who had a primary endpoint event for CV death, all cause death or MI versus those who do not have a primary efficacy event and survived (study TIMI 51: analysis set: all randomised subjects)

All Strata	All randomized Rivaroxaban 2.5mgBID N= 5174(%)	All randomized Rivaroxaban 5mg BID N= 5176 (%)	All Randomized Placebo N=5176 (%)	Subjects who Died Total N=537 (%)	Subjects who Survived Total N=14989 (%)	Subjects who withdrew consent Total N=1294 (%)	Subjects with primary endpoint MI (mITT) Total N=613 (%)	Subjects Without primary endpoint event Total N=12527 (%)
Male	3875 (74.9)	3843 (74.2)	3882 (75.0)	402 (74.9)	11198 (74.7)	939 (72.6)	435 (71.0)	9395 (75.0)
Race								
White	3798 (73.4)	3815 (73.7)	3796 (73.3)	376 (70.0)	11033 (73.6)	853 (65.9)	517 (84.3)	9433 (75.3)
Black/African American	34 (0.7)	34 (0.7)	39 (0.8)	3 (0.6)	104 (0.7)	10 (0.8)	2 (0.3)	80 (0.6)
Asian	1099 (21.2)	1055 (20.4)	1075 (20.8)	124 (23.1)	3105 (20.7)	387 (29.9)	73 (11.9)	2364 (18.9)
Age								
Mean ± SD (years)	61.8 ± 9.23	61.9 ± 9.03	61.5 ± 9.39	65.1 ±10.21	61.6 ± 9.16	63.0 ± 10.06	63.2 ±10.22	61.6 ± 8.94
Admitting Diagnosis:								
STEMI	2601 (50.3)	2584 (49.9)	2632 (50.9)	241 (44.9)	7576 (50.5)	614 (47.4)	277 (45.2)	6388 (51.0)
NSTEMI	1321 (25.5)	1335 (25.8)	1323 (25.6)	160 (29.8)	3819 (25.5)	309 (23.9)	213 (34.7)	3203 (25.6)
Unstable Angina	1252 (24.2)	1257 (24.3)	1221 (23.6)	136 (25.3)	3594 (24.0)	371 (28.7)	123 (20.1)	2936 (23.4)
Baseline PCI for Index Event	3117 (60.2)	3106 (60.0)	3101 (59.9)	193 (35.9)	9131 (60.9)	781 (60.4)	323 (52.7)	7738 (61.8)
Prior MI	1363 (26.3)	1403 (27.1)	1415 (27.3)	228 (42.4)	3953 (26.4)	373 (28.8)	257 (41.9)	3194 (25.5)
Baseline Diabetes Mellitus	1669 (32.3)	1648 (31.8)	1647 (31.8)	196 (36.4)	4768 (31.8)	468 (36.2)	222 (36.2)	3895 (31.1)

An additional evaluation of safety and efficacy events occurring in the 30 days prior to the date of last contact for those subjects with an unknown vital status at the GTED (N=1,298) showed that with the exception of "All bleeding", there were no clinically important imbalances between treatment groups (Table 19, below). Non-bleeding AEs were balanced across the treatment groups.

Table 19. Incidence of efficacy and safety events in the 30 days prior to the last contact date for subjects who had unknown vital status at GTED (study TIMI 51: ITT analysis set)

	Rivaroxaban			
Subject Stratification Parameter	2.5 mg BID (N=441) n (%)	5 mg BID (N=456) n (%)	Combined (N=897) n (%)	Placebo (N=401) n (%)
All Strata				
Stroke	0	2 (0.44)	2 (0.22)	1 (0.25)
MI	4 (0.91)	3 (0.66)	7 (0.78)	2 (0.50)
Non-cabg TIMI Major	1 (0.23)	2 (0.44)	3 (0.33)	0
All bleeding	20 (4.54)	15 (3.29)	35 (3.90)	8 (2.00)

Evaluator's comment

Although there was an imbalance in "All bleeding", ~60% of these subjects subsequently had their vital status ascertained with no imbalance in deaths between the treatment groups.

A[information redacted]analysis of important safety and efficacy events was conducted by the sponsor [information redacted] in those subjects who withdrew consent. Similar proportions of bleeding events, MIs, strokes and AEs were seen in the rivaroxaban 2.5 mg bd and placebo groups, with higher proportions seen in some of the events for the subjects receiving rivaroxaban 5 mg bd (Table 20, below).

Table 20. Incidence of efficacy and safety events in the 30 days prior to the last contact date (study TIMI 51: all randomised subjects who withdrew consent)

Bleeding events	Rivaroxaban 2.5 mg BID n/N (%)	Rivaroxaban 5 mg BID n/N (%)	Placebo n/N (%)
Non-CABG TIMI Major Bleeding	1/448 (0.2)	3/441 (0.7)	0/405
CABG Related TIMI Major Bleeding	0/448	0/441	1/405 (0.2)
TIMI Minor Bleeding	1/448 (0.2)	2/441 (0.5)	1/405 (0.2)
TIMI Bleeding Requiring Medical Attention	7/448 (1.6)	8/441 (1.8)	6/405 (1.5)
MI, Stroke	4/441 (0.91)	4/434 (0.92)	4/396 (1.01)
Non-Bleeding AEs	20/241 (8.3)	18/222 (8.1)	20/220 (9.1)

All events are CEC adjudicated except for non-bleeding adverse events.

Attempts were made by the sponsor after the GTED of the study to contact those subjects who had withdrawn consent. This resulted in 399 subjects being approached by study site staff. Since this time further attempts have been initiated to determine the vital status via a combination of site directed activities and national database queries, where this was permitted by the relevant national health authorities. As a result of these activities the vital status of an additional 521 (3.4%) subjects was determined and only 278 (1.8%) of subjects in the mITT analysis set and 495 (3.2%) of subjects in the ITT analysis set have an unknown vital status as at 10 August 2012. It is estimated that the missing duration of follow up for all cause death was reduced to <0.1% and 2.4% overall in the mITT and ITT analysis sets, respectively.

In analyses performed by the sponsor [information redacted], analyses of all cause death in the mITT and ITT analysis sets were replicated after including the additional vital status information. In the mITT analysis HRs were essentially unchanged from the original results (Table 21, below). Similarly, the ITT analysis was consistent with the original ITT results.

Table 21. Effect of rivaroxaban compared with placebo on death incorporating new vital status data (study TIMI 51: mITT (excluding sites 091001, 091019 and 091026) analysis set)

	Rivaroxaban								-- 2.5 mg BID --	--- 5 mg BID ---	--- Combined ---
	----- 2.5 mg BID -----		------ 5 mg BID -----		------ Combined ------		------ Placebo ------		------ vs. -----	------ vs. -----	------ vs. -----
Subject Stratum	(N=5114)	Event Rate	(N=5115)	Event Rate	(N=10229)	Event Rate	(N=5113)	Event Rate	---- Placebo ---	---- Placebo ---	---- Placebo ---
Parameter	n(%)	(100 pt-yr)	n(%)	(100 pt-yr)	n(%)	(100 pt-yr)	n(%)	(100 pt-yr)	HR (95% CI)	HR (95% CI)	HR (95% CI)
All Strata	5114		5115		10229		5113				
Death-CSR	103(2.0)	1.90	142(2.8)	2.68	245(2.4)	2.28	153(3.0)	2.78	0.68 (0.53,0.87)	0.95 (0.76,1.19)	0.81 (0.66,1.00)
Death-all	106(2.1)	1.95	144(2.8)	2.71	250(2.4)	2.32	155(3.0)	2.81	0.69 (0.54,0.88)	0.95 (0.76,1.19)	0.82 (0.67,1.00)
ASA	349		348		697		353				
Death-CSR	13(3.7)	3.69	9(2.6)	2.54	22(3.2)	3.11	10(2.8)	2.84	1.30 (0.57,2.96)	0.89 (0.36,2.20)	1.09 (0.52,2.31)
Death-all	13(3.7)	3.68	9(2.6)	2.54	22(3.2)	3.11	11(3.1)	3.12	1.18 (0.53,2.64)	0.81 (0.34,1.96)	1.00 (0.48,2.05)
ASA + Thieno	4765		4767		9532		4760				
Death-CSR	90(1.9)	1.77	133(2.8)	2.69	223(2.3)	2.22	143(3.0)	2.78	0.64 (0.49,0.83)	0.95 (0.75,1.21)	0.79 (0.64,0.98)
Death-all	93(2.0)	1.83	135(2.8)	2.72	228(2.4)	2.27	144(3.0)	2.79	0.65 (0.50,0.85)	0.96 (0.76,1.22)	0.81 (0.65,0.99)

Note: Except for death from the newly collected vital status data, all the death events were adjudicated by CEC
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: 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: 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.
Note: Death-all = Death-incorporated new vital status.

Evaluator's comment

As a result of the sponsor's clarification of the categorisation of subjects with incomplete follow-up and additional efforts to obtain vital status information, it now appears that efficacy endpoints are known for 94.9% of subjects (13,661 completed or dead plus 1,066 with known ischemic outcome), vital status known for an additional 3.4%, and only 1.8% have an unknown vital status (mITT population). Comparison of demographic, baseline disease, and safety and efficacy events occurring in subjects who withdrew consent or had missing vital status data, does not reveal major imbalances in events that may have influenced both the decision to withdraw and subsequent CV outcome. As the primary analysis was a time to first primary (and secondary) efficacy endpoint analysis, the major data loss with premature discontinuation in the subjects with a known ischemic outcome is in adverse event (particularly bleeding) data.

The updated percentage follow-up along with the balanced distribution of baseline demographic and risk factor characteristics, and efficacy and safety events in the 30 days prior to the last contact date (ITT population) provide reassurance about the validity of the study efficacy results. However bleeding AEs may be underestimated, particularly as there was a higher proportion of permanent discontinuation as a result of bleeding in the rivaroxaban treated subjects.

Q5. The sponsor was requested to provide a copy of its responses to all of issues raised by the US FDA

Sponsor's response

The sponsor provided a copy of their response to the US FDA.

Q6. Please provide a tabulation of the effect of rivaroxaban compared with placebo on the primary efficacy endpoint and treatment-emergent bleeding separately for Stratum 1, and Stratum 2 stratified by 2C19 inhibitor use.

Sponsor's response

The sponsor provided [information redacted]sensitivity analyses [information redacted]in subjects [information redacted] on a thienopyridine and not taking either omeprazole or esomeprazole[13][information redacted]. Subjects were censored on the earlier of

1. the day of thienopyridine cessation, or
2. in subjects who were receiving a thienopyridine, the day before starting omeprazole or esomeprazole.

The point estimates of these sensitivity analyses are consistent with the originally reported overall study results for both the primary efficacy endpoint and treatment-emergent bleeding, although 6 of the original 11 statistically significant efficacy results (All Strata and Stratum 2 only) lost their statistical significance. The same sensitivity analysis was also performed in the intent-to-treat (ITT) analysis set, which had more endpoint events available for analysis. The results were consistent with the sensitivity results seen in the mITT analysis set (similar point estimates, with 2 of the original 13 statistically significant efficacy results losing their statistical significance).

An [information redacted]sensitivity analysis [information redacted]was performed as a result of a TGA request for information, with the addition of other strong and moderate CYP2C19 inhibitors to omeprazole or esomeprazole (Table 22 and Table 23, below). Again, the point estimates are consistent with the originally reported overall study results, with some loss of statistical significance for the primary efficacy endpoint and its components (circled p-values are those that were statistically significant in the primary analysis and lost statistical significance in this sensitivity analysis).

Table 22.Effect of rivaroxaban compared with placebo on the primary efficacy endpoint and its components censored at the earlier of the day before the start of 2C19 inhibitor or of the last thienopyridine use (TIMI 51: mITT analysis set).

Subject Stratum	Rivaroxaban 2.5 mg BID (N=4,291)	Rivaroxaban 5 mg BID (N=4,248)	Rivaroxaban Combined (N=8,539)	Placebo (N=4,268)	2.5 mg BID vs. Placebo		5 mg BID vs. Placebo		Combined vs. Placebo	
Parameter	n(%)	n(%)	n(%)	n(%)	HR (95% CI)	Log-Rank P-value	HR (95% CI)	Log-Rank P-value	HR (95% CI)	Log-Rank P-value
All Strata	4291	4248	8539	4268						
Primary	217(5.1)	208(4.9)	425(5.0)	258(6.0)	0.86 (0.71,1.03)	0.090	0.84 (0.70,1.01)	0.070	0.85 (0.73,0.99)	0.040
CV_Dth	40(0.9)	71(1.7)	111(1.3)	70(1.6)	0.58 (0.39,0.85)	0.005	1.07 (0.77,1.48)	0.702	0.82 (0.61,1.10)	0.187
MI	163(3.8)	131(3.1)	294(3.4)	176(4.1)	0.94 (0.76,1.17)	0.594	0.78 (0.62,0.98)	0.033	0.86 (0.72,1.04)	0.126
Stroke	30(0.7)	32(0.8)	62(0.7)	26(0.6)	1.18 (0.70,2.00)	0.535	1.32 (0.78,2.21)	0.295	1.24 (0.79,1.97)	0.350
ASA + Thieno	4231	4205	8436	4201						
Primary	211(5.0)	203(4.8)	414(4.9)	243(5.8)	0.87 (0.73,1.03)	0.148	0.86 (0.72,1.04)	0.116	0.87 (0.74,1.02)	0.079
CV_Dth	40(0.9)	70(1.7)	110(1.3)	70(1.7)	0.58 (0.39,0.85)	0.005	1.05 (0.75,1.46)	0.775	0.81 (0.60,1.09)	0.161
MI	157(3.7)	127(3.0)	284(3.4)	164(3.9)	0.97 (0.78,1.21)	0.791	0.80 (0.64,1.01)	0.065	0.89 (0.73,1.08)	0.253
Stroke	30(0.7)	31(0.7)	61(0.7)	24(0.6)	1.28 (0.75,2.18)	0.371	1.36 (0.80,2.32)	0.252	1.32 (0.82,2.11)	0.250

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 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.
Circled p-values are those that were statistically significant in the primary analysis and lost statistical significance in this sensitivity analysis.

[13]That is, drugs that inhibit CYP2C19.

Circled p-values are those that were statistically significant in the primary analysis and lost statistical significance in this sensitivity analysis.

Table 23. Effect of rivaroxaban compared with placebo on bleeding endpoints censored at the earlier of the day before the start of 2C19 inhibitor or of the last thienopyridine use (TIMI 51: mITT analysis set).

	Rivaroxaban									
Subject Stratum	2.5 mg BID (N=4299)	5 mg BID (N=4253)	Combined (N=8552)	Placebo (N=4283)	-- 2.5 mg BID vs. Placebo --		-- 5 mg BID vs. Placebo --		-- Combined vs. Placebo --	
Parameter	n(%)	n(%)	n(%)	n(%)	HR (95% CI)	Log-Rank P-value	HR (95% CI)	Log-Rank P-value	HR (95% CI)	Log-Rank P-value
All Strata	4299	4253	8552	4283						
Primary	45(1.0)	54(1.3)	99(1.2)	12(0.3)	3.83 (2.02,7.23)	<0.001	4.76 (2.55,8.90)	<0.001	4.28 (2.35,7.80)	<0.001
Clinical Sig.	432(10.0)	560(13.2)	992(11.6)	243(5.7)	1.83 (1.56,2.14)	<0.001	2.47 (2.12,2.87)	<0.001	2.14 (1.86,2.47)	<0.001
ASA + Thieno	4243	4211	8454	4218						
Primary	45(1.1)	54(1.3)	99(1.2)	12(0.3)	3.83 (2.02,7.23)	<0.001	4.76 (2.55,8.90)	<0.001	4.28 (2.35,7.80)	<0.001
Clinical Sig.	431(10.2)	558(13.3)	989(11.7)	240(5.7)	1.85 (1.58,2.16)	<0.001	2.49 (2.14,2.89)	<0.001	2.16 (1.88,2.49)	<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 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.

Evaluator's comment

These were post-hoc analyses with a reduction in power as the number of subjects with the primary efficacy outcome decreased from 1,002 to 683 (983 primary efficacy endpoints were estimated to have approximately 96% power to detect a 22.5% relative reduction between pooled doses of rivaroxaban and placebo arms pooled across All Strata, with a 2-sided type I error rate of 0.05). Therefore the lack of statistical significance is not surprising. The consistency of the point estimates with those of the original analysis support the robustness of the TIMI 51 study findings.

[information redacted]Rivaroxaban 2.5 mg bd prevented 101 (95% CI: -9, 211) non-haemorrhagic CV death, MI and ischemic stroke events per 10,000 patient-years compared with placebo (NNT = 99 patient-years), while causing an additional 16 (95% CI:-7, 39) fatal bleeding or ICH events (NNH = 622 patient-years) (Table 24, below). This suggests a favourable benefit-risk ratio of ~6.3 to 1 (compared with a ratio of ~11 to 1 in the original analysis). This benefit-risk ratio is even more favourable during the first 30 days of treatment, when clinical risk is highest (Table 25, below). The benefit-risk ratio is reduced but remains positive at 1.3:1 if all TIMI life-threatening and TIMI Major bleeding events (77 additional events caused with rivaroxaban per 10,000 patient-years compared with placebo) are taken in to consideration.

Table 24. Ischemic and haemorrhagic events censored at the earlier of the day before the start of omeprazole/esomeprazole or of the last thienopyridine use for 2.5 mg bd dose in stratum 2 (TIMI 51: mITT (excluding sites 091001, 091019 and 091026) analysis set)

Time to Event Category	Endpoints	Event Rate(a) (/100 Pt-yrs) Rivaroxaban	Event Rate(a) (/100 Pt-yrs) Placebo	Excess Number of Events (Rivaroxaban - Placebo) Excess # events for 10,000 pt-yrs	95% CI	NNT/NNH(b)
Efficacy	Non-bleeding CV death, MI or ischemic stroke	5.42	6.44	-101	(-211, 9)	-99
	Non-bleeding CV death	0.99	1.73	-73 *	(-126, -21)	-136
	MI excl CV death	3.98	4.06	-9	(-99, 82)	-1164
	Ischemic stroke excl CV death	0.52	0.51	1	(-31, 34)	6986
	Non-CV death excl fatal bleed	0.16	0.18	-2	(-22, 18)	-4727
Safety	TIMI life threatening bleeding + TIMI major bleeding	1.33	0.56	77 *	(33, 121)	129
	Fatal Bleeding + symptomatic ICH	0.31	0.15	16	(-7, 39)	622
	Fatal Bleeding	0.13	0.10	3	(-14, 20)	3462
	Intracranial Bleeding (ICH)	0.26	0.08	18	(-2, 39)	542
	Fatal ICH	0.08	0.03	5		1892
	Non-fatal ICH	0.18	0.05	13	(-4, 31)	759
	Non-fatal, non-ICH TIMI life threatening bleeding	0.47	0.18	29 *	(3, 56)	342
	TIMI Major Bleeding, non-life threatening	0.57	0.23	35 *	(5, 64)	289

(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 deaths are deaths that were adjudicated as due to non-hemorrhagic causes (i.e., CV deaths with CEC adjudicated cause neither 'Intracranial hemorrhage' nor 'Hemorrhage, not intracranial') and did not have fatal bleeding complications (e.g. trauma, malignancy).
All hemorrhagic CV deaths (i.e., CV deaths with CEC adjudicated cause of 'Intracranial hemorrhage' or 'Hemorrhage, not intracranial') 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.

Table 25. Comparison between efficacy events prevented and bleeding events caused by treatment with rivaroxaban 2.5 mg bd in stratum 2 (TIMI 51: mITT (excluding sites 091001, 091019 and 091026) analysis set)

Subgroup	Excess Number of Events/10,000 Patient-years (Rivaroxaban - Placebo) Non-bleeding CV death+MI+ischemic stroke Risk difference /10,000 Pt-yrs	95% CI	NNT/NNH	Fatal Bleeding + ICH Risk difference /10,000 Pt-yrs	95% CI	NNT/NNH	Net Clinical Benefit Diff	95% CI
MITT	-115.18	(-211.96, -18.41)	-87	10.16	(-11.24, 31.57)	984	-105.02	(-204.13, -5.90)
Up to the earlier between the day before start of omeprazole/ esomeprazole use and the last dose of thienopyridine	-101.28	(-211.10, 8.53)	-99	16.07	(-6.74, 38.87)	622	-85.21	(-197.37, 26.94)
Up to the earliest of day 30, the day before start of omeprazole/ esomeprazole use and the last dose of thienopyridine	-685.43	(-1364.73, -6.14)	-15	-29.46	(-197.62, 138.71)	-339	-714.89	(-1414.69, -15.09)

Note: * Event rates per 10,000 patient years.
Note: ** Difference of event-rates (efficacy + safety) per 10,000 patient-years.
Note: Negative value of Net Clinical Benefit favors Rivaroxaban, and a positive value favors Placebo.

Evaluator's comment

Although reduced compared with the original analysis, the benefit-risk ratio remains in favour of rivaroxaban compared with placebo in subjects on "optimal" thienopyridine therapy, particularly when comparing fatal/irreversible events.

Q7. On page 276 of the CSR for the pivotal efficacy study (ATLAS ACS 2 TIMI 51), it is reported that "24/10,209 (0.24%) rivaroxaban-treated and 13/5,114 (0.25%) placebo-treated subjects had elevations in ALT and total bilirubin that met the thresholds of >3xULN and >2xULN, respectively." However it was not reported whether these cases also had an elevated ALP or other underlying cause for their abnormal LFTs. The sponsor was requested to provide these additional details for these subjects.

Sponsor's response

The sponsor reiterated that the percentage of subjects with elevations in ALT and total bilirubin that met the thresholds of >3xULN and >2xULN, respectively was similar in the rivaroxaban-

treated and placebo-treated groups. They also provided extracted clinical narratives for all these subjects, which demonstrated an alternative reason for the LFT abnormalities.

Evaluator's comment

No Hy's Law cases were identified based on a similar incidence of subjects with elevations in ALT and total bilirubin that met the thresholds of >3xULN and >2xULN, respectively and the finding of an alternative explanation for the elevated liver enzymes.

Q8. It is considered that the requested indication for "Prevention of cardiovascular death, myocardial infarction and stent thrombosis..." is not supported by the data for the 2.5 mg bid dose of rivaroxaban. The study was powered to look at a composite endpoint, not the individual components. Additionally, the 2.5 mg rivaroxaban dose did not show a significant reduction in MI and the conclusions regarding stent thrombosis are the result of a post-hoc analysis. The sponsor was invited to provide an alternative appropriately worded indication with justification for the change proposed.

Sponsor's response

The sponsor proposed the following alternative ACS indication:

> *Prevention of atherothrombotic events (cardiovascular death, myocardial infarction or stroke) and stent thrombosis in patients with an acute coronary syndrome (ACS) ST elevation myocardial infarction (STEMI), non-ST elevation myocardial infarction (NSTEMI) or unstable angina (UA) in combination with aspirin alone or with aspirin plus a thienopyridine (clopidogrel or ticlopidine).*

They stated that stent thrombosis was not a post-hoc analysis, and that stent thrombosis was listed as a pre-specified efficacy endpoint. The sponsor also included reference to similar methodology being used for the assessment of stent thrombosis for ticagrelor[4] and prasugrel[6].

Evaluator's comment

That stent thrombosis was an adjudicated, pre-specified component of the composite primary and major secondary endpoints is not in question. However, as the sponsor points out in their response, Section 2.2.10.4.2 Analysis Methods of the SAP (Amendment 2) states that:

> *"These endpoints, except for stent thrombosis, will be analysed using the same methods as those used for the primary efficacy endpoint, including log-rank test, Cox model, and Kaplan-Meier estimates. Stent thrombosis and its sub-categories will be summarized by treatment group since this endpoint is not a formal study endpoint in the study protocol (even though it's adjudicated), thus it's expected only few of these events to warrant more involved analyses."*

This was also referred to in the TIMI 51 CSR. Section 3.11.3 of the TIMI 51 CSR also declares that:

> *"The following analyses were not planned and were performed after the unblinding of treatment assignments.*
>
> - *The hazard ratio and 95% confidence interval based on Cox proportional hazards (stratified for all strata only) model were provided for time to first occurrence of stent thrombosis."*

While the evaluator agrees that the summary statistics do show reduced stent thrombosis compared with placebo and that this was also seen in an analysis based on the modified mITT analysis set requested by the EMA, the other analyses of this endpoint were post-hoc. It is therefore not considered appropriate to select out the stent thrombosis component of a composite endpoint (that was "not a formal endpoint") for inclusion in the indication. It is acceptable for the descriptive analysis results to be discussed in the Clinical Trials section of the

PI, but any reference to HRs should state that they were post-hoc analyses. The PI needs to be revised accordingly.

While the evaluator cannot comment on the methodology or statistical analysis used for the assessment of stent thrombosis for ticagrelor and prasugrel, neither product has an indication for reduction in stent thrombosis, with stent outcomes only discussed in the Clinical Trials sections of their PIs[14, 15].

Q9. Adverse Effects - Prevention of CV death, MI and stent thrombosis after ACS: The Sponsor is requested to advise how the following event rates in paragraph 2 of this section were calculated: "Bleeding of any type or severity was reported with an event rate of 22 per 100 patient years. Anaemia was reported with an event rate of 1.4 per 100 patient years."

Sponsor's response

The sponsor advised that 2,252 (22%) of rivaroxaban subjects had treatment-emergent bleeding-related adverse events and that 1.4% of the subjects in the rivaroxaban group had treatment-emergent anaemia.

The sponsor reported converting raw percentages of subjects to patient years based on the following information: *"Across all treatment groups, 78.9% had cumulative durations of exposure ≥6 months, 53.8% for ≥12 months, and 30.9% for ≥18 months. The median exposure to study treatment was slightly more than a year (386.0 days for all treated subjects), the event rate calculated as per 100 patient-year is in general slightly lower than the raw percentage."*

Evaluator's comment

While anaemia was reported as a Preferred Term under a number of different Body Systems or Organ Class, the overall number of treatment-emergent anaemia cases could not be located by the evaluator in the data submitted by the sponsor. However, the evaluator is prepared to accept this figure.

Q10. In the pivotal efficacy study it was stated that "Randomization was to occur as soon as possible after the initial treatments for the index ACS event, including revascularization procedures, but could not occur during the first 24 hr following hospitalization". There was a median of 4.8 days from index event to randomisation and commencement of Xarelto, but in the Dosage and Administration section of the PI it is advised that "Xarelto should be started within 24 hr after admission to hospital". The Sponsor was requested to advise whether this has the potential to affect the safety and/or efficacy of Xarelto or if earlier commencement of Xarelto in the trial may have altered the results of the study. That is, how many efficacy endpoints may have occurred in this 5 day period?

Sponsor's response:

The sponsor advised that no efficacy endpoints were collected in between index event and randomisation and did not comment on whether the delay of ~5 days may have affected either the safety or efficacy results seen in the TIMI 51 trial. To be consistent with the study protocol they proposed revising the Dosage and Administration section of the PI to:

"Xarelto should be started earliest 24 hr after admission to hospital"

[14]Brilinta Product Information. Date of Approval: 9 June 2011; pages 9 & 24
[15]Effient Product Information. Date of Approval: 3 May 2012

Evaluator's comment

This is acceptable, although would read better as *"Xarelto should be started, at the earliest, 24 hr after admission to hospital"*.

12. Second round benefit-risk assessment

12.1. Second round assessment of benefits

After consideration of the responses to clinical questions, the benefits of rivaroxaban 2.5 mg bd in the proposed usage are unchanged from those identified in the First Round Evaluation. The original concern regarding the high discontinuation rate has been addressed, with clarification by the sponsor that efficacy endpoints are known for 94.9% of subjects (13,661 completed or dead plus 1,066 with known ischemic outcome), vital status known for an additional 3.4%, and only 1.8% have an unknown vital status (mITT population).

Based on a sensitivity analysis of the post-hoc benefit-risk analysis for ACS subjects on "optimal" thienopyridine therapy, in Stratum 2 rivaroxaban 2.5 mg bd prevented 101 (95% CI: -9, 211) non-haemorrhagic CV death, MI and ischemic stroke events per 10,000 patient-years compared with placebo. This equates to 1 less non-haemorrhagic CV death, MI and ischemic stroke event per 99 patient-years (NNT = 99 patient-years). This compares with the prevention of 115 events (95% CI: 18.40, 211.96) and an NNT of 87 patient-years reported for the same subject group in the original analysis.

12.2. Second round assessment of risks

After consideration of the responses to clinical questions, the risks of rivaroxaban 2.5 mg bd in the proposed usage are unchanged from those identified the First Round Evaluation.

Based on a sensitivity analysis of the post-hoc benefit-risk analysis for subjects on "optimal" thienopyridine therapy, in Stratum 2 rivaroxaban 2.5 mg bd caused an additional 16 (95% CI:-7, 39) fatal bleeding or ICH events per 10,000 patient-years compared with placebo. This equates to 1 additional fatal bleeding or ICH event every 622 patient-years (NNH = 622 patient-years). This compares with the causation of 10 events (95% CI:-11.25, 31.57) and an NNH of 984 patient-years for the same subject group in the original analysis. If less severe bleeding is also considered (TIMI major or TIMI life-threatening bleeding) then in Stratum 2 rivaroxaban 2.5 mg bd caused an additional 77 (95% CI 33, 121) events with an NNH of 129 patient-years. This compares with the causation of 78 events and an NNH of 128 patient-years reported or the same subject group in the original analysis.

12.3. Second round assessment of benefit-risk balance

The benefit-risk balance of rivaroxaban (Xarelto) 2.5 mg bd, given the proposed usage, is favourable. Comparison of the fatal/irreversible benefits and risks (presented above) for subjects on "optimal" thienopyridine therapy suggests a favourable benefit-risk ratio for rivaroxaban 2.5 mg bd of ~6.3 to 1 (ratio of ~11 to 1 in the original analysis). If a more conservative benefit-risk assessment is considered (by including some less severe bleeding events), the benefit-risk ratio reduces to 1.3 to 1 (101 non-haemorrhagic CV death, MI and ischemic stroke events prevented:77 TIMI major or TIMI life-threatening bleeding events caused). This ratio was 1.5:1 in the original analysis (Table 26, below).

Table 26. Comparison between efficacy events prevented and bleeding events caused by treatment with rivaroxaban 2.5 mg bd in stratum 2 (TIMI 51: mITT (excluding sites 091001, 091019 and 091026) analysis set)

	Excess Number of Events/10,000 Patient-years (Rivaroxaban – Placebo)					
	Non-Haemorrhagic CV Death + MI + Ischemic Stroke		Fatal Bleeding + ICH		Net Clinical Benefit	Benefit-Risk Ratio
	Risk Difference / 10,000 pt-yrs	NNT / NNH	Risk Difference / 10,000 pt-yrs	NNT / NNH	Difference	Efficacy Risk Diff : Safety Risk Diff
Original mITT	-115	-87	10	984	-105	11:1
Sensitivity – optimal thienopyridine mITT	-101	-99	16	622	-85	6.3:1
			TIMI Major or TIMI Life-Threatening			
Original mITT			78	128	-37	1.5:1
Sensitivity – optimal thienopyridine mITT			77	129	-24	1.3:1

13. Second round recommendation regarding authorisation

Based on the satisfactory answers received to the questions raised, it is recommended that rivaroxaban (Xarelto) 2.5 mg bd is approved for the treatment of acute coronary syndrome, subject to modification of the PI and CMI as recommended. In particular, it is considered that the requested indication for "*Prevention of atherothrombotic events and stent thrombosis...*" is not supported by the data as the study was powered to look at a composite endpoint, not the individual components, and stent thrombosis was a component endpoint. Use of Xarelto should also be restricted to ACS patients receiving combination therapy with aspirin plus a thienopyridine (clopidogrel or ticlopidine).

14. References

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