Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for Rivaroxaban

Proprietary Product Name: Xarelto

Sponsor: Bayer Australia Ltd

November 2013

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <http://www.tga.gov.au>.

About AusPARs

- An Australian Public Assessment Record (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations, and extensions of indications.
- An AusPAR is a static document, in that it will provide information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

List of abbreviations

Abbreviation	Meaning
ACC	American College of Cardiology
ACCF	American College of Cardiology Foundation
ACS	acute coronary syndrome
AF	atrial fibrillation
AHA	American Heart Association
ALT	alanine aminotransferase
aPTT	activated partial thromboplastin time
ASA	acetyl salicylic acid / aspirin
AST	aspartate aminotransferase
AUC	area under the plasma concentration versus time curve from zero to infinity after single (first) dose
AUC24	area under the rivaroxaban concentration-time curve at steady state over 24 hr
AUC/D	AUC divided by dose (mg)
bd	twice-daily
BMI	body mass index
CABG	coronary artery bypass graft
CAD	coronary artery disease
CEC	Clinical Events Committee

Abbreviation	Meaning
CHD	coronary heart disease
CHF	congestive heart failure
CI	confidence interval
CL/F	apparent oral clearance
cm	centimetre
CMI	Consumer Medicines Information
C_{max}	maximum drug concentration in plasma after single dose administration
C_{max}/D	maximum drug concentration in plasma after single dose administration divided by dose (mg)
C_{min}	the lowest rivaroxaban concentration during a dosing interval
Cp	drug concentration in plasma
CPMP	Committee for Proprietary Medicinal Products
CrCl	creatinine clearance
CRF	case report form
CRL	Complete Response Letter
CSR	clinical study report
CV	cardiovascular
CVD	cardiovascular disease
CYP	cytochrome P450
dL	decilitre
DVT	deep venous thromboembolism
EC	Executive Committee
ECG	electrocardiogram
eDISH	electronic tool for Drug Induced Serious Hepatotoxicity
EMA	European Medicines Agency
E_{max}	maximum effect (of the effect versus time curve)

Abbreviation	Meaning
ER	extended release
ESC	European Society of Cardiology
ETP	endogenous thrombin potential
EU	European Union
EWP	Efficacy Working Party
F1	relative bioavailability (F1=1 for 2.5 mg tablet rivaroxaban)
F1.2	prothrombin fragment 1 and 2
FXa	Factor Xa
g	grams
GTED	Global Treatment End Date
GUSTO	Global Strategies for Opening Occluded Coronary Arteries
HEAC	Hepatic Event Assessment Committee
HepTest	Factor Xa activity
HR	hazard ratio
ICH	intracranial haemorrhage
IDMC	Independent Data Monitoring Committee
IIV	inter-individual variability
IOV	inter-occasion variability
IPD	Individual Patient Data
IR	immediate release
ISTH	International Society on Thrombosis and Haemostasis
ITT	Intent-to-Treat
KA	absorption rate constant
LBM	calculated lean body mass
LLOQ	lower limit of quantification

Abbreviation	Meaning
LMWH	low-molecular-weight heparin
LFT	liver function test
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligrams
MI	myocardial infarction
min	minute
mITT	modified intent-to-treat
mL	millilitre
NCO	net clinical outcome
NDA	New Drug Application
ng	nanograms
NNH	the number of subjects needed to be treated with rivaroxaban versus placebo to cause 1 additional ICH excluding CV death event
NNT	the number of subjects needed to be treated with rivaroxaban versus placebo to prevent 1 additional harmful efficacy event
NONMEM	non-linear mixed effects modelling
NSAID	non-steroidal anti-inflammatory drugs
NSS	not statistically significant
NSTEMI	non-ST-segment elevation myocardial infarction
OC	Operations Committee
od	once daily
PCI	percutaneous coronary intervention
PD	pharmacodynamics
PE	pulmonary embolism
P-gp	P-glycoprotein
PI	Product Information

Abbreviation	Meaning
PiCT	prothrombinase-induced clotting time
PK	pharmacokinetics
POPPK	population pharmacokinetics
PPI	proton pump inhibitor
PT	prothrombin time
QT/QTc	QT interval/QT interval corrected for heart rate
QTcB	QTc according to Bazett
QTcF	QT interval corrected for heart rate using Fridericia ' s formula
reMI	repeat myocardial infarction
RMP	Risk Management Plan
RRR	relative risk reduction
SAE	serious adverse event
SAP	Statistical Analysis Plan
SCRE, SCR	serum creatinine
SCS	Summary of Clinical Safety
SMQ	Standardised MedDRA Query
sNDA	Supplemental New Drug Application
SRI	severe recurrent ischemia
SRIH	severe recurrent ischemia leading to hospitalisation
SRIR	severe recurrent ischemia requiring revascularisation
STEMI	ST-segment elevation myocardial infarction
TDD	total daily dose
TEAE	treatment-emergent adverse event
TEBE	treatment-emergent bleeding event
TGA	Therapeutic Goods Administration

Abbreviation	Meaning
TIA	transient ischemic attack
TIMI	thrombolysis in myocardial infarction
$t_{1/2}$	half-life associated with the terminal slope
t_{max}	time to reach maximum drug concentration in plasma after single (first) dose
US/USA	United States of America
UA	unstable angina
UFH	unfractionated heparin
ULN	upper limit of normal
USPI	United States Package Insert
V/F	apparent volume of distribution
VTE	venous thromboembolism
yr	year
µL	microlitres

I. Introduction to product submission

Submission details

Type of submission:	Extension of Indications and New strength
Decision:	Withdrawn
Date of decision:	31 May 2013
Active ingredient:	Rivaroxaban
Product name:	Xarelto
Sponsor's name and address:	Bayer Australia Ltd 875 Pacific Highway Pymble, NSW 2073
Dose form:	Tablets
Strength:	2.5 mg
Container:	Blister pack
Pack sizes:	14, 56, 100 and 168
Approved therapeutic use:	Not applicable
Route of administration:	Oral
Dosage:	One tablet (2.5 mg) twice daily
ARTG number:	Not applicable

Product background

Rivaroxaban (Xarelto®) is currently approved in Australia in 10, 15 and 20 mg strength tablets for various antithrombotic indications at a maximum daily dose of 15 mg twice (initially) and 20 mg once (long-term) daily.

This AusPAR describes the application by the sponsor to register a new strength of Xarelto (2.5 mg) for a new indication. The proposed additional indication for Xarelto (2.5 mg) is:

> *Prevention of cardiovascular death, myocardial infarction and stent thrombosis in patients after an acute coronary syndrome (ACS) (non-ST elevation or ST elevation myocardial infarction or unstable angina) in combination with acetylsalicylic acid (ASA) alone or with ASA plus a thienopyridine (clopidogrel or ticlopidine).*

Xarelto (rivaroxaban) is a selective, direct acting Factor Xa inhibitor. Xarelto (rivaroxaban) has been considered previously by the Advisory Committee on Prescription Medicines (ACPM; previously called Australian Drug Evaluation Committee (ADEC)) on two occasions, the first for the initial registration of a 10 mg tablet for the indication of prevention of venous thromboembolism (VTE) in adult patients who have undergone major orthopaedic surgery of the lower limbs (considered at the 260th meeting of the ADEC on 3 October 2008) and the

second for the consideration of an application to include two new dosage strengths (15 and 20 mg tablets) on the Australian Register of Therapeutic Goods (ARTG) for two additional indications, namely stroke prevention in atrial fibrillation and deep vein thrombosis (DVT) treatment and prevention of recurrent DVT and pulmonary embolism (PE) (considered at the 282nd meeting of the ACPM on 3 February 2012) .

A maximum clinical oral dose of 2.5 mg twice daily is proposed.

There are no generic products containing rivaroxaban.

Guidelines applicable to this submission are:

- EU Guidelines adopted by the TGA
  - CPMP/EWP/570/98. *Points to Consider on the Clinical Investigation of New Medicinal Products in the Treatment of Acute Coronary Syndrome (ACS) Without Persistent ST-Segment Elevation*. Effective: 19 April 2001.
  - pp. 127 - 132 of Rules 1998 (3C) - 3CC6a. *Clinical Investigation of Medicinal Products for Long-Term Use*. Replaces: pp. 163 - 165 of Rules 1989. Effective: 12 February 2002. See also: pp. 121 - 125 of Rules 1998 (3C) - 3CC5a (Adopted by TGA with conditions)
  - CPMP/EWP/2330/99. *Points to Consider on Application with: 1. Meta-Analyses; 2. One Pivotal Study*. Published: TGA Internet site. Effective: 27 March 2002
  - CHMP/EWP/185990/06. *Guideline on Reporting the results of Population Pharmacokinetic Analysis*. Published: TGA Internet site. Effective: 27 January 2009
- Australian regulatory guidelines for prescription medicines. Appendix 8: Product Information.

Regulatory status

Tablets containing 10 mg of rivaroxaban were approved for use in Australia in November 2008 for the indication

> *'Prevention of venous thromboembolism (VTE) in adult patients who have undergone major orthopaedic surgery of the lower limbs (elective total hip replacement, treatment for up to 5 weeks; elective total knee replacement, treatment for up to 2 weeks)'.*

Tablets containing 15 mg and 20 mg of rivaroxaban were approved for use in Australia in May 2012 for the indication

> *'Prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation and at least one additional risk factor for stroke. Treatment of deep vein thrombosis (DVT) and for the prevention of recurrent DVT and pulmonary embolism (PE)'.*

Bayer Australia Ltd is the sponsor of the current submission and of the registered 10 mg, 15 mg and 20 mg tablets.

Table 1 summarises the international regulatory status of Xarelto at the time the pre Committee on Prescription Medicines (ACPM) response was submitted in January 2013.

Table 1. International regulatory status

Country	Date of Submission	Date of Approval
European Union Rapporteur – Sweden Co-Rapporteur - Germany	22 December 2011	Decision expected in late Feb 2013
United States of America	Response to Complete Response Letter submitted in Sep 2012	Decision expected in early Mar 2013
Canada	8 March 2012	Pending
Switzerland	20 January 2012	Pending
New Zealand	Not yet submitted	N/A

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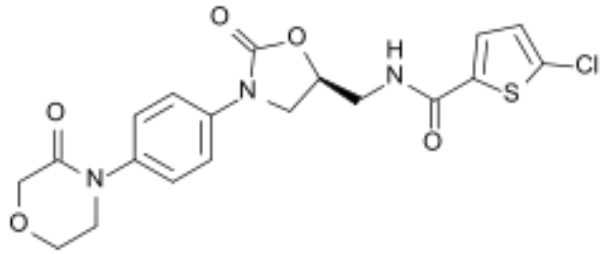
II. Quality findings

Drug substance (active ingredient)

Rivaroxiban has the following structure (Figure 1).

Figure 1. Chemical structure



It is a selective serine protease coagulation Factor Xa inhibitor. Three polymorphic crystalline forms are known, Form I is the form used (in all tablet strengths). It is practically insoluble in water (0.007 mg/mL).

All aspects relating to the drug substance for the proposed products are identical to those approved for the registered tablets.

Drug product

The manufacturing process consists of wet granulation, followed by drying, blending, compression, film-coating and polishing (as per the registered strengths).

The different strengths are not direct scales. The 2.5 mg strength is distinguished from the registered strengths by the colourant, iron oxide yellow (the registered strengths contain varying amounts of iron oxide red), used in the film coating and tablet markings.

The tablets are well controlled with satisfactory limits at release and expiry.

The stability data provided supports a shelf life of 3 years when stored below 30°C in the proposed packaging.

Biopharmaceutics

The absolute bioavailability of the 20 mg tablet was previously shown to be 66% in the fasted state. The absolute bioavailability of the 2.5 mg tablet (and the registered 10 mg strength) has been estimated to be 80-100%.

The area under the plasma concentration time curve (AUC) was found to increase in proportion to dose in the range 2.5 mg to 10 mg; however, the corresponding increase in peak plasma concentration (C_{max}) was somewhat less than dose proportional.

Quality summary and conclusions

There are no objections to the registration of Xarelto 2.5 mg rivaroxaban tablets with regard to chemistry, manufacturing and controls.

III. Nonclinical findings

Introduction

The sponsor has provided several new studies not previously evaluated by the TGA examining aspects of primary pharmacodynamics, pharmacodynamic and pharmacokinetic drug interactions and repeat dose toxicity in juvenile animals. These studies were provided in order to further characterise the nonclinical profile of rivaroxaban with respect to its mechanism of action, potential for drug interactions and paediatric use. Pivotal repeat dose toxicity studies were conducted in compliance with Good Laboratory Practice (GLP). Changes to the '*Carcinogenicity'* section of the Product Information document were also noted and are discussed in the current submission.

Pharmacology

Primary pharmacology

Consistent with previous investigations, rivaroxaban was shown to be a potent inhibitor of platelet aggregation (15 ng/mL in plasma), thrombin generation (≥ 2.3 nM or ≥ 15 ng/mL in plasma) and thrombus formation (at 300 ng/mL in mechanical heart valves) *in vitro*. In contrast to the direct thrombin inhibitors, melagatran and dabigatran, rivaroxaban did not increase thrombin generation in the presence of thrombomodulin, suggesting it does not suppress the protein C negative feedback system. Rivaroxaban showed anti-thrombotic efficacy comparable to unfractionated heparin and enoxaparin. Rivaroxaban (≥ 1μM) also effectively suppressed FXa-mediated inflammatory signalling in human atrial tissue slices *in vitro*, as shown by inhibition of the FXa-mediated increases in PAR2-4, ICAM-1, PAI-1 mRNA expression, and NF-κB and MAPK activation.

Rivaroxaban demonstrated antithrombotic efficacy *in vivo*, preventing arterial thrombosis in wild-type mice (≥ 1 mg/kg intravenously (IV)) and hypercholesterolemic atherosclerotic mice (≥ 1.5 mg/kg IV) and inhibiting stent thrombosis in an extracorporeal circuit in minipigs (≥ 0.11 μg/kg/min IV). Whilst chronic rivaroxaban administration to atherosclerotic mice for 6 months at 1 or 5 mg/kg/day PO did not markedly alter atherosclerotic plaque progression, it down-regulated the expression of inflammatory mediators and promoted lesion stability *in vivo*.

Pharmacodynamic drug interactions

The antithrombotic efficacy of rivaroxaban was potentiated by the addition of ASA and a P2Y12 receptor blocker such as clopidogrel or ticagrelor *in vitro* and *in vivo*. The rivaroxaban induced inhibition of platelet aggregation and thrombin generation *in vitro* (at ≥ 15 ng/mL) was enhanced by the addition of ticagrelor (≥1000 ng/mL) and ASA (100 µg/mL), leading to an inhibition that was greater than that observed with any agent alone. Similarly, the protection afforded by rivaroxaban (0.11=1 µg/kg/min IV) against thrombosis development in bare metal stents placed in a minipig arteriovenous extracorporal circuit was enhanced by the addition of ASA (1 mg/kg IV) and clopidogrel (0.5 mg/kg IV) and was observed at clinically relevant rivaroxaban concentrations (19-180 µg/L compared to a C_{max} of 125 µg/L in ACS patients given 2.5 mg twice a day (bid)).

Pharmacokinetics

Pharmacokinetic drug interactions

Rivaroxaban is a substrate of the cytochrome P450 isozymes CYP3A4/5, CYP2J2, and the P-gp and ATP-binding cassette G2 (ABCG2) transporters. Inhibitors and inducers of these CYP450 enzymes or transporters (for example, P gp) may result in changes in rivaroxaban exposure.

The drug transporter characteristics of rivaroxaban and its potential for pharmacokinetic drug interactions were investigated in recombinant cell lines *in vitro*. The inhibition of P-gp mediated efflux of rivaroxaban by dronedarone (antiarrhythmic) and fluconazole (antifungal) was investigated in cell systems *in vitro*. In addition, the transporter characteristics of OATP (organic anion transporting polypeptide), OAT (organic anion transporter) and OCT (organic cation transporter) were addressed in cell-based assays.

Fluconazole, which is classified as a moderate CYP3A4 inhibitor also caused a slight decrease of P-gp mediated rivaroxaban efflux at high concentrations (50% inhibitory concentration (IC_{50}) >300 µM). According to the clinical drug interaction study with fluconazole (PH036370), the mild (1.3 to1.4 fold) increase of the rivaroxaban C_{max} and AUC was within the normal range of inter-individual variability. Thus, the inhibitory effects of fluconazole on P-gp and/or CYP3A4 do not appear to be sufficient to increase plasma rivaroxaban levels in any clinically meaningful way.

Dronedarone, which is classified as a moderate CYP3A4 inhibitor, was also a strong inhibitor of P-gp mediated rivaroxaban efflux *in vitro* (IC_{50} = 0.37 µM) suggesting that it may also inhibit intestinal P-gp *in vivo*. In the absence of clinical PK interaction data there is a potential cause for concern for increased systemic exposure to rivaroxaban when co-administered with dronedarone.

Rivaroxaban is neither a substrate nor an inhibitor of OATP1B1 (Organic Anion Transporting Polypeptide 1B1), OATP1B3, OAT1 (Organic Anion Transporter 1) or OCT2 (Organic Cation Transporter 2) *in vitro*. However, rivaroxaban showed a slight inhibitory effect on OAT3 and is a weak substrate of this drug transport protein. Nonetheless, clinically relevant drug-drug interactions due to inhibition of OAT3 by rivaroxaban are unlikely, since the concentrations used for the *in vitro* studies (0.1-50 µM) were well above the clinically relevant unbound plasma concentrations of rivaroxaban.

Toxicity in juvenile animals

Three repeat-dose toxicity studies were conducted in neonatal Wistar rats given oral (gavage) micronised rivaroxaban doses (suspended in 0.5% aqueous Tylose® or ethanol/Solutol HS15®/water) of up to 60 mg/kg/day from postnatal Day 4 (preliminary study only) or

postnatal Day 10 onwards for 3 to 14 weeks. The two pivotal 3 month studies were conducted in accordance with GLP, using an appropriate species, adequate (but low) numbers, appropriate dose levels (based on absorption limits) and were of sufficient duration to identify any novel toxicities associated with juvenile dosing. The age of dosing (from postnatal Day 10 onwards) in the pivotal studies was considered sufficient to support paediatric dosing (2-18 years of age).

In the pivotal 13 week study, a decrease in rivaroxaban exposure was observed with repeated dosing, which was not seen in the subsequent 14 week study. This was attributed to reduced intestinal absorption of rivaroxaban due to reduced milk intake in the juvenile rats through weaning, since the lipids in the breast milk are known to have an emulsifying and solubilising effect. Rivaroxaban exposure was increased to levels similar to those found in the early lactation phase when the vehicle formulation in the 14 week study was changed to ethanol/Solutol HS15®/tap water formulation (the same as used in adult rat studies previously evaluated). This vehicle is also known to have a strong emulsifying and solubilising effect.

A comparison of studies using micronised rivaroxaban and the ethanol/Solutol HS15®/tap water vehicle formulation demonstrated that neonatal and juvenile rat exposure (PH-36598; area under the plasma concentration time curve from time zero to 24 h postdose ($AUC_{0–24\,h}$)= 26-62 mg.h/L) was very similar to that of adult rats (PH-34379; $AUC_{0–24\,h}$ = 26-55 mg.h/L) given doses of 60 mg/kg/day over a 3 month study duration.

Consistent with previous studies conducted in adult rats, the mild toxicological effects of rivaroxaban were characterised by exaggerated pharmacological effects of the compound (mild changes in haematological parameters: reduced erythrocyte counts, increased mean corpuscular haemoglobin (MCH), mean corpuscular haemoglobin concentration (MCHC), thrombocyte and reticulocyte counts) at the highest dose levels (40-60 mg/kg/day). Mild changes in liver enzyme levels (that is, aspartate aminotransferase (AST), alanine aminotransferase (ALT) and Lactic Acid Dehydrogenase (LDH)) and occasional liver weight increases were noted in both pivotal studies, also consistent with previous findings and are considered adaptive in the absence of adverse histopathological correlates. Minor histopathological findings in the pancreas, thyroid gland and kidneys in the first 3 month study were limited to a single gender, were not associated with any other toxicological correlates, and were not observed in the second 3 month study (associated with higher exposure levels), suggesting that these findings are not treatment-related.

Overall, the three month repeat dose toxicity studies in neonatal rats did not reveal any novel toxicity that would alter the risk benefit profile of rivaroxaban in paediatric patients.

New dose regimen

The proposed new daily dose of 2.5 mg bid is substantially lower than the currently approved maximum long-term rivaroxaban dose (20 mg once daily) for its DVT indications. At the approved dose of 20 mg/day, total human rivaroxaban exposure ($AUC_{0\text{-}24\,h}$) was reported as 3.31 mg.h/L. At the proposed new daily dose of 2.5 mg bid, total rivaroxaban exposure was 4 fold lower ($AUC_{0\text{-}24\,h}$ of 0.752 mg.h/L; calculated as twice the value of $AUC_{0\text{-}12\,h}$ [0.376 ng.h] reported for ACS patients in Report R-8642). Thus, the effect of the new dose regimen is to improve the safety margins for potential toxicological effects by 4 fold.

Paediatric use

While rivaroxaban is currently not proposed for paediatric use, studies in juvenile animals were conducted and evaluated as part of this nonclinical submission. Repeat dose toxicity studies conducted in neonatal rats (from 10 days old) given oral rivaroxaban doses of up to 60 mg/kg/day for 3 months, did not reveal any novel safety concerns (see *Toxicity in juvenile animals*).

Nonclinical summary and conclusions

- In the current submission the sponsor provided studies not previously evaluated by the TGA which examined aspects of primary pharmacodynamics, pharmacodynamic and pharmacokinetic drug interactions and repeat dose toxicity in juvenile animals.
- Rivaroxaban was shown to be a potent inhibitor of platelet aggregation, thrombin generation and thrombus formation *in vitro* and thrombosis formation *in vivo*.
- The antithrombotic efficacy of rivaroxaban was potentiated in the presence of ASA and/or a P2Y12 receptor blocker such as clopidogrel or ticagrelor *in vitro*, ex vivo or *in vivo*. Stent thrombosis was inhibited *in vivo* at clinically relevant concentrations by rivaroxaban alone or synergistically in combination with ASA and clopidogrel.
- Fluconazole was a mild inhibitor (IC_{50} >300 μM) and dronedarone was a strong inhibitor (IC_{50} = 0.37 μM) of P-gp mediated rivaroxaban efflux *in vitro*, suggesting their potential, to varying degrees, to enhance rivaroxaban exposure in humans.
- Rivaroxaban was neither a substrate nor an inhibitor of drug transporter proteins OATP1B1, OATP1B3, OAT1 or OCT2 *in vitro*. While it was found to have a slight inhibitory effect on OAT3 and is a weak substrate of this drug transport protein, clinically relevant drug interactions are not anticipated.
- No novel safety concerns were noted in three month repeat dose toxicity studies conducted in neonatal rats at identical rivaroxaban doses (and similar rivaroxaban exposure) as previously given to adult rats.
- The nonclinical risk benefit profile of rivaroxaban is unchanged for the new indication as the proposed new daily dose of 2.5 mg twice daily for the ACS indication is lower than the currently approved maximum long-term rivaroxaban dose (20 mg once daily).

Conclusions and recommendation

Rivaroxaban alone, and synergistically in combination with ASA and clopidogrel, was shown to inhibit thrombus development in a minipig stent thrombosis model at clinically relevant rivaroxaban concentrations *in vivo*. Nonclinical studies also demonstrated a potential for drug interactions with strong inhibitors of P-glycoprotein (that is, dronedarone) *in vivo*. The sponsor has acknowledged this potential interaction in Table 13 of the Product Information.

No novel safety concerns were raised by toxicity studies in juvenile animals.

There are no nonclinical objections to the registration of rivaroxaban for the proposed indication and treatment regimen, nor changes recommended to the proposed Risk Management Plan. Amendments to the draft Product Information document were recommended.

IV. Clinical findings

Introduction

A summary of the clinical findings is presented in this section. Further details of these clinical findings can be found at Attachment 1 of this AusPAR.

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."

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 (Anti-Xa Therapy to Lower cardiovascular events in addition to Aspirin with or without thienopyridine therapy in Subjects With Acute Coronary Syndrome) (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 bid, 5,176 on rivaroxaban 5 mg bid and 5,176 on placebo).

- Literature references

Evaluator's comment

The dose-finding study (TIMI 46) has been previously evaluated by the TGA as part of a specific condition of the original registration of Xarelto 10 mg 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 bid (n=153) or 5 mg bid (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.

Paediatric data

A paediatric development program for Xarelto has been agreed with the European Medicines Agency (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.

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.

Pharmacokinetics

Summaries of the evaluated pharmacokinetic studies are presented in the clinical evaluation report (CER at Attachment 1). Table 2 shows the studies relating to each pharmacokinetic topic and the location of each study summary.

Table 2. 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.

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 submission, 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.

Pharmacodynamics

Studies providing pharmacodynamic data

Table 3 shows the studies relating to each pharmacodynamic topic.

Table 3. 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.

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.

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 dosing. Therefore, bid 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 bid and 5 mg bid 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 regarding this in the application. The sponsor was requested to provide the basis for the decision to use the 2.5 mg dose including data on Factor Xa inhibition.

Efficacy

Evaluator's conclusions on clinical efficacy

The pivotal efficacy study (TIMI 51) compared 2 doses of rivaroxaban, 2.5 mg bid and 5 mg bid, 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 modified Intent-to-Treat (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 bid and 5 mg bid 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 bid 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 bid, and by a reduction in non-fatal MIs for rivaroxaban 5 mg bid (fatal MIs were higher in the 5 mg bid group).
- Sensitivity analyses generally confirmed the results, although in the ITT analysis rivaroxaban 5 mg bid was also superior to placebo in Stratum 2.

[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

- 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 bid and 5 mg bid 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 bid and 5 mg bid 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 bid 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 bid rivaroxaban dose is preferred to the 5 mg bid dose.

Only approval for the 2.5 mg bid dose was sought by the sponsor for the ACS indication.

Safety

Studies providing evaluable safety data

The pivotal efficacy study (TIMI 51), TIMI 46 as well as Studies 12361, 12570, 12571 and 14883 provided safety data for this submission.

Patient exposure

Pivotal efficacy study

The All Strata treatment exposure data for TIMI 51 are summarised below in Table 4. 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 bid and 5 mg bid 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 4. 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)

Dose-response and non-pivotal efficacy studies

The exposure data for TIMI 46 are summarised below in Table 5. 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 5. 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.

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.

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).

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.

Study 14883

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

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 adverse events (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 Hepatic Event Assessment Committee (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.

Evaluator's overall conclusions on clinical safety

The pivotal efficacy study (TIMI 51) compared 2 doses of rivaroxaban, 2.5 mg bid and 5 mg bid, 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 bid and 5 mg bid 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 bid rivaroxaban: 1.3% versus 0.4%, HR: 3.46; 95% CI: 2.08-5.77; p<0.001

- 5 mg bid 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 bid dose of rivaroxaban associated with higher event rates than the 2.5 mg bid dose.

· Fatal bleeding events were low overall and generally comparable between the 2.5 mg bid rivaroxaban dose and placebo. Rates were numerically higher in the rivaroxaban 5 mg bid 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 bid rivaroxaban dose is preferred to the 5 mg bid dose.

Only approval for the 2.5 mg bid dose is being sought by the sponsor for the ACS indication.

List of questions

Pharmacokinetics

Please see Questions 1 under *Second Round evaluation of clinical data submitted in response to questions* below for the sponsor's answer.

Efficacy

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

Safety

Please see Question 7 (with the sponsor's answer) under *Second Round evaluation of clinical data submitted in response to questions* below.

Clinical summary and conclusions

First round benefit-risk assessment

First round assessment of benefits

Based on the key efficacy and safety findings, the 2.5 mg bid rivaroxaban dose is preferred to the 5 mg bid dose. As the 2.5 mg bid dose is the only dose for which approval is being sought by the sponsor for the ACS indication, only the 2.5 mg bid 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 bid 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).

First round assessment of risks

As expected with an anticoagulant, the major risks associated with the use of rivaroxaban 2.5 mg bid 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 bid 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 bid 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).

First round assessment of benefit-risk balance

The benefit-risk balance of rivaroxaban 2.5 mg bid 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 bid 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 6, below, Stratum 2 only).

In Stratum 2, rivaroxaban 2.5 mg bid 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 6. Ischemic and haemorrhagic events for 2.5 mg bid 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.

First round recommendation regarding authorisation

At this stage the clinical evaluator is unable to recommend approval of rivaroxaban 2.5 mg bid 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 by the evaluator.

Second round evaluation of clinical data submitted in response to questions

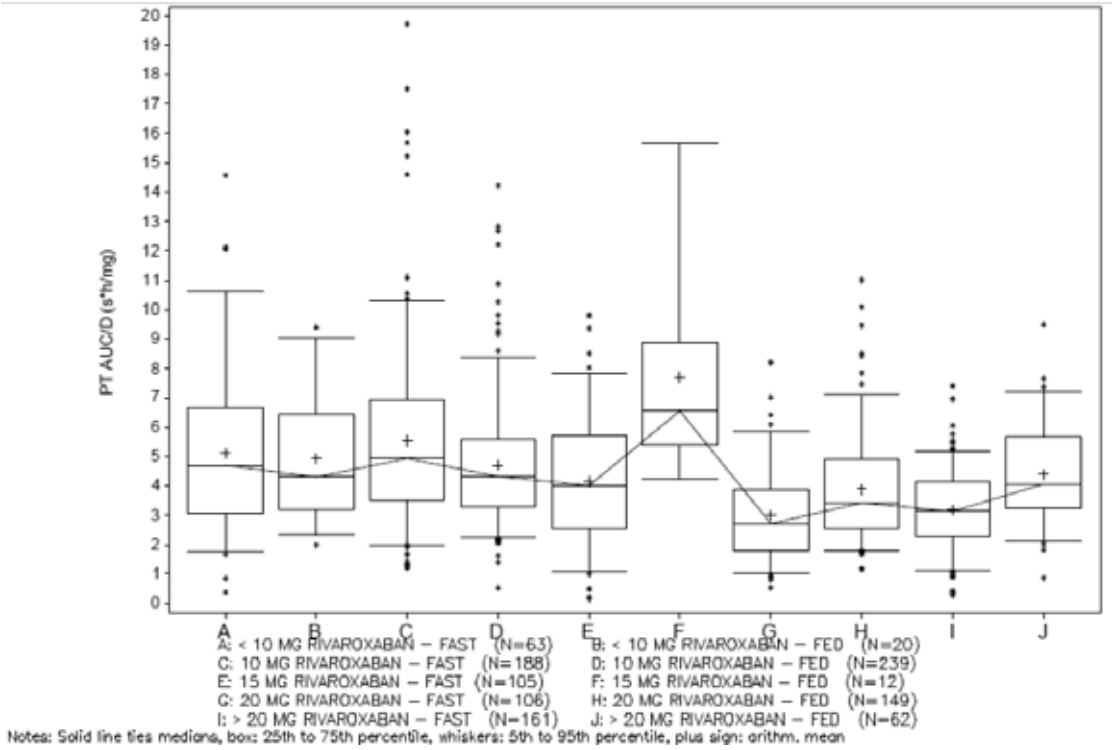
The clinical evaluator's questions and the sponsor's responses were as follows:

Q1. The sponsor was asked to provide the results and conclusions to support the lack of food effect with the 2.5 mg tablet.[2]

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 2 below).

Figure 2. 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 2 is consistent with the results of Study 11937 and supports the lack of a food-effect with doses of rivaroxaban ≤ 10 mg.

[2] 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.

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 bid rivaroxaban doses in stratum 1 for the endpoint of CV death/MI/stroke, and 45% for the combined 2.5 mg and 5 mg bid 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 bid doses combined and 41% for the combined 2.5 mg and 5 mg bid doses.

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

Q3. While it is clear why the 2.5 mg bid 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[3] 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 bid 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.

Evaluator's comment

No new information was provided by the sponsor in this response. While it is understood that the 2.5 mg bid dose was the lowest effective dose tested in the VTE prophylaxis studies, because

[3]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

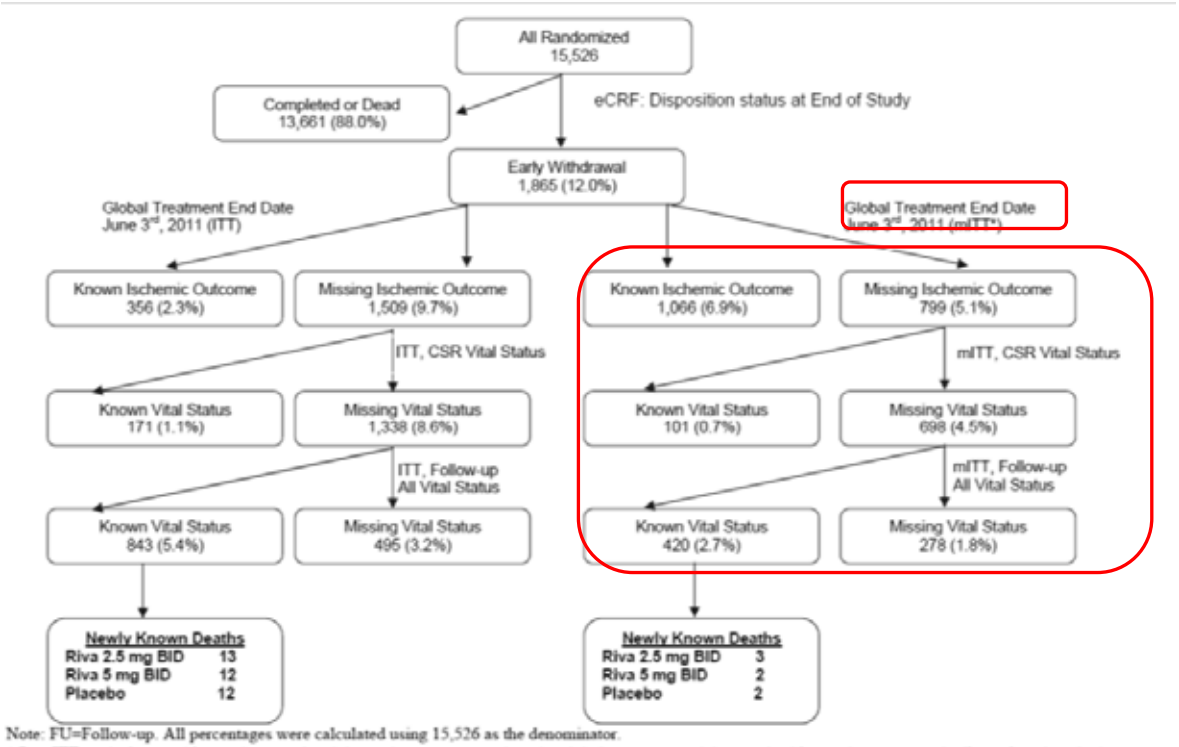
there is no information on the factor Xa inhibition of doses between the 1.25 mg "no effect" dose and the 5 mg dose tested in Study 10842, it remains unclear whether a dose lower than 2.5 mg bid may have been clinically effective with fewer adverse events.

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

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



Note: FU=Follow-up. All percentages were calculated using 15,526 as the denominator.
* In mITT analysis set subjects who completed the study were censored on the global treatment end date, and subjects who prematurely discontinued study drug were censored 30 days after their discontinuation date.

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 7 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 7. 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 8 below). Non-bleeding AEs were balanced across the treatment groups.

Table 81. 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.

An analysis of important safety and efficacy events was conducted by the sponsor in those subjects who withdrew consent. Similar proportions of bleeding events, MIs, strokes and AEs were seen in the rivaroxaban 2.5 mg bid and placebo groups, with higher proportions seen in some of the events for the subjects receiving rivaroxaban 5 mg bid (Table 9Table, below).

Table 9. 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, 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 10 below). Similarly, the ITT analysis was consistent with the original ITT results.

Table 10. 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						Placebo		-- 2.5 mg BID -- vs. Placebo	--- 5 mg BID --- vs. Placebo	--- Combined --- vs. Placebo
	----- 2.5 mg BID -----		------ 5 mg BID ------		------ Combined ------		------ Placebo ------				
Subject Stratum	(N=5114)	Event Rate	(N=5115)	Event Rate	(N=10229)	Event Rate	(N=5113)	Event Rate			
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 response to all issues raised by the FDA

Sponsor's response

The sponsor provided a copy of their response to issues raised by 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

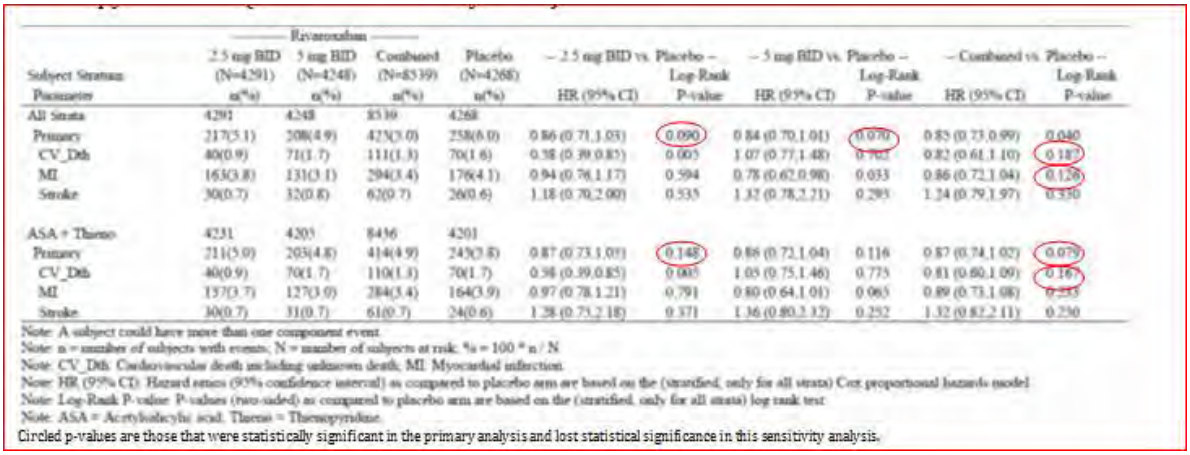
The sponsor provided sensitivity analyses in subjects on a thienopyridine and not taking either omeprazole or esomeprazole (drugs that inhibit CYP2C19). Subjects were censored on the earlier of

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).

A sensitivity analysis 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 (Tables 11 and 12 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 11.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 / Parameter	Rivaroxaban 2.5 mg BID (N=4291) n(%)	Rivaroxaban 5 mg BID (N=4248) n(%)	Rivaroxaban Combined (N=8539) n(%)	Placebo (N=4265) n(%)	2.5 mg BID vs. Placebo HR (95% CI)	2.5 mg BID vs. Placebo Log-Rank P-value	5 mg BID vs. Placebo HR (95% CI)	5 mg BID vs. Placebo Log-Rank P-value	Combined vs. Placebo HR (95% CI)	Combined vs. Placebo 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)	0.703	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	0.88 (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)	0.167
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)	0.255
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.

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

Table12. 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).

Subject Stratum / Parameter	Rivaroxaban 2.5 mg BID (N=4299) n(%)	Rivaroxaban 5 mg BID (N=4253) n(%)	Rivaroxaban Combined (N=8552) n(%)	Placebo (N=4283) n(%)	2.5 mg BID vs. Placebo HR (95% CI)	2.5 mg BID vs. Placebo Log-Rank P-value	5 mg BID vs. Placebo HR (95% CI)	5 mg BID vs. Placebo Log-Rank P-value	Combined vs. Placebo HR (95% CI)	Combined vs. Placebo 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.

Rivaroxaban 2.5 mg bid 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 13 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 14 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 13. 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 bid 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 # 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 14. Comparison between efficacy events prevented and bleeding events caused by treatment with rivaroxaban 2.5 mg bid in stratum 2 (TIMI 51: mITT (excluding sites 091001, 091019 and 091026) analysis set)

Subgroup	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 agreed 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.[4, 5]

Q 9. 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 was 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"*

[4]Brilinta Product Information. Date of Approval: 9 June 2011; pages 9 & 24
[5]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"*.

Second round benefit-risk assessment

Second round assessment of benefits

After consideration of the responses to clinical questions, the benefits of rivaroxaban 2.5 mg bid 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 bid 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.

Second round assessment of risks

After consideration of the responses to clinical questions, the risks of rivaroxaban 2.5 mg bid 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 bid 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 bid 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.

Second round assessment of benefit-risk balance

The benefit-risk balance of rivaroxaban (Xarelto) 2.5 mg bid, 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 bid 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 15 below).

Table 15. Comparison between efficacy events prevented and bleeding events caused by treatment with rivaroxaban 2.5 mg bid 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

Second round recommendation regarding authorisation

Based on the satisfactory answers received to the questions raised, it is recommended that rivaroxaban (Xarelto) 2.5 mg bid 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...*" was 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).

V. Pharmacovigilance findings

Risk management plan

The sponsor submitted a Risk Management Plan which was reviewed by the TGA's Office of Product Review (OPR).

Safety specification

Subject to the evaluation of the clinical aspects of the SS by the OMA, the summary of the Ongoing Safety Concerns as specified by the sponsor is shown in Table 16 below.

Table 16. Summary of the ongoing safety concerns

Important identified risks	• Haemorrhage
Important potential risks	• Embryo-fetal toxicity
Important missing information	• Patients undergoing major orthopaedic surgery other than elective hip or knee replacement surgery • Patients with severe renal impairment (CrCl < 30 mL/min) • Patients receiving concomitant systemic inhibitors of CYP3A4 or P-gp other than azole antimycotics (e.g. ketoconazole) and HIV-protease inhibitors (e.g. ritonavir) • Remedial pro-coagulant therapy for excessive haemorrhage • Pregnant or breast-feeding women • Patients with AF and a prosthetic heart valve

OPR reviewer comment

In comparison to the RMP documents previously reviewed for these products, the Important potential risk: '*Embryo-foetal toxicity*' has now been added based on nonclinical data. Animal studies have shown reproductive toxicity related to the pharmacological mode of action of rivaroxaban (haemorrhagic complications). Embryo-foetal toxicity (post-implantation loss, retarded/progressed ossification, hepatic multiple light-coloured spots) and an increased incidence of common malformations as well as placental changes were observed at clinically relevant plasma concentrations. This was considered acceptable. However, the Important potential risk: '*Increases in liver enzymes, including bilirubin*' has now been excluded without any apparent explanation. The sponsor was asked to provide compelling justification as to why this Ongoing Safety Concern was excluded.

The sponsor's correspondence, dated 7 August 2012, reports that the current European Union (EU) RMP is Version: 7.2. In comparison the proposed Australian (AU) RMP includes the same Ongoing Safety Concerns, except for the Important missing information: '*Long term therapy with rivaroxaban in VTE treatment and SPAF under real-life conditions*'. The sponsor was asked to provide compelling justification as to why this Ongoing Safety Concern is not included in the AU RMP.

Notwithstanding the evaluation of the nonclinical and clinical aspects of the SS, it is recommended that the sponsor include the Important missing information: '*Paediatric population*' as an Ongoing Safety Concern when the AU RMP is next updated. The AU RMP states there are no data available to support appropriate dosing, safety or efficacy in this population (subjects aged < 18 years) but recognises that prescribers may make use of rivaroxaban in a paediatric population, either in a population undergoing major orthopaedic surgery, in those receiving conservative treatment of fractures by plaster cast, in those being treated for acute thrombosis, or in those with AF.

In fact this same recommendation was made when the RMPs submitted in support of the previous application were evaluated. The sponsor's correspondence, dated 14 December 2011,

provided an assurance that the Important missing information: '*Paediatric population*' would be included as an Ongoing Safety Concern and the relevant sections of the RMP would be amended accordingly. It is apparent this assurance was not honoured.

Pharmacovigilance plan

Proposed pharmacovigilance activities

The sponsor states that routine pharmacovigilance activities, consistent with the activities outlined in 3.1.2 Routine pharmacovigilance practices, *Note for Guidance on Planning Pharmacovigilance Activities* (CPMP/ICH/5716/03), are proposed to monitor all the specified Ongoing Safety Concerns, including the use of SAE questionnaires for the Important identified risk: '*Haemorrhage'* and the Important missing information: '*Patients with severe renal impairment (CrCl < 30 mL/min)*' and '*Patients receiving concomitant systemic inhibitors of CYP3A4 or P-gp other than azole antimycotics (e.g. ketoconazole) and HIV-protease inhibitors (e.g. ritonavir)*'. Copies of the proposed specific questionnaires are listed as being part of Annex 2 of the AU RMP but this annex does not appear to have been provided.

OPR reviewer's comments in regard to the pharmacovigilance plan (PP) and the appropriateness of milestones

The sponsor was asked to provide Annex 2 of the AU RMP, which contain copies of the proposed specific questionnaires.

In comparison to the RMP documents previously reviewed for these products and the current EU RMP (Version: 7.2), the following additional pharmacovigilance activities have now been excluded without any apparent explanation:

- In regard to the approved VTE prevention indication, the ongoing open-label postmarketing observational study (XAMOS – XA0801 – Study 13802) to compare bleeding risk in standard regimen for VTE prevention in elective hip or knee replacement surgery in a real-life setting.
- To further monitor the Important identified risk: *'Haemorrhage' and the Important missing information: 'Patients receiving concomitant systemic inhibitors of CYP3A4 or P-gp other than azole antimycotics (e.g. ketoconazole) and HIV protease inhibitors (such as ritonavir)' and 'Pregnant or breast-feeding women'* the sponsor proposed to conduct Drug utilisation cohort studies in European databases (THIN in the UK, PHARMO in the Netherlands and GePaRD in Germany). The post authorisation safety study program planned for the UK was a population-based study to characterise the risk of bleeding associated with rivaroxaban treatment in comparison with treatment with the most widely used vitamin K antagonist, warfarin, in routine clinical practice in the United Kingdom (UK).
- To further monitor the Important identified risk: *'Haemorrhage' and the Important missing information: 'Patients receiving concomitant systemic inhibitors of CYP3A4 or P-gp other than azole antimycotics (e.g. ketoconazole) and HIV protease inhibitors (e.g. ritonavir)' and 'Pregnant or breast-feeding women'* the sponsor proposed to conduct a Modified Prescription-Event Monitoring (M-PEM) study, the aim of which is to proactively capture safety and drug utilisation data in the postmarketing phase of licence approval of rivaroxaban as prescribed to patients by general practitioners (GPs) in primary care in England.
- Secondary to the M-PEM study, an observational, population-based open cohort design to study the short-term (up to 12 weeks) safety and use of rivaroxaban as initiated by specialists in the secondary care setting in the immediate post-marketing period was proposed. This Specialist Cohort Event Monitoring (SCEM) is intended to proactively monitor the short-term safety and drug utilisation of rivaroxaban as prescribed to patients for medical conditions requiring anticoagulation by specialists in this setting, with a

particular focus on obtaining information on patients who stop taking rivaroxaban prior to transfer of care to their GP.

The sponsor was asked to provide compelling justification as to why these additional pharmacovigilance activities have now been excluded.

Furthermore the current EU RMP (Version: 7.2) also includes the following additional pharmacovigilance activities:

- Xalia: Xarelto for Long-term and Initial Anticoagulation in Venous Thromboembolism (VTE).
- Xantus: Xarelto in prevention of stroke and non-embolism in patients with non-valvular atrial fibrillation: A non-interventional study.

The sponsor was asked to provide compelling justification as to why these additional pharmacovigilance activities have not been included in the AU RMP. Alternatively the sponsor should provide all relevant information in the AU RMP, including at least a draft study protocol, for any postmarketing safety study agreed to be conducted in the EU.

In addition the nonclinical and clinical aspects of the SS remain subject to the evaluation by the relevant Offices of the TGA.

Risk minimisation activities

Planned actions

Routine risk minimisation activities will comprise labelling, including indications, contraindications, special warning and precaution statements, instructions for use, overdose statements, notification of interactions and/or notification of undesirable effects for all the specified ongoing safety concerns.

The sponsor states: *"At present no additional risk minimisation measures are planned for Important identified or Potential risks."*

OPR reviewer comment

Section 4: '*Risk Minimisation Plan*' of the AU RMP will need to extensively revised to include additional risk minimisation activities for the Important identified risk: '*Haemorrhage'* as per the European Medicines Agency (EMA) Annex C: Template for EU Risk Management Plan (EU RMP).

In regard to the proposed routine risk minimisation activities, the draft product information document was considered satisfactory.

In regard to the proposed routine risk minimisation activities, the draft consumer medicine information was considered satisfactory.

Summary of recommendations

The OPR provides these recommendations in the context that the submitted AU RMP is supportive to the application; the implementation of a RMP satisfactory to the TGA is imposed as a condition of registration; and the draft product information and consumer medicine information documents should *not* be revised until the Delegates Overview has been received:

- Safety considerations may be raised by the nonclinical and clinical evaluators through the TGA consolidated request for information and/or the nonclinical and clinical evaluation reports respectively. It is important to ensure that the information provided in response to these includes a consideration of the relevance for the Australian Risk Management Plan and any specific information needed to address this issue in the AU RMP. For any safety considerations so raised, the sponsor should provide information that is relevant and necessary to address the issue in the AU RMP.

- In comparison to the RMP documents previously reviewed for these products, the Important potential risk: '*Embryo-foetal toxicity*' has now been added based on nonclinical data. Animal studies have shown reproductive toxicity related to the pharmacological mode of action of rivaroxaban (for example, haemorrhagic complications). Embryo-foetal toxicity (post-implantation loss, retarded/progressed ossification, hepatic multiple light-coloured spots) and an increased incidence of common malformations as well as placental changes were observed at clinically relevant plasma concentrations. This was considered acceptable. However, the Important potential risk: '*Increases in liver enzymes, including bilirubin*' has now been excluded without any apparent explanation. The sponsor was asked to provide compelling justification as to why this Ongoing Safety Concern was excluded.
- The sponsor's correspondence, dated 7 August 2012, reports that the current EU RMP is Version: 7.2. In comparison the proposed AU RMP includes the same ongoing Safety Concerns, except for the Important missing information: '*Long term therapy with rivaroxaban in VTE treatment and SPAF under real-life conditions*'. The sponsor was asked to provide compelling justification as to why this Ongoing Safety Concern is not included in the AU RMP.
- Notwithstanding the evaluation of the nonclinical and clinical aspects of the SS, it was recommended that the sponsor include the Important missing information: '*Paediatric population*' as an Ongoing Safety Concern when the AU RMP is next updated. The AU RMP states there are no data available to support appropriate dosing, safety or efficacy in this population (subjects aged < 18 years), but recognises that prescribers may make use of rivaroxaban in a paediatric population, either in a population undergoing major orthopaedic surgery, in those receiving conservative treatment of fractures by plaster cast, in those being treated for acute thrombosis or in those with AF. In fact this same recommendation was made when the RMPs submitted in support of the previous application were evaluated. The sponsor's correspondence, dated 14 December 2011, provided an assurance that the Important missing information: '*Paediatric population*' would be included as an Ongoing Safety Concern and the relevant sections of the RMP would be amended accordingly. It is apparent this assurance was not honoured.
- The sponsor was asked to provide Annex 2 of the AU RMP, which contain copies of the proposed specific questionnaires.
- In comparison to the RMP documents previously reviewed for these products and the current EU RMP (Version: 7.2), additional pharmacovigilance activities have now been excluded without any apparent explanation. The sponsor was asked to provide compelling justification as to why these additional pharmacovigilance activities have now been excluded.
- The current EU RMP (Version: 7.2) also includes other additional pharmacovigilance activities. The sponsor should provide compelling justification as to why these additional pharmacovigilance activities have not been included in the AU RMP. Alternatively the sponsor was asked to provide all relevant information in the AU RMP, including at least a draft study protocol, for any postmarketing safety study agreed to be conducted in the EU.
- The sponsor's conclusion that at present routine risk minimisation activities are sufficient for all the specified Ongoing Safety Concerns does not appear to be consistent with the current EU RMP (Version: 7.2), which the sponsor reports as stating:
  - *"Routine Risk Minimization Activities sufficient except for hemorrhage".*
  - *"Patient alert card is introduced as an additional risk minimisation activity for hemorrhage to reinforce patient counseling about the important safety information during treatment with rivaroxaban."*

- *"Prescriber guide is introduced to increase awareness about the risk of bleeding during treatment with rivaroxaban and to provide guidance on how to manage that risk."*

· In addition the AU RMP states: *"The Prescriber Guide gives prescribing physicians an overview of Xarelto (rivaroxaban) in a booklet for future reference including dosing recommendations, identifying patients at an increased risk of bleeding and management of bleeding."* and *"All the above measures (proposed additional risk minimisation activities) have been put in place to minimise medication errors and the key messages from these activities will ensure appropriate patient selection, compliance and management of bleeding."* Notwithstanding the evaluation of the nonclinical and clinical aspects of the SS, it was recommended the sponsor should conclude that at present routine risk minimisation activities are sufficient for all the specified Ongoing Safety Concerns, except for the Important identified risk: 'Haemorrhage' and amend the relevant sections of the AU RMP accordingly.

· Section 3.1: '*Summary table of planned actions*' and Section 5: '*Summary of the Risk Management Plan*' of the AU RMP should refer to details of routine risk minimisation in the Australian PI, not the Company Core Data Sheet (CCDS).

· The sponsor should provide for review copies of the printed materials associated with each element of the proposed additional risk minimisation activities and be included as an annex to the AU RMP. If such printed materials are not yet available, the sponsor should indicate when it is anticipated they will become available and provide an assurance that they will be provided to the TGA for review once they become available. In fact a similar recommendation was made when the RMPs submitted in support of the previous application were evaluated. The sponsor's correspondence, dated 14 December 2011, provided an assurance that a copy of the prescriber guide, including the dosing card, would be provided to the TGA before distribution in Australia and include it in the RMP. Given the receipt of the first edition of 3 monthly report on prescriber education program and product familiarisation program for Xarelto, it is apparent this assurance was not honoured.

· It is apparent that the results reported in the first edition of 3 monthly report on prescriber education program and product familiarisation program for Xarelto are purely qualitative and subjective. The sponsor's correspondence, dated 14 December 2011, provided an assurance that a postmarket periodic schedule for the prescriber and patient survey testing would be proposed and implemented for as long as these additional risk minimisation activities were considered necessary. No such survey testing program appears to have been proposed or implemented, and it appears this assurance was not honoured. Furthermore the sponsor's correspondence, dated 28 October 2011, stated that to measure the success of these additional risk minimisation activities, the sponsor proposed to conduct a prescriber, patient and pharmacist survey to test stakeholder understanding of the key aspects in the prescriber guide to aid correct use of Xarelto. The feedback would then be used to refine the prescriber guide and patient information. Consequently the sponsor must honour these assurances and specify the quantitative criteria, suitably justified, to be used to verify the success of the proposed risk minimisation activities.

· Section 4: '*Risk Minimisation Plan*' of the AU RMP will need to be extensively revised to include additional risk minimisation activities for the Important identified risk: '*Haemorrhage'* as per the EMA Annex C: Template For EU Risk Management Plan (EU RMP).

· In regard to the proposed routine risk minimisation activities, the draft product information document was considered satisfactory.

· In regard to the proposed routine risk minimisation activities, the draft consumer medicine information was considered satisfactory.

Second round evaluation of sponsor's response to questions and recommendations

In summary the sponsor has adequately addressed all OPR recommendations, except for the following:

- The sponsor was reminded of its previous assurances that a postmarket periodic schedule for the prescriber and patient survey testing would be proposed and implemented for as long as additional risk minimisation activities were considered necessary and the feedback would then be used to refine the prescriber guide and patient information. However, the sponsor has now advised that such survey testing will not commence until February 2013, and then 6 and/or 12 months after Pharmaceutical Benefits Scheme (PBS) listing. This response is considered to be inadequate in the light of previous assurances and the fact that supply of these products has commenced in Australia, presumably since 4 June 2012, via the Product Familiarisation Program (PFP). The sponsor has reported that as of 28 September 2012 almost 4,000 prescribers and almost 3,000 patients have enrolled in the PFP. Furthermore no quantitative criteria, suitably justified, to be used to verify the success of the proposed additional risk minimisation activities have been specified. Consequently this remains an outstanding recommendation which the sponsor must address in an appropriate and adequate manner before this application is approved, given that such activity is the subject of specific conditions of registration for these products (see *TGA Question 11*).

- The sponsor was advised that Section 3.1: '*Summary table of planned actions*' and Section 5: '*Summary of the Risk Management Plan*' of the AU RMP should refer to details of routine risk minimisation in the Australian PI, not the CCDS. In response the sponsor has now attached the approved and proposed Australian PI to the ASA. This is not entirely satisfactory and it is reiterated that a short description, including the location within the Australian PI, of routine risk minimisation for all of the specified Ongoing Safety Concerns should be provided in the ASA when it is next updated (see *TGA Question 9*).

At the 14th meeting of Advisory Committee on the Safety of Medicines (ACSOM), the committee considered whether the printed materials associated with the Xarelto education program and the PFP for the existing indications, which aimed to highlight the Important identified risk: '*Haemorrhage'* and to minimise medication error, were adequate in addressing these issues. Ratified advice from the committee provided detailed comment on the suitability of these materials. In summary: *"ACSOM advised that the printed materials provided were not adequate. The committee expressed concern that the PFP documents were overly promotional; and not presented clearly or logically. In particular, the statement that monitoring was unnecessary was considered misleading, and the emotive aspects such as smiling faces were not considered appropriate. The materials were not of the same standard as the PI/CMI, and there was not enough emphasis on education and safety."* Consequently all printed materials associated with the Xarelto education program and the PFP must be revised in the light of such advice and provided to the TGA for review before this application can be approved, given that such activity is the subject of specific conditions of registration for these products.

If this application is approved the following specific conditions of registration should be applied:

- The European Risk Management Plan identified as Version: 7.2, dated 29 March 2012, and an Australian Specific Annex (ASA) identified as Version 1, dated September 2012, with revised details of a Risk Minimisation Plan within the ASA as agreed with the TGA, must be implemented.
- Post marketing reports are to be provided in line with the current published list of European Union (EU) reference dates and frequency of submission of periodic safety update reports (PSURs) until the period covered by such reports is not less than three years from the date of this approval letter. The reports are to meet the requirements in accordance with

ICH E2C (R2) guideline on Periodic Benefit-Risk Evaluation Reports and Module VII of the EMA Guideline on Good Pharmacovigilance (GPV) Practices relating to PSURs. Submission of the report must be within the 70 days of the data lock point for PSURs covering intervals up to and including 12 months and within 90 days of the data lock point for PSURs covering intervals in excess of 12 months. The submission may be made up of periodic Safety Update Reports each covering six months.

For completeness advice on each specific question follows:

TGA question 1

The sponsor has stated that no safety considerations have been raised by the nonclinical and clinical evaluators as a result of assessment. This was considered acceptable.

TGA question 2

The sponsor has provided justification and concluded that deletion of the Important potential risk: 'I*ncreases in liver enzymes, including bilirubin*' is supported by the data. The clinical evaluator agreed with this and therefore it was considered acceptable.

TGA question 3

The sponsor agreed that the Important missing information: '*Long term therapy with rivaroxaban in VTE treatment and SPAF under real-life conditions*' is relevant to Australia and therefore will adopt the EU RMP Version: 7.2 and an ASA Version 1. This was considered acceptable.

TGA question 4

The sponsor agreed that the Important missing information: '*Paediatric population*' should be included as an ongoing Safety Concern and this has been captured in the ASA Version 1. This was considered acceptable.

TGA question 5

The sponsor has provided copies of the questionnaires to monitor the Important identified risk: '*Haemorrhage'* as attachments to the EU RMP Version: 7.2 under Annex 6.1 & Annex 6.2. This was considered acceptable.

TGA question 6 & 7

With the adoption of the EU RMP Version: 7.2 and an ASA Version 1, additional pharmacovigilance activities to be conducted in Europe will now be captured. This was considered acceptable.

TGA questions 8 & 12

The sponsor agreed that at present routine risk minimisation activities are sufficient for all the specified Ongoing Safety Concerns, except for the Important identified risk: '*Haemorrhage'* for which additional risk minimisation activities are proposed. With the adoption of the EU RMP Version: 7.2 and an ASA Version 1, these additional risk minimisation activities will now be captured. This was considered acceptable.

TGA question 9

The sponsor was advised that Section 3.1: '*Summary table of planned actions*' and Section 5: '*Summary of the Risk Management Plan*' of the AU RMP should refer to details of routine risk minimisation in the Australian PI, not the CCDS. In response the sponsor has now attached the approved and proposed Australian PI to the ASA. This is not entirely satisfactory and it is reiterated that a short description, including the location within the Australian PI, of routine risk minimisation for all of the specified Ongoing Safety Concerns should be provided in the ASA when it is next updated.

TGA question 10

The sponsor has provided copies of the printed materials (Doctor PFP Guides and Patient Alert Cards) associated with the Xarelto education program and the PFP for the existing indications as Appendices 5-8 of the ASA. This was considered acceptable, although as previously noted these materials, including Patient Guides and Enrolment Packs, will require extensive revision in the light of ACSOM advice as to the suitability of these materials to highlight the Important identified risk: '*Haemorrhage'* and to minimise medication error.

TGA question 11

The sponsor's was reminded of its previous assurances that a postmarket periodic schedule for the prescriber and patient survey testing would be proposed and implemented for as long as additional risk minimisation activities were considered necessary and the feedback would then be used to refine the prescriber guide and patient information. However, the sponsor has now advised that such survey testing will not commence until February 2013, and then 6 and/or 12 months after PBS listing. This response is considered to be inadequate in the light of previous assurances and the fact that supply of these products has commenced in Australia, presumably since 4 June 2012, via the PFP. The sponsor has reported that as of 28 September 2012 almost 4,000 prescribers and almost 3,000 patients have enrolled in the PFP. Furthermore no quantitative criteria, suitably justified, to be used to verify the success of the proposed additional risk minimisation activities have been specified. Consequently this remains an outstanding recommendation which the sponsor must address in an appropriate and adequate manner before this application is approved, given that such activity is the subject of specific conditions of registration for these products.

VI. Overall conclusion and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations.

There are two clinical evaluation reports which were included in the ACPM papers for this submission. There was the principal clinical evaluation report which comments on all of the clinical data mentioned. There is also a smaller clinical evaluation report which evaluates the dose-finding study, that is, the ATLAS ACS TIMI 46 trial or TIMI 46. The clinical study report for TIMI 46 was submitted to the TGA back in December 2009 in order to satisfy a specific condition of registration imposed at the time of the original approval of rivaroxaban. The principal clinical evaluation report which is of course a more recent document refers to the earlier clinical evaluation report when summarising the findings of TIMI 46. In this overview, if the Delegate makes reference to a clinical evaluation report without further qualification, it will always be a reference to the principal clinical evaluation report. If the Delegate needs to refer specifically to the other clinical evaluation report it is refer to it as the TIMI 46 clinical evaluation report.

Quality

There are no objections to the registration of Xarelto (rivaroxaban) 2.5 mg tablets with regard to chemistry, manufacturing and controls.

All aspects relating to the drug substance for the proposed 2.5 mg tablets are identical to those approved for the currently registered tablets, that is, the 10, 15 and 20 mg tablets.

The different dosage strengths are not direct scales of each other. The 2.5 mg strength is distinguished from the registered strengths by the colourant, iron oxide yellow used in the film coating. The strengths already registered contain varying amounts of iron oxide red.

The tablets are well controlled with satisfactory limits at both release and expiry.

The stability data provided supports a shelf life of 3 years when stored below 30°C in the proposed packaging.

The absolute bioavailability of the 20 mg tablet was previously shown to be 66% in the fasted state. The absolute bioavailability of the 2.5 mg tablet and that of the registered 10 mg strength have been estimated to be 80-100%.

AUC was found to be increase in proportion to dose in the range 2.5 mg to 10 mg. The corresponding increases in C_{max} were somewhat less than dose proportional.

Nonclinical

The anti-thrombotic efficacy of rivaroxaban was potentiated in the presence of ASA and/or a $P2Y_{12}$ receptor blocker such as clopidogrel or ticagrelor *in vitro*, *ex vivo* and *in vivo*. Stent thrombosis was inhibited *in vivo* at clinically relevant concentrations by rivaroxaban alone or synergistically in combination with ASA and clopidogrel.

Fluconazole was a mild inhibitor [IC_{50} > 300 μM] and dronedarone was a strong inhibitor [IC_{50} = 0.37 μM] of P-gp mediated rivaroxaban efflux *in vitro*, suggesting their potential, to varying degrees, to enhance rivaroxaban exposure in humans. The sponsor has acknowledged the potential interaction in the PI.

Rivaroxaban was neither a substrate nor an inhibitor of drug transporter proteins OATP1B1, OATP1B3, OAT1 or OCT2 *in vitro*. While it was found to have a slight inhibitory effect on OAT3 and is a weak substrate of this drug transport protein, clinically relevant drug interactions on this basis are not anticipated. Only the key drug interaction transporter proteins were investigated.

No novel safety concerns were noted in three month repeat dose toxicity studies conducted in neonatal rats at identical rivaroxaban doses (and similar rivaroxaban exposure) as previously given to adult rats.

The nonclinical risk-benefit profile of rivaroxaban was judged to be unchanged for the new indication as the proposed new daily dose of 2.5 mg twice daily for the ACS indication is lower than the currently approved maximum long-term rivaroxaban dose (20 mg once daily).

There were no nonclinical objections to the registration of rivaroxaban for the proposed indication and treatment regimen, nor changes recommended to the proposed Risk Management Plan. The nonclinical evaluator recommended some amendments to the draft Product Information document, amendments which are endorsed by the Delegate.

Clinical

The contents of the submission have been outlined earlier. The clinical evaluator has recommended that the extensions of indication sought by the sponsor should be approved but with two important amendments to the proposed extensions. The first is that the requested indication for "*prevention of atherothrombotic events and stent thrombosis...*" was not supported by the data since the study was powered to look at a composite endpoint, not the individual components and stent thrombosis was simply one of the individual component endpoints. The second is that the use of Xarelto should be restricted to ACS patients receiving combination therapy with aspirin plus a thienopyridine (clopidogrel or ticlopidine) and not be recommended for those ACS patients on aspirin without a concomitant thienopyridine.

Pharmacology

Pharmacokinetics

Conventional PK studies

- In the fasted state, the half life ($t_{1/2}$), 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 bid) did not seem to affect clearance (CL/F) or time to peak plasma concentration (t_{max})
- The mean plasma concentration time curves and derived pharmacokinetic (PK) parameters generally increased with increasing dose within the dosing regimen
- The $AUC_{0\text{-}24h}$ 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.

As noted by the clinical evaluator, the pharmacokinetics of rivaroxaban have been well characterised for higher dose tablets in other indications. The pharmacokinetics of the 2.5 mg tablet in patients with ACS are 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. The sponsor was asked to provide data to support the lack of food effect with the 2.5 mg tablet in response to the consolidated list TGA questions.

Pharmacodynamics

- The pharmacodynamics of rivaroxaban have 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. $AUC_{0\text{-}24h}$ 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 $AUC_{0\text{-}24h}$ in subjects treated with rivaroxaban. The $AUC_{0\text{-}24h}$ 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.

Dosage selection and clinical efficacy

Study TIMI 46

- 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), was a Phase II, randomised, double-blind, double-dummy, parallel-group, placebo-controlled, dose-finding 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). The clinical study report of TIMI 46 was submitted to the TGA in December 2009 in compliance with a specific condition of registration attached to the approval of the original application for registration of rivaroxaban.
- The goal of this Phase II study was to define the dosing regimens of rivaroxaban with a favourable balance of safety and efficacy to be implemented in a definitive Phase III study. The study was originally intended to be conducted in 2 stages (Stage 1 dose escalation and Stage 2 dose confirmation), with the primary objective of Stage 1 being safety and that of Stage 2 being efficacy. It became apparent during the conduct of the study that to gain better estimates of the potential treatment effect of rivaroxaban, larger numbers of subjects would need to be enrolled into Stage 1, in order to allow selection of doses for future study. Stage 1 was intended to enrol approximately 1350 subjects but ultimately 3491 subjects were randomised into that stage. After review of the available data, the decision was made to proceed directly to test rivaroxaban in a definitive Phase III study, obviating the need for Stage 2 of the ATLAS ACS TIMI 46 study. Thus, Stage 2 was not performed.
- Stage 1 of the ATLAS TIMI 46 study was conducted at 297 centres in 27 countries between 17 November 2006 and 19 September 2008. It was a randomised, double-blind, placebo-controlled, dose-escalation study of placebo versus increasing total daily doses of rivaroxaban on background low-dose ASA treatment. Randomisation of subjects was stratified by the intent to use thienopyridine therapy. Stratum 1 comprised subjects for whom there was no plan for thienopyridine therapy. Stratum 2 comprised subjects who were already either receiving a thienopyridine or in whom thienopyridine use was planned within 30 days of randomisation. Randomisation to the various rivaroxaban dose groups started with the lowest total daily dose of 5 mg (either as 5 mg once daily or 2.5 mg bid) and then separate cohorts escalated to the 10 mg and 20 mg total daily doses (again either as once daily or in divided doses twice daily).
- Demographic and baseline characteristics, including medical history, in the ITT analysis set were reasonably well balanced between the pooled rivaroxaban and pooled placebo groups and within each stratum.
- The primary efficacy endpoint was the composite of all cause death, myocardial infarction (MI) (or repeat MI), stroke (ischaemic, haemorrhagic or unknown) or severe recurrent ischaemia requiring revascularisation in the following 6 months. The key secondary endpoint was the composite of death (all cause), MI (or repeat MI) or stroke (ischaemic, haemorrhagic or unknown) in the following 6 months.
- The overall treatment effects by pooled dosing regimen, that is, pooled placebo, pooled once daily rivaroxaban, pooled twice daily rivaroxaban & all rivaroxaban (both once and twice daily) are shown in Table 17. For all strata, that is, Strata 1 and 2 combined, the incidence rates for the primary efficacy endpoint were 7.2% (83/1160) in the pooled placebo group, 6.4% (75/1166) in the pooled once daily rivaroxaban group [with a HR versus placebo

{95%CI} of 0.90 {0,66, 1.22}], 5.7% (66/1165) in the pooled twice daily rivaroxaban group [with a HR versus placebo {95%CI} of 0.79 {0.57, 1.09}] and 6.0% (141/2331) in the all rivaroxaban group [with a HR versus placebo {95%CI} of 0.84 {0.64, 1.1}. It must be remembered that these results are for the pooled groups with each pooled rivaroxaban group covering a wide range of total daily dosing, from 5 mg to 20 mg and so, in terms of dose selection, the information in Table 17 is of limited value. Table 10 of the principal clinical evaluation report (Attachment 1) displays the main results for all rivaroxaban versus placebo extracted from Table 17.

- While the results shown in Table 17 may suggest that the results were more impressive in Stratum 1 than in Stratum 2, this must be tempered by the observation that the numbers in Stratum 1 were quite small. The numbers of subjects in Stratum 1 were smaller than those in Stratum 2 by a factor of approximately 3.6 across all pooled dosage groups.
- The overall treatment effect of rivaroxaban on the primary and key secondary efficacy endpoints for each rivaroxaban total daily dose level across both strata compared with the pooled placebo group is presented in Table 18. The Delegate has included this table to highlight one seemingly alarming result. The death rate in the rivaroxaban 5 mg total daily dose groups combined (that is, 5 mg once daily and 2.5 mg twice daily) is 11/308 or 3.6%. This result is more than double (and compared with the combined 10 mg total daily dose groups it is four times) the corresponding rate for any of the other comparator groups, including the placebo group. Can one really ascribe this to chance; 11 deaths in a group of 308 subjects, simply because the group is small in size? What then is one to make of the comparability of the corresponding results for the combined 15 mg total daily dose and the combined 20 mg total daily dose groups? The ACPM and the sponsor were asked to comment on this issue.

Table 17. Overall treatment effects, i.e. by pooled dosage groups, for the primary and key secondary efficacy endpoints as adjudicated by the clinical events committee, study ATLAS ACS TIMI 46, ITT analysis set

Stratum	Parameter	Pooled Placebo K/N (%)	-- Rivaroxaban: OD (5/10/15/20 mg) - K/N (%)	HR (95% CI)	-- Rivaroxaban: BID (5/10/15/20 mg) -- K/N (%)	HR (95% CI)	All Rivaroxaban OD+BID (5/10/15/20 mg K/N (%)	HR (95% CI)	Wald p-value
All Strata	Primary	83/1160 (7.2)	75/1166 (6.4)	0.90 (0.66,1.22)	66/1165 (5.7)	0.79 (0.57,1.09)	141/2331 (6.0)	0.84 (0.64,1.1)	0.213
	Dth/MI/St	66/1160 (5.7)	54/1166 (4.6)	0.81 (0.56,1.16)	47/1165 (4.0)	0.70 (0.48,1.02)	101/2331 (4.3)	0.76 (0.55,1.03)	0.077
	Death	18/1160 (1.6)	16/1166 (1.4)	0.89 (0.45,1.75)	17/1165 (1.5)	0.94 (0.49,1.83)	33/2331 (1.4)	0.92 (0.52,1.63)	0.766
	MI	47/1160 (4.1)	44/1166 (3.8)	0.93 (0.61,1.4)	35/1165 (3.0)	0.74 (0.48,1.14)	79/2331 (3.4)	0.83 (0.58,1.19)	0.319
	Stroke	7/1160 (0.6)	3/1166 (0.3)	0.43 (0.11,1.65)	3/1165 (0.3)	0.43 (0.11,1.65)	6/2331 (0.3)	0.43 (0.14,1.27)	0.126
	SRI Rev	18/1160 (1.6)	23/1166 (2.0)	1.28 (0.69,2.37)	23/1165 (2.0)	1.28 (0.69,2.37)	46/2331 (2.0)	1.28 (0.74,2.21)	0.375
	CV-D/MI/St	63/1160 (5.4)	54/1166 (4.6)	0.85 (0.59,1.22)	46/1165 (3.9)	0.72 (0.49,1.05)	100/2331 (4.3)	0.78 (0.57,1.07)	0.130
Stratum 1	Primary	34/253 (13.4)	19/254 (7.5)	0.54 (0.31,0.95)	21/254 (8.3)	0.60 (0.35,1.03)	40/508 (7.9)	0.57 (0.36,0.9)	0.016
	Dth/MI/St	29/253 (11.5)	17/254 (6.7)	0.57 (0.32,1.04)	18/254 (7.1)	0.60 (0.33,1.08)	35/508 (6.9)	0.59 (0.36,0.96)	0.034
	Death	7/253 (2.8)	7/254 (2.8)	1.01 (0.35,2.87)	9/254 (3.5)	1.29 (0.48,3.47)	16/508 (3.1)	1.15 (0.47,2.79)	0.760
	MI	22/253 (8.7)	12/254 (4.7)	0.53 (0.26,1.08)	11/254 (4.3)	0.48 (0.23,1)	23/508 (4.5)	0.51 (0.28,0.91)	0.024
	Stroke	3/253 (1.2)	2/254 (0.8)	0.67 (0.11,3.99)	2/254 (0.8)	0.66 (0.11,3.94)	4/508 (0.8)	0.66 (0.15,2.96)	0.590
	SRI Rev	5/253 (2.0)	3/254 (1.2)	0.60 (0.14,2.49)	6/254 (2.4)	1.19 (0.36,3.89)	9/508 (1.8)	0.89 (0.3,2.66)	0.838
	CV-D/MI/St	29/253 (11.5)	17/254 (6.7)	0.57 (0.32,1.04)	18/254 (7.1)	0.60 (0.33,1.08)	35/508 (6.9)	0.59 (0.36,0.96)	0.034
Stratum 2	Primary	49/907 (5.4)	56/912 (6.1)	1.14 (0.78,1.68)	45/911 (4.9)	0.92 (0.61,1.38)	101/1823 (5.5)	1.03 (0.73,1.45)	0.853
	Dth/MI/St	37/907 (4.1)	37/912 (4.1)	1.00 (0.63,1.57)	29/911 (3.2)	0.78 (0.48,1.27)	66/1823 (3.6)	0.89 (0.59,1.33)	0.568
	Death	11/907 (1.2)	9/912 (1.0)	0.82 (0.34,1.97)	8/911 (0.9)	0.72 (0.29,1.79)	17/1823 (0.9)	0.77 (0.36,1.64)	0.498
	MI	25/907 (2.8)	32/912 (3.5)	1.27 (0.76,2.15)	24/911 (2.6)	0.96 (0.55,1.68)	56/1823 (3.1)	1.12 (0.7,1.79)	0.640
	Stroke	4/907 (0.4)	1/912 (0.1)	0.25 (0.03,2.22)	1/911 (0.1)	0.25 (0.03,2.25)	2/1823 (0.1)	0.25 (0.05,1.37)	0.109
	SRI Rev	13/907 (1.4)	20/912 (2.2)	1.54 (0.77,3.1)	17/911 (1.9)	1.32 (0.64,2.71)	37/1823 (2.0)	1.43 (0.76,2.69)	0.268
	CV-D/MI/St	34/907 (3.7)	37/912 (4.1)	1.08 (0.68,1.73)	28/911 (3.1)	0.82 (0.5,1.36)	65/1823 (3.6)	0.95 (0.63,1.44)	0.818

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

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

Stratum 1= Aspirin, Stratum 2=Aspirin +Thienopyridine OD= once-daily; BID= twice-daily.

K/N: Number of subjects having events / number of subjects at risk; HR (95% CI): Hazard ratio (95% confidence interval) as compared to pooled placebo groups; p-value: 2-sided p-value for the hazard ratio estimation based on Wald test;

For each stratum, perform a Cox model with dose regimen (Placebo/OD/BID) as class variable; For all strata, also add strata (Aspirin / Aspirin+ Thienopyridine); For all rivaroxaban, perform another Cox model with dose regimen replaced by treatment group (all rivaroxaban vs. pooled placebo); For subjects who didn't have events, the minimum of last visit date or death date was used as censoring day.

Table 18. Treatment effect of primary and key secondary efficacy endpoints by dose level (once daily and twice daily combined) against pooled placebo group as adjudicated by the clinical events committee, dose-finding study, study ATLAS ACS TIMI 46, ITT

Table 15: Treatment Effect of Primary and Key Secondary Efficacy Endpoints by Dose Level Against Pooled Placebo Group as Adjudicated by Clinical Events Committee (Study ATLAS ACS TIMI 46: Intent-to-Treat Analysis Set)

		Pooled Placebo	------- Rivaroxaban 5 mg ------		--------- Rivaroxaban 10 mg ------		--------- Rivaroxaban 15 mg ---		--------- Rivaroxaban 20 mg --------	
Stratum	Parameter	K/N (%)	K/N (%)	HR (95% CI)	K/N (%)	HR (95% CI)	K/N (%)	HR (95% CI)	K/N (%)	HR (95% CI)
All Strata	Primary	83/1160 (7.2)	23/308 (7.5)	0.85 (0.53,1.36)	55/1056 (5.2)	0.75 (0.53,1.05)	27/356 (7.6)	1.28 (0.82,2)	36/611 (5.9)	0.78 (0.53,1.16)
	Dth/MI/St	66/1160 (5.7)	18/308 (5.8)	0.77 (0.45,1.31)	40/1056 (3.8)	0.69 (0.47,1.03)	21/356 (5.9)	1.38 (0.83,2.3)	22/611 (3.6)	0.59 (0.36,0.96)
	Death	18/1160 (1.6)	11/308 (3.6)	1.72 (0.8,3.71)	9/1056 (0.9)	0.58 (0.26,1.29)	4/356 (1.1)	1.00 (0.33,3.03)	9/611 (1.5)	0.89 (0.4,1.99)
	MI	47/1160 (4.1)	10/308 (3.2)	0.61 (0.3,1.21)	32/1056 (3.0)	0.78 (0.5,1.22)	19/356 (5.3)	1.72 (0.99,3)	18/611 (2.9)	0.68 (0.4,1.18)
	Stroke	7/1160 (0.6)	1/308 (0.3)	0.35 (0.04,2.92)	4/1056 (0.4)	0.68 (0.2,2.31)	0/356	0.00	1/611 (0.2)	0.25 (0.03,2.04)
	SRI Rev	18/1160 (1.6)	5/308 (1.6)	1.04 (0.38,2.85)	18/1056 (1.7)	1.11 (0.58,2.13)	7/356 (2.0)	1.28 (0.53,3.09)	16/611 (2.6)	1.70 (0.86,3.33)
	CV-D/MI/St	63/1160 (5.4)	18/308 (5.8)	0.79 (0.46,1.35)	40/1056 (3.8)	0.73 (0.49,1.08)	21/356 (5.9)	1.48 (0.88,2.47)	21/611 (3.4)	0.59 (0.36,0.96)
Stratum 1	Primary	34/253 (13.4)	14/154 (9.1)	0.65 (0.35,1.22)	17/196 (8.7)	0.64 (0.36,1.15)			9/158 (5.7)	0.40 (0.19,0.84)
	Dth/MI/St	29/253 (11.5)	14/154 (9.1)	0.78 (0.41,1.47)	14/196 (7.1)	0.62 (0.33,1.18)			7/158 (4.4)	0.37 (0.16,0.84)
	Death	7/253 (2.8)	8/154 (5.2)	1.89 (0.68,5.21)	5/196 (2.6)	0.95 (0.3,2.98)			3/158 (1.9)	0.68 (0.18,2.63)
	MI	22/253 (8.7)	7/154 (4.5)	0.51 (0.22,1.2)	11/196 (5.6)	0.64 (0.31,1.32)			5/158 (3.2)	0.35 (0.13,0.92)
	Stroke	3/253 (1.2)	1/154 (0.6)	0.54 (0.06,5.23)	3/196 (1.5)	1.32 (0.27,6.53)			0/158	0.00
	SRI Rev	5/253 (2.0)	0/154	0.00	6/196 (3.1)	1.56(0.48,5.11)			3/158(1.9)	0.95(0.23,3.97)
	CV-D/MI/St	29/253 (11.5)	14/154 (9.1)	0.78 (0.41,1.47)	14/196 (7.1)	0.62(0.33,1.18)			7/158(4.4)	0.37(0.16,0.84)
Stratum 2	Primary	49/907 (5.4)	9/154 (5.8)	1.07 (0.53,2.19)	38/860 (4.4)	0.82 (0.54,1.26)	27/356 (7.6)	1.43 (0.89,2.29)	27/453 (6.0)	1.10 (0.69,1.76)
	Dth/MI/St	37/907 (4.1)	4/154 (2.6)	0.62 (0.22,1.73)	26/860 (3.0)	0.75 (0.45,1.23)	21/356 (5.9)	1.47 (0.86,2.51)	15/453 (3.3)	0.80 (0.44,1.47)
	Death	11/907 (1.2)	3/154 (1.9)	1.56 (0.44,5.6)	4/860 (0.5)	0.39 (0.12,1.21)	4/356 (1.1)	0.95 (0.3,2.97)	6/453 (1.3)	1.07 (0.4,2.9)
	MI	25/907 (2.8)	3/154 (1.9)	0.69 (0.21,2.28)	21/860 (2.4)	0.89 (0.5,1.6)	19/356 (5.3)	1.96 (1.08,3.57)	13/453 (2.9)	1.04 (0.53,2.03)
	Stroke	4/907 (0.4)	0/154	0.00	1/860 (0.1)	0.27 (0.03,2.38)	0/356	0.00	1/453 (0.2)	0.51 (0.06,4.54)
	SRI Rev	13/907 (1.4)	5/154 (3.2)	2.27 (0.81,6.38)	12/860 (1.4)	0.98 (0.45,2.16)	7/356 (2.0)	1.38 (0.55,3.47)	13/453 (2.9)	2.02 (0.94,4.37)
	CV-D/MI/St	34/907 (3.7)	4/154 (2.6)	0.67 (0.24,1.89)	26/860 (3.0)	0.81 (0.49,1.35)	21/356 (5.9)	1.60 (0.93,2.76)	14/453 (3.1)	0.82 (0.44,1.52)

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

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

Stratum= Aspirin, Stratum 2=Aspirin +Thienopyridine

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

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

Table 19 displays the treatment effects of the primary efficacy and the key secondary endpoints by each total daily dose level (5, 10, 15 and 20 mg) for the once daily, twice daily and the combined once and twice daily dosage regimens. Firstly observe the rivaroxaban once daily results for the primary endpoint for all strata. As one moves down the column, that is, as the dose increases, the rate of the primary efficacy endpoint alternates from high to low and back to high and finally back to low, viz. 9.0% for 5 mg once daily, 5.5% for 10 mg once daily, 9.0% for 15 mg once daily and finally 5.3% for 20 mg daily. The corresponding rate for the pooled placebo group was 7.2%. Thus dosage regimens of 5 mg once daily and 15 mg once daily performed worse than placebo. However, one can also see that these two dosage groups were much smaller in size than the 10 mg once daily and 20 mg once daily groups. There is more consistency or uniformity in the results for rivaroxaban twice daily. As one moves down this column, that is, as the dose increases, the rates of the primary efficacy endpoint are as follows: 5.9% for 2.5 mg bid, 4.9% for 5 mg bid, 6.2% for 7.5 mg bid and finally 6.5% for 10 mg bid. At least all the latter four rates are below the pooled placebo rate of 7.2%. Once again the numbers in the 2.5 mg bid and 7.5 mg bid groups were much smaller than those in the other two groups, that is, the 5 mg bid and 10 mg bid groups. All these same patterns are by and large repeated for the key secondary efficacy endpoint of all cause death or MI or stroke. Given the relatively small size of some of the dosage groups, it is difficult to know what precisely to make of the results. However, given the generally more consistent and better results in the rivaroxaban twice daily groups compared with the once daily groups, the two most promising dosage regimens appeared to be the 2.5 mg bid and the 5 mg bid. One could have also mounted a case for 10 mg once daily. There is also the anomalous result for 20 mg once daily with a primary efficacy endpoint rate of a very respectable 5.3%. Such a high dose would have been ruled out of further contention because of demonstrably higher bleeding rates associated with this dose compared with the lower doses eventually taken forward. Nonetheless the anomalous nature of the result, especially when compared to the result for 15 mg once daily with a primary endpoint rate of 9.0%, does further add to the reservations which the Delegate has concerning the robustness of this dose-finding study.

Table 19. Treatment effects for the primary and the key secondary efficacy endpoints by each dose level as adjudicated by the clinical events committee, study ATLAS TIMI 46, ITT analysis set

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

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

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

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

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

Pivotal efficacy data supporting use in ACS

Study TIMI 51

- The ATLAS ACS 2 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 (ST Elevation MI (STEMI), Non-ST Elevation MI (NSTEMI) or unstable angina (UA)) who were receiving standard care including either low-dose ASA (Stratum 1) or the combination of low-dose ASA plus a thienopyridine (Stratum 2). The study was conducted at 766 sites in 44 countries worldwide between November 2008 and 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.
- Eligibility criteria were standard except that the Delegate has concerns that 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. Presumably the rationale for this requirement is that such patients are at higher risk of an outcome event than patients in this age group without either diabetes mellitus or a prior MI. However, the question that will have to be asked at some point is how the study findings can be applied to this latter sub-group presumed to be at lower risk of an outcome event. The latest version of the Cardiovascular Therapeutic Guidelines in Australia (version 5, 2008) describes STEMI as a life-threatening event, that is, regardless of the patient's age or co-morbidities. The same guideline only attempts to quantify risk as high, intermediate or low for Non-ST elevation acute coronary syndrome (NSTEACS). Features consistent with high risk include prior percutaneous coronary intervention within 6 months or prior coronary artery bypass surgery. Age by itself is not a high-risk feature but age above *65 years* is classified as an intermediate risk marker. The guideline also mentions a simplified risk stratification of acute coronary syndromes applicable to the majority of patients. From the construction of the relevant table in the guideline this simplified approach is applicable to either STEMI or NSTEMI. Essentially, this approach means that patients are considered to be at high risk if there are either changes on electrocardiogram (ECG) or an elevated troponin level (irrespective of the history of pain and, importantly in this context, irrespective of any co-morbidities). The European Society of Cardiology guidelines on acute coronary syndromes refers in particular to the GRACE risk score[6] which is based on a large unselected population of an international registry with a full spectrum of ACS patients. Into this GRACE ACS risk model one inserts the patient's age, heart rate, systolic blood pressure (BP), creatinine level and grade of congestive heart failure (CHF) (by Killip class[7]) and then ticks whether or not the patient had cardiac arrest at admission, ST-segment deviation or elevated cardiac enzyme markers. Co-morbidities such as diabetes mellitus and prior MI are not assessed. Thus the Delegate was concerned that the imposition of the requirement that patients aged 18 to 54 years had to have also at least one of these co-morbidities has skewed the study population. As mentioned before, it does raise the issue of whether one can recommend the use of the medicine in the younger ACS population who do not have either diabetes mellitus or a history of prior MI. The Delegate was particularly concerned about such younger patients presenting with STEMI. The sponsor is requested to state, in its pre-ACPM response, the precise numbers of subjects in this younger age group who had diabetes mellitus, a history of MI or both diabetes mellitus and a history of MI. The ACPM was asked to express its views on this matter as was the sponsor.

[6] Further details available at <http://www.outcomes-umassmed.org/grace/>
[7] The Killip classification is a system used in individuals with an acute myocardial infarction (heart attack), in order to risk stratify them. Individuals with a low Killip class are less likely to die within the first 30 days after their myocardial infarction than individuals with a high Killip class.

- Subjects were randomly assigned in a 1:1:1 ratio to one of 3 treatment groups: rivaroxaban 2.5 mg bid, rivaroxaban 5 mg bid or placebo bd. All subjects received also standard care, including either low-dose ASA therapy (75 mg to 100 mg daily) or the combination of low-dose ASA therapy plus a thienopyridine (clopidogrel or ticlopidine only). The two newer anti-platelet agents, prasugrel and ticagrelor were not approved for use at the beginning of the TIMI 51 trial and were therefore not use in this trial.
- The primary efficacy endpoint was the composite of cardiovascular death, MI or stroke. There were 4 secondary efficacy endpoints and these were subject to a hierarchical testing strategy. The first two in order and most important of these four endpoints were the composite of all-cause death, MI or stroke followed by net clinical outcome (defined as the composite of cardiovascular death, MI, ischaemic stroke or TIMI major bleeding event not associated with coronary artery by-pass (CABG) surgery). The TGA adopted EU guideline prefers the primary endpoint to include all-cause mortality rather than cardiovascular mortality. It is not uncommon nowadays to see clinical outcome trials for cardiovascular medicines to include cardiovascular mortality rather than all-cause mortality in the primary endpoint. At least one can derive reassurance from the fact that the key secondary endpoint included all-cause mortality. Stent thrombosis was evaluated as a pre-specified standalone efficacy endpoint. However, as pointed out by the evaluator, stent thrombosis was not considered a formal endpoint according to the TIMI 51 protocol although it was considered by the Clinical Events Committee. As noted further by the evaluator stent thrombosis contributed to individual components of the primary or secondary composite endpoints as a potential underlying cause of death, MI, severe recurrent ischaemia leading to revascularisation or severe recurrent ischaemia leading to hospitalisation. The Delegate agreed with the evaluator that stent thrombosis is acting in a similar manner to that of any other composite endpoint. It was not one that was formalised with respect to the study analysis, in particular as to how it would be handled in the context of the hierarchical testing strategy applied to the secondary endpoints. Moreover, the analysis of stent thrombosis was largely *post hoc* nature. Both the ACPM and the sponsor were asked for their views on the appropriateness of the inclusion of stent thrombosis in the indication.
- There were six analysis sets, three of which, the modified Intent-to-Treat (mITT), the ITT and the ITT-total, were based on the efficacy population and differed from each other in censoring rules for determining evaluable events. The mITT analysis set was the primary efficacy analysis set but the other two were submitted also as sensitivity analyses, which is reassuring.
- 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 bid and 5 mg bid) and placebo arms within each strata. The Delegate agreed with the evaluator that the sample size calculations are acceptable.
- Of the 15,526 subjects randomised, 15,342 (98.8%) subjects (5,114 in the 2.5 mg bid group, 5,115 in the 5 mg bid 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 bid group, 5,110 in the 5 mg bid group, and 5,125 in the placebo group) received at least 1 dose of study drug and were included in the safety population.
- 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%)).

- More rivaroxaban-treated subjects prematurely discontinued study drug due to an adverse event (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 bid group than in the 2.5 mg bid 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 bid rivaroxaban (7.0%) and placebo (6.8%) groups, but was numerically higher in the 5 mg bid (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 bid group (5.0%) compared with the 2.5 mg bid (3.6%) and placebo (1.8%) groups.
- As noted by the evaluator and as can be surmised from the preceding two paragraphs, the percentage of subjects who discontinued prematurely from the study was relatively high at about 15% with about half the latter due to withdrawal of consent. As part of the TGA's consolidated round of questions process, the evaluator requested the sponsor to compare the baseline demographic and disease characteristics of those subjects who discontinued prematurely with those of the subjects who completed the study to see whether any biases may have been introduced.
- 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 creatinine clearance (CrCl) <50 mL/min), and the majority of subjects had at least one cardiovascular (CV) risk factor, such as hypertension (67%), DM (32%), history of MI (27%), or hypercholesterolemia (49%). It is important to note that the two most common CV risk factors were hypertension and hypercholesterolaemia. Yet if a patient was aged between 18 and 54 years and had both of these risk factors (or just one) and neither diabetes mellitus (DM) nor a history of MI, that patient was excluded from the study. The ACPM and the sponsor were asked to comment on this fact and any implications it may have for the generalisability of the study results to such excluded patients.
- 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 bid - 6.1% versus 7.4%; HR: 0.84; 95% CI: 0.72-0.97; p=0.020 and 5 mg bid - 6.1% versus 7.4%; HR: 0.85; 95% CI: 0.73-0.98; p=0.028. Please see Table 20 (this is Table 9 in the principal clinical evaluation report (Attachment 1)). One can observe from Figure 4 attached to this overview (Figure 4 in the principal clinical evaluation report (Attachment 1)) which displays the graphs of the Kaplan-Meier estimates of the primary efficacy endpoint for all strata that the graphs of the two rivaroxaban treatment arms are almost superimposable. In other words, the higher dose of 5 mg bid confers no extra efficacy benefit when compared with that of the lower dose of 2.5 mg bid.

Table 20. Effect of rivaroxaban compared with placebo on the primary and selected secondary efficacy endpoints in the pivotal study (study TIMI 51, mITT analysis set)

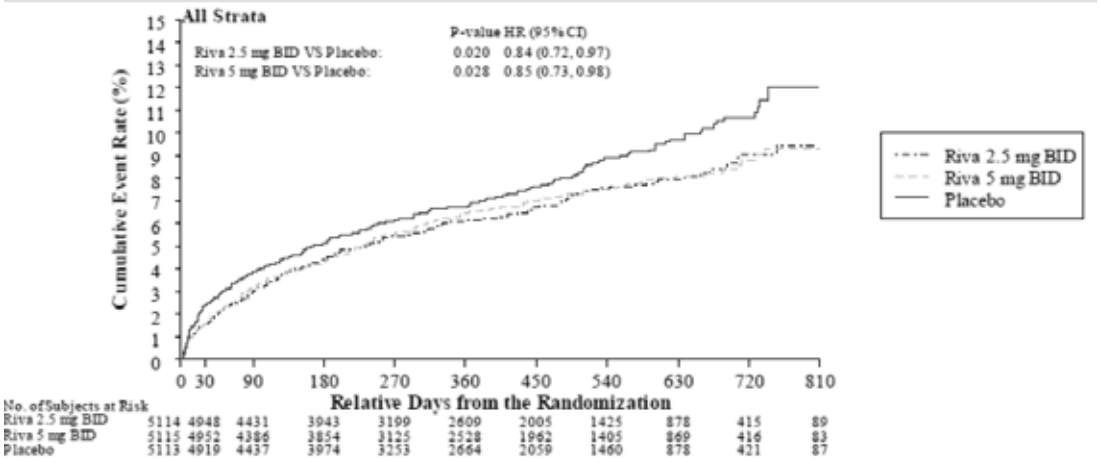
Subject Stratum	Rivaroxaban									
	2.5 mg bd	5 mg bd	Combined	Placebo	2.5 mg bid versus Placebo		5 mg bid versus Placebo		Combined versus Placebo	
	n (%)	n (%)	n (%)	n (%)	HR (95% CI)	Log-Rank P-value	HR (95 % CI)	Log-Rank P-value	HR (95 % CI)	Log-Rank P-value
All Strata (N)	5114	5115	10229	5113						
CV Dth/MI/St	313 (6.1)	313 (6.1)	626 (6.1)	376 (7.4)	0.84 (0.72, 0.97)	0.020	0.85 (0.73, 0.98)	0.028	0.84 (0.74, 0.96)	0.008
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/MI/St	27 (7.7)	24 (6.9)	51 (7.3)	36 (10.2)	0.74 (0.45,1.22)	0.234	0.64 (0.38, 1.07)	0.089	0.69 (0.45, 1.05)	0.084

Subject Stratum	Rivaroxaban									
	2.5 mg bd	5 mg bd	Combined	Placebo	2.5 mg bid versus Placebo		5 mg bid 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
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/St	286 (6.0)	289 (6.1)	575 (6.0)	340 (7.1)	0.85 (0.72, 0.99)	0.039	0.87 (0.74, 1.01)	0.075	0.86 (0.75, 0.98)	0.024
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.

Figure 4. Kaplan-Meier estimates of the primary efficacy endpoint for all strata (i.e. stratum 1 and stratum 2 combined) in the pivotal study (study TIMI 51, mITT analysis set)



- The effect of rivaroxaban 2.5 mg bid 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 bid 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. Please see Table 21. One can observe that the rates of cardiovascular death are relatively close to one another in each of the rivaroxaban 5 mg bid and placebo groups. This would be of immense concern if the 5 mg bid were the proposed dose. Also, the rates of MI are relatively close to one another in each of the rivaroxaban 2.5 mg bid and placebo groups. The rates of death attributable to MI, that is, fatal MI, show no advantage conferred by either active treatment with higher rates than placebo in the rivaroxaban 5 mg bid group [rivaroxaban 34/5110, 0.7% versus placebo 23/5125, 0.4%] and equal rates in the rivaroxaban 2.5 mg bid and placebo groups [rivaroxaban 22/5115, 0.4% versus placebo 23/5125, 0.4%]. Please see Table 22. This switching of benefit between dosage regimens has not been satisfactorily explained and was of concern to the Delegate. Is it simply a matter of chance in that the study was not powered to make robust pronouncements about each component or is there is a plausible biological basis to explain this phenomenon? Finally, neither rivaroxaban treatment regimen offered any benefit with regard to stroke. In fact the opposite was the case, the rates of stroke in each case being lower in the placebo group. The Delegate sought the views of both ACPM and the sponsor on these issues.

Table 21. Effect of rivaroxaban compared with placebo on the primary efficacy endpoint as adjudicated by the Clinical Events Committee (first occurrence of CV death, MI or stroke) in the pivotal study (study TIMI 51, mITT analysis set)

	---------- Rivaroxaban ----------									
	2.5 mg BID	5 mg BID	Combined	Placebo	-- 2.5 mg BID vs. Placebo --		-- 5 mg BID vs. Placebo --		-- Combined vs. Placebo --	
Subject Stratum	(N=5114)	(N=5115)	(N=10229)	(N=5113)		Log-Rank		Log-Rank		Log-Rank
Parameter	n(%)	n(%)	n(%)	n(%)	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value
All Strata	5114	5115	10229	5113						
Primary	313(6.1)	313(6.1)	626(6.1)	376(7.4)	0.84 (0.72,0.97)	0.020	0.85 (0.73,0.98)	0.028	0.84 (0.74,0.96)	0.008
CV_Dth	94(1.8)	132(2.6)	226(2.2)	143(2.8)	0.66 (0.51,0.86)	0.002	0.94 (0.75,1.20)	0.633	0.80 (0.65,0.99)	0.038
MI	205(4.0)	179(3.5)	384(3.8)	229(4.5)	0.90 (0.75,1.09)	0.270	0.79 (0.65,0.97)	0.020	0.85 (0.72,1.00)	0.047
Stroke	46(0.9)	54(1.1)	100(1.0)	41(0.8)	1.13 (0.74,1.73)	0.562	1.34 (0.90,2.02)	0.151	1.24 (0.86,1.78)	0.246
ASA	349	348	697	353						
Primary	27(7.7)	24(6.9)	51(7.3)	36(10.2)	0.74 (0.45,1.22)	0.234	0.64 (0.38,1.07)	0.089	0.69 (0.45,1.05)	0.084
CV_Dth	12(3.4)	9(2.6)	21(3.0)	10(2.8)	1.20 (0.52,2.77)	0.673	0.89 (0.36,2.20)	0.805	1.04 (0.49,2.21)	0.913
MI	16(4.6)	10(2.9)	26(3.7)	22(6.2)	0.72 (0.38,1.37)	0.310	0.44 (0.21,0.93)	0.026	0.58 (0.33,1.02)	0.053
Stroke	2(0.6)	8(2.3)	10(1.4)	7(2.0)	0.28 (0.06,1.37)	0.095	1.13 (0.41,3.12)	0.812	0.71 (0.27,1.86)	0.483
ASA + Thieno	4765	4767	9532	4760						
Primary	286(6.0)	289(6.1)	575(6.0)	340(7.1)	0.85 (0.72,0.99)	0.039	0.87 (0.74,1.01)	0.075	0.86 (0.75,0.98)	0.024
CV_Dth	82(1.7)	123(2.6)	205(2.2)	133(2.8)	0.62 (0.47,0.82)	<0.001	0.95 (0.74,1.21)	0.669	0.78 (0.63,0.97)	0.028
MI	189(4.0)	169(3.5)	358(3.8)	207(4.3)	0.92 (0.75,1.12)	0.401	0.83 (0.68,1.02)	0.077	0.88 (0.74,1.04)	0.131
Stroke	44(0.9)	46(1.0)	90(0.9)	34(0.7)	1.31 (0.84,2.05)	0.238	1.39 (0.89,2.16)	0.144	1.35 (0.91,2.00)	0.135

Note: The data shown are for all randomized subjects and the endpoint events occurring at or after randomization and the earliest date of the global treatment end date, 30 days after study drug was prematurely discontinued and 30 days after randomization for those subjects who were randomized but not treated.
Note: A subject could have more than one component event.
Note: n = number of subjects with events; N = number of subjects at risk; % = 100 * n / N.
Note: CV_Dth: Cardiovascular death including unknown death; MI: Myocardial infarction.
Note: HR (95% CI): Hazard ratios (95% confidence interval) as compared 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.

Table 22. Summary of all-cause deaths by primary cause as adjudicated by the Clinical Events Committee in the pivotal study (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.

- 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 bid group (6.0% versus 7.1%; HR: 0.85; 95% CI: 0.72-0.99; p=0.039); in the 5 mg bid 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).
- 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.
- For the primary efficacy endpoint the superiority of the 2.5 mg bid, 5 mg bid and combined rivaroxaban groups compared to placebo was confirmed in the ITT and ITT-total analysis sets.
- The first secondary efficacy endpoint, that is, the composite of all-cause death, MI or stroke 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 for the first secondary efficacy endpoint 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 bid (HR: 0.83; 95% CI: 0.72-0.97; p=0.016) and 5 mg bid (HR: 0.84; 95% CI: 0.73-0.98; p=0.025). In Stratum 2, a statistically

significant reduction in the occurrence of the first secondary efficacy endpoint was observed in the rivaroxaban 2.5 mg bid group compared with the placebo group (HR: 0.84; 95% CI: 0.72 - 0.98; p = 0.028).

- Neither the combined rivaroxaban doses nor each individual dose demonstrated a statistically significant reduction compared with placebo for the second secondary efficacy endpoint for All Strata or Stratum 2. As a result of the hierarchical testing strategy, testing of the remaining secondary endpoints for statistical significance was not performed.
- 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 bid and 5 mg bid groups, respectively, and 1.2% for the placebo group. As noted by the clinical evaluator, according to the SAP stent thrombosis was initially only to be summarised by treatment group as it was not a formal study endpoint. As observed, a *post hoc* analysis was performed and based on the results of this analysis the sponsor now seeks the inclusion of stent thrombosis in the indication. The Delegate strongly agreed with the evaluator that this is not appropriate. The primary and secondary endpoints were all composite endpoints and subject to strict hierarchical testing. Stent thrombosis should have been subject to the same criteria. This issue was canvassed again in the TGA request for information. The latter will be summarised later in this overview. The ACPM and the sponsor were requested to express their views on this issue.
- In the dose-finding Study TIMI 46, there was a steady climb in the cumulative incidence of clinically significant bleeding with increasing dose.
- In the pivotal Study TIMI 51 in All Strata, the combined, 2.5 mg bid and 5 mg bid rivaroxaban doses all significantly increased the incidence of the primary safety endpoint (non-CABG TIMI major bleeding) compared with placebo. Results in Stratum 2 were similar.
- In TIMI 51 in All Strata and in Stratum 2 each of the rivaroxaban dose groups also increased the risk of clinically significant bleeding, intracranial bleeding, haemorrhagic stroke and life-threatening bleeding.
- In TIMI 51 fatal bleeding events were low overall and generally comparable between the 2.5 mg bid rivaroxaban dose and placebo. Rates were numerically higher in the rivaroxaban 5 mg bid dose group.

Safety

- The studies which provided evaluable safety data were the pivotal efficacy & safety study TIMI 51, the dose-finding efficacy and safety study TIMI 46 and 4 small clinical pharmacology studies.
- In the pivotal Study TIMI 51 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 bid and 5 mg bid 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. In the dose-finding study TIMI 46 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.
- In the pivotal Study TIMI 51, a total of 15,350 subjects (5,115 in the rivaroxaban 2.5 mg bid group; 5,110 in the rivaroxaban 5 mg bid group and 5,125 in the placebo group) who

received at least one dose of study drug were included in the safety analysis set. There were 3 analysis sets based on the safety population, that is, all randomised subjects who received at least one dose of study drug. These were the treatment-emergent safety set; the primary safety analysis set, the mITT safety set and the safety observation period set. These 3 sets differed from each other in the censoring rules for determining evaluable events. The treatment-emergent safety set included all events from the first dose up to the date of the last dose of study drug plus 2 days and was also used as a sensitivity analysis for efficacy. In the dose-finding Study TIMI 46 a total of 3462 subjects (2,309 subjects in the rivaroxaban groups and 1,153 in the placebo groups) who received at least one dose of study drug were included in the safety analysis set.

- In the pivotal Study TIMI 51 in All Strata, the combined, 2.5 mg bid and 5 mg bid 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 bid rivaroxaban: 1.3% versus 0.4%, HR: 3.46; 95% CI: 2.08-5.77; p<0.001
  - 5 mg bid 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 TIMI 51 in All Strata and in Stratum 2 each of the rivaroxaban dose groups also increased the risk of:
  - Clinically significant bleeding, that is, TIMI major bleeding, TIMI minor bleeding and 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.

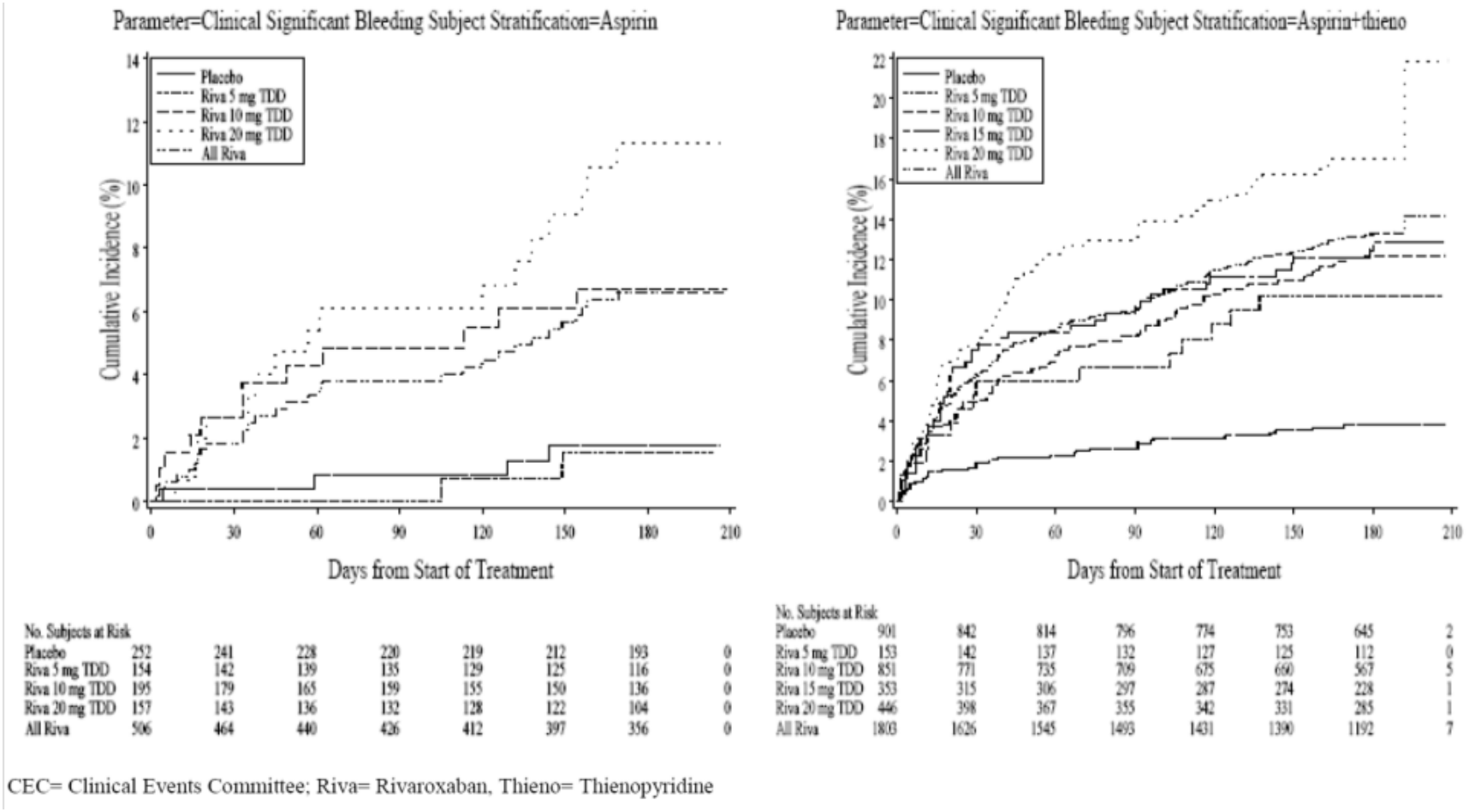
In all bleeding categories but haemorrhagic stroke there was a clear dose response with the 5 mg bid dose of rivaroxaban associated with higher event rates than the 2.5 mg bid dose.

- In TIMI 51 fatal bleeding events were low overall and generally comparable between the 2.5 mg bid rivaroxaban dose and placebo. Rates were numerically higher in the rivaroxaban 5 mg bid group.
- In TIMI 51 sensitivity analyses generally confirmed the above results.
- In TIMI 51 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. As noted by the evaluator it was not possible from the data to assess whether subjects with both an ALT >3 x ULN and total bilirubin >2 x ULN also had an elevated alkaline phosphatase (ALP) or other underlying cause for the abnormal liver function tests (LFTs). Thus it was not possible to determine whether any of these cases represented potential Hy's Law cases. This issue was raised by the evaluator in the consolidated list of TGA questions.
- Bearing in mind the shorter duration of the dose-finding Study TIMI 46, the safety data from that study for the rivaroxaban 5 mg and 10 mg total daily doses were consistent with those of TIMI 51. Analysis of the bleeding events by dose in TIMI 46 demonstrated almost a tripling of the risk of TIMI and a quadrupling of the risk of TIMI major bleeding above a total daily dose of 5 mg. There was a steady climb in the cumulative incidence of clinically

significant bleeding at all dose levels of rivaroxaban with a notable bunching of these incidence rates for the low to intermediate dose levels. Please refer to Figure 5. In TIMI 46 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. The sponsor is asked to confirm whether or not there were any confirmed Hy's Law cases in TIMI 46.

- As noted by the clinical evaluator, overall the safety profile of rivaroxaban from the post-marketing surveillance data provided appears consistent with that of the underlying disease being treated and/or with the safety profile known from the clinical studies. No new or unexpected safety signals were identified.

Figure 5. Kaplan-Meier estimates of treatment-emergent clinically significant bleeding as adjudicated by the clinical events committee, study ATLAS ACS TIMI 46, the dose-finding study



CEC= Clinical Events Committee; Riva= Rivaroxaban, Thieno= Thienopyridine

First round risk-benefit balance (clinical evaluator)

- The clinical evaluator was of the opinion that the benefit-risk balance of rivaroxaban 2.5 mg bid was unfavourable given the proposed usage, but may become favourable if the recommended amendments to the PI were adopted and if satisfactory answers were received to the consolidated list of TGA questions.
- As noted by the evaluator, the sponsor attempted to quantify the benefit-risk balance shown in the pivotal study TIMI 51 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 bid 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 have a negative impact on the health and/or quality of life of the patient.
- The sponsor therefore provided an alternative post-hoc assessment from TIMI 51 of benefit-risk analysis based on number needed to treat (NNT) and number needed to harm (NNH). Endpoints were re-categorised to show ischaemic events as efficacy and haemorrhagic events as safety. Please see Table 23 which displays ischaemic and haemorrhagic event rates for the 2.5 mg bid rivaroxaban dose in Stratum 2.

Table 23. Ischaemic and haemorrhagic events for the 2.5 mg bid rivaroxaban dose in stratum in the pivotal study, TIMI 51 mITT

Time to Event Category	Endpoints	------ Event Rate(a) ----- ------ (/100 Pt-yrs) ----- Rivaroxaban	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 $\geq$ 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.

- In Stratum 2, rivaroxaban 2.5 mg bid 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 haemoglobin (Hb) of 3 to <5 g/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, as noted by the clinical evaluator, 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. The clinical evaluator concluded that, on balance, the benefit-risk ratio remains in favour of rivaroxaban compared with placebo.
- The clinical evaluator further noted that the 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. The clinical evaluator was of the view that it is 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. The Delegate strongly endorsed these views. To this end the sponsor will have to engage seriously in a comprehensive program of education of potential prescribers, a program which must adequately highlight all the risks associated with the use of rivaroxaban, particularly bleeding.

Clinical list of questions and second round evaluation of the data submitted by the sponsor in response

- Question 1 asked the sponsor to provide the results and conclusions to support the lack of food effect with the 2.5 mg tablet. The Delegate would agree with the evaluator that the limited information available does suggest the lack of such an effect.
- Question 2 requested clarification of the basis for the choice of the various relative reduction estimates used in the calculation of the required number of primary efficacy endpoint events and of sample size. The Delegate agreed with the evaluator that the estimates based on findings from the literature and/or on earlier studies was acceptable.
- Question 3 raised the issue of why there were no data supplied in the submission or an adequate explanation given for the original choice of 2.5 mg bid as the lowest dosage

regimen in the Phase III trial. As made quite clear by the evaluator no new information was provided by the sponsor in its response to the question. While it is understood by both the clinical evaluator and the Delegate that the 2.5 mg bid dosage regimen was the lowest effective regimen *tested* in the VTE prophylaxis studies and while a dose of 1.25 mg was found to have no effect on Factor Xa inhibition, there is no information available on intermediate doses. Thus it remains unclear whether alternative dosage regimens, for example, 2 mg bid or 1.5 mg bid may have been clinically effective with fewer adverse events. The Delegate viewed this as a serious deficiency and requests both ACPM and the sponsor to provide comment on this issue.

- Question 4 concerned the high percentage, approximately 15%, of subjects who withdrew prematurely from the TIMI 51 study. From the answer to this question, it would appear that efficacy endpoints are now known for a final 94.9% of subjects, vital status known for an additional 3.4% of subjects. Therefore vital status remains unknown for approx. 1.8% of subjects. The clinical evaluator was of the opinion that the up-dated follow-up and 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) do provide reassurance about the validity of the study efficacy results. However, one must keep in mind that these are *post hoc* corrections. The Delegate requested the sponsor to provide, in its ACPM response, the equivalent of Table 9 in the CER (Attachment 1) updated with information about the efficacy endpoints known now for the 94.9% of subjects. It is also worth noting the clinical evaluator's comment that the up-dated data may still underestimate bleeding adverse events as there was a higher proportion of permanent discontinuation as a result of bleeding in the rivaroxaban treated subjects.
- Question 5 requested the sponsor to provide a copy of its responses to all the issues raised by the US FDA. This was provided. The sponsor provided a justification for the adequacy of a single pivotal trial which is consistent with the relevant EU guideline.[8] The Delegate had concerns about the adequacy of a single pivotal trial in the face of such a large percentage of premature withdrawals. The Delegate stated that further sensitivity analyses, now necessarily *post hoc* in nature, cannot substitute for better follow-up.
- Question 6 raised the issue of optimal thienopyridine treatment, in particular the concomitant use of a thienopyridine with a CYP2C19 inhibitor. Stratum 2 subjects on clopidogrel (a pro-drug which requires metabolism by CYP2C19) may not have been receiving effective treatment if they were also receiving drugs that inhibit CYP2C19. Sensitivity analyses were therefore performed in subjects receiving "optimal" thienopyridine therapy which was defined as being on a thienopyridine and not taking either of the proton pump inhibitors omeprazole or esomeprazole. Please note also that the sensitivity analysis also took into account those who stopped using the thienopyridine for whatever reason. The results from this re-analysis were consistent with those from the original mITT analysis set. A similar sensitivity analysis was requested by the TGA but with a slight widening of the definition of "optimal" thienopyridine treatment. This time "optimal" thienopyridine treatment was defined as being on a thienopyridine and not taking either omeprazole or esomeprazole and also not taking any other moderate or strong CYP2C19 inhibitors. Table 23 in the CER (Attachment 1) shows the re-analysis of the primary efficacy endpoint on this reduced population of subjects considered to be on "optimal" thienopyridine treatment. One can see from this table that the numbers in each treatment arm have been reduced by about 700-800. That is to say that, in each arm, there were about 700-800 subjects who were on a CYP2C19 inhibitor. What one is relying on is a reverse inference. If one can demonstrate that the sensitivity re-analysis is comparable with the original analysis, that is, that the results in Table 23 are comparable with the results in Table 9 in the CER (both in Attachment 1), then one makes an inference that the effect of the

[8]CPMP/EWP/2330/99 *Points to Consider on Applications with: 1. Meta-Analyses and 2. One Pivotal Study*

700-800 subjects not on "optimal" thienopyridine treatment has not been sufficient to sway or to reverse the original findings. The Delegate has reproduced Table 23 from the CER, that is, the table showing the results of the re-analysis, as Table 24 attached to this overview. It is then a matter of comparing this Table 24 to Table 20, both attached to this overview. The point estimates in the re-analysis of rivaroxaban 2.5 mg bid versus placebo for the primary efficacy endpoint in All Strata and Stratum 2 (those subjects on concomitant ASA and a thienopyridine) are consistent with those from the original analysis. In each case they are marginally worse. For each there was also a loss of statistical significance (see the circled p-values in Table 24 attached to this overview). The Delegate views these results as counter-intuitive. With the removal of those not on "optimal" thienopyridine one would expect if anything better results in the remaining subjects. The loss of statistical significance would at least partly be explained by the loss of statistical power due to the reduction in sample size. The sponsor is requested to carry out the primary efficacy analysis in those 700-800 subjects who were censored as not being on "optimal" thienopyridine treatment.

Table 24. Effect of rivaroxaban compared with placebo on the primary efficacy endpoint and its components censored at the earlier of the following two days: the day before the start of CYP2C19 inhibitor use or the day of the last thienopyridine use, pivotal study (TIMI 51, mITT analysis)

	Rivaroxaban									
Subject Stratum	2.5 mg BID (N=4291)	5 mg BID (N=4248)	Combined (N=8539)	Placebo (N=4268)	– 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 (0.71,1.05)	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)	245(5.8)	0.87 (0.73,1.05)	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)	0.167
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)	0.233
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.

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

- Question 7 raised the issue of identification of potential Hy's Law cases. No Hy's Law cases were identified. This was based firstly on a similar incidence of subjects with elevations in ALT and in total bilirubin that met the thresholds of > 3 x ULN and 2 x ULN, respectively, and secondly on the finding of an alternative explanation for the elevated liver enzymes. The sponsor was reminded that the Delegate has requested the same information with regard to potential Hy's Law cases in the dose-finding Study TIMI 46.
- Question 8 concerned the issue of the indication for stent thrombosis. The sponsor argues in its reply to the questions that the analysis in question was not *post hoc*. As has been pointed out by the evaluator it was declared in the Statistical Analysis Plan that stent thrombosis and its sub-categories would be summarised by treatment group since this endpoint was not a formal study endpoint in the study protocol even though it was adjudicated. Furthermore, as again pointed out by the evaluator, the TIMI 51 CSR states that the calculations of the relevant hazard ratio and 95% confidence interval for the time to first occurrence of stent thrombosis were not planned and were performed after the unblinding of treatment assignments. Finally and probably most importantly the endpoint of stent thrombosis was not, in any way, positioned or defined in relation to the hierarchical testing strategy applied to the efficacy endpoints. It would be highly inappropriate to allow the inclusion of such an end-point in the indications. Under such circumstances the Delegate would only permit a purely descriptive analysis of the results in the *Clinical Trials* section of the PI.
- Question 9 concerned the issue of treatment-emergent anaemia. The Delegate was not prepared to accept the figure supplied in answer to the question until the sponsor can demonstrate the location in the data of the overall number of treatment-emergent anaemia cases and provide for the perusal of the Delegate and the ACPM in the ACPM response all the necessary explanatory tables.
- Question 10 concerned an amendment to the PI which was considered acceptable although the Delegate agreed with the clinical evaluator's amendment which is more readable.

Further questions posed by the evaluator concerned amendments to the PI which are beyond the scope of this AusPAR.

Second round assessment of risk-benefit balance by the clinical evaluator

- The clinical evaluator was of the view that the benefit-risk balance of rivaroxaban (Xarelto) 2.5 mg bid, given the proposed usage, was favourable. Comparison of the fatal/irreversible benefits and risks for subjects on "optimal" thienopyridine therapy suggests a favourable benefit-risk ratio for rivaroxaban 2.5 mg bid 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.
- The clinical evaluator was of the view that, based on the answers received to the questions raised by the TGA, it should be recommended that rivaroxaban (Xarelto) 2.5 mg bid is approved for the treatment of acute coronary syndrome, subject to modification of the PI and CMI as recommended in the CER. In particular, it was considered that the requested indication for "*Prevention of atherothrombotic events and stent thrombosis...*" was 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. Furthermore, the clinical evaluator recommended that use of Xarelto should also be restricted to ACS patients

receiving combination therapy with aspirin plus a thienopyridine (clopidogrel or ticlopidine).

Risk management plan

The Office of Product Review (OPR) has notified the Delegate that it has completed its review of the RMP and that, as a result, the OPR was of the view that the sponsor has adequately addressed all OPR recommendations except for some outstanding issues which will be summarised in the following paragraphs.

- The sponsor was reminded of its previous assurances that a postmarket periodic schedule for the prescriber and patient survey testing would be proposed and implemented for as long as additional risk minimisation activities were considered necessary and the feedback would then be used to refine the prescriber guide and patient information. However, the sponsor has now advised that such survey testing will not commence until February 2013, and then 6 and/or 12 months after PBS listing. This response is considered to be inadequate in the light of previous assurances and the fact that supply of these products has commenced in Australia, presumably since 4 June 2012, via the Product Familiarisation Program (PFP). The sponsor has reported that as of 28 September 2012 almost 4,000 prescribers and almost 3,000 patients have enrolled in the PFP. Furthermore no quantitative criteria, suitably justified, to be used to verify the success of the proposed additional risk minimisation activities have been specified. Consequently this remains an outstanding recommendation which the sponsor must address in an appropriate and adequate manner before this application is approved, given that such activity is the subject of specific conditions of registration for these products. Bayer responded that its intention was always to commence a survey when there was sufficient experience with the product in the market to provide meaningful data for OPR to review.
- The sponsor was advised that Section 3.1: '*Summary table of planned actions*' and Section 5: *'Summary of the Risk Management Plan*' of the AU RMP should refer to details of routine risk minimisation in the Australian PI, not the CCDS. In response the sponsor has now attached the approved and proposed Australian PI to the ASA. This is not entirely satisfactory and it is reiterated that a short description, including the location within the Australian PI, of routine risk minimisation for all of the specified Ongoing Safety Concerns should be provided in the ASA when it is next updated. In response the sponsor has confirmed that an updated ASA will be provided to the TGA as requested.
- At the 14th meeting of ACSOM, the committee considered whether the printed materials associated with the Xarelto education program and the PFP for the existing indications, which aimed to highlight the Important identified risk: '*Haemorrhage'* and to minimise medication error, were adequate in addressing these issues. Ratified advice from the committee provided detailed comment on the suitability of these materials. In summary: *"ACSOM advised that the printed materials provided were not adequate. The committee expressed concern that the PFP documents were overly promotional; and not presented clearly or logically. In particular, the statement that monitoring was unnecessary was considered misleading, and the emotive aspects such as smiling faces were not considered appropriate. The materials were not of the same standard as the PI/CMI, and there was not enough emphasis on education and safety."* Consequently all printed materials associated with the Xarelto education program and the PFP must be revised in the light of such advice and provided to the TGA for review before this application can be approved, given that such activity is the subject of specific conditions of registration for these products. In response Bayer has said that it will consider the OPR's comments regarding the clarity of the monitoring message in future materials to ensure that clinicians are advised that general

patient monitoring should continue to be conducted given the potential for bleeding with Xarelto.

- If this application is approved, the Office of Product Review recommended that the following specific conditions of registration should be applied:
  - The European Risk Management Plan identified as Version: 7.2, dated 29 March 2012, and an Australian Specific Annex (ASA) identified as Version 1, dated September 2012, with revised details of a Risk Minimisation Plan within the ASA as agreed with the TGA, must be implemented.
  - Post marketing reports are to be provided in line with the current published list of European Union (EU) reference dates and frequency of submission of periodic safety update reports (PSURs) until the period covered by such reports is not less than three years from the date of this approval letter. The reports are to meet the requirements in accordance with ICH E2C (R2) guideline on *Periodic Benefit-Risk Evaluation Reports* and Module VII of the EMA *Guideline on Good Pharmacovigilance* (GPV) Practices relating to PSURs. Submission of the report must be within the 70 days of the data lock point for PSURs covering intervals up to and including 12 months and within 90 days of the data lock point for PSURs covering intervals in excess of 12 months. The submission may be made up of periodic Safety Update Reports each covering six months.

The Delegate, prior to the writing of this overview, forwarded the advice of the OPR to the sponsor. This advice which is tantamount to a Round 2 evaluation report from the OPR refers to some important issues as detailed above. The sponsor has responded to the OPR advice and at this stage, the responses appear reasonable. However, the Delegate will seek formal feedback from OPR regarding Bayer's response.

Risk-benefit analysis

Delegate considerations

- The Delegate has already expressed concerns about the robustness of the findings of the dose-finding Study TIMI 46. It was a relatively small study conducted over just 6 months with highly variable numbers in the various dose level groups. For example in the 5 mg total daily dose group, that is, counting both once daily and twice daily regimens there were 308 patients studied while in the 10 mg total daily dose group, again counting both once daily and twice daily regimens, there were well over 3 times as many studied, namely 1056. Yet the 5 mg total daily dose regimens were carried forward. As noted previously, based only on efficacy results and given the generally more consistent and better results in the rivaroxaban twice daily groups compared with the once daily groups, the two most promising dosage regimens appeared to be the 2.5 mg bid and the 5 mg bid. However, the latter was ruled out of contention presumably because of the higher rates of bleeding events associated with higher doses. The Delegate has already commented on the impressive outcome for the primary efficacy endpoint for the 20 mg once daily dose. By contrast, the Delegate has also pointed out the seemingly alarmingly high death rate in the combined 5 mg total daily dose groups. All in all it was difficult to extrapolate from the results of the TIMI 46 study and confidently predict the most promising doses.
- With regard to the pivotal Study TIMI 51, the Delegate had a number of concerns, which were detail in this and subsequent paragraphs. The first of these is to do with the study enrolment which required that 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 event. The motivation for this would appear to have been to increase the likelihood of an outcome event in this age stratum. Has this skewed the patient population in TIMI 51 significantly

enough so that it is not precisely representative of the ACS population? The sponsor is seeking an indication for the broad ACS population without qualification. Can one apply the results of TIMI 51 to subjects aged from 18 to 54 years inclusive who do not have either diabetes mellitus or a prior history of MI? Also, as noted by the Delegate, the two most common cardiovascular risk factors in the study population overall were hypertension and hypercholesterolaemia. Yet if a patient in this younger age group had both of these risk factors (or just one) and neither diabetes mellitus nor a history of MI, that patient was excluded from the study. The Delegate has asked for further clarification of the issue by the sponsor.

- In TIMI 51 the proportion of subjects who discontinued prematurely from the study was relatively high at about 15% with about half the latter due to withdrawal of consent. The proportion of premature discontinuations was relatively evenly spread across the treatment arms. As a result of further follow-up, efficacy endpoints are now known for a final 94.9% of subjects, vital status known for an additional 3.4% of subjects with vital status remaining unknown for approx. 1.8% of subjects. While all the relevant re-analyses were in accord with the original results, it must be kept in mind that all these re-analyses are derived from *post hoc* corrections. The Delegate requested the sponsor to report on the primary efficacy outcome updated with information about the efficacy endpoints known now for the 94.9% of subjects. The Delegate also endorsed the view of the clinical evaluator that the up-dated data may still underestimate bleeding adverse events as there was a higher proportion of permanent discontinuation arising from bleeding in the rivaroxaban treated subjects.
- In TIMI 51 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 bid - 6.1% versus 7.4%; HR: 0.84; 95% CI: 0.72-0.97; p=0.020 and 5 mg bid - 6.1% versus 7.4%; HR: 0.85; 95% CI: 0.73-0.98; p=0.028.
- From the results for the individual components of the primary efficacy endpoint, one can see that the effect of rivaroxaban 2.5 mg bid 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). This was at the expense of the rate for MI which was comparable with that of placebo. By contrast the effect in the 5 mg bid 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. The reduction in the rate of MI was at the expense of the rate of CV death which was comparable with that of placebo. This switching of benefit between dosage regimens was of concern to the Delegate and betrays a lack of internal consistency. Finally, for the third individual component, stroke, there was no benefit with rates being higher in both rivaroxaban groups than in the placebo group.
- The rates of fatal MI showed no advantage conferred by either active treatment with higher rates than placebo in the rivaroxaban 5 mg bid group and equal rates in the rivaroxaban 2.5 mg bid and placebo groups.
- In TIMI 51 rivaroxaban was 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 bid group (6.0% versus 7.1%; HR: 0.85; 95% CI: 0.72-0.99; p=0.039); in the 5 mg bid 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).
- In TIMI 51 in Stratum 1, although the HR point estimates were the most favourable, they were not statistically significant. This no doubt is a result of the relatively very small size of the sub-groups in Stratum 1. Generally, the treatment groups in Stratum 1 averaged 350 in size compared with treatment group sizes of around 4,750 in Stratum 2, that is, less than a

tenth in comparison. Given such small numbers, the Delegate agreed with the clinical evaluator that results from such small groups, results which were not statistically significant, should not be reflected in the indications. Indications should ideally only ever reflect robustly evidenced primary efficacy endpoints. The ACPM was asked to express its views on this issue.

- In a post-hoc analysis of "definite", "probable" or "possible" stent thromboses in the pivotal Study TIMI 51, 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 bid and 5 mg bid groups, respectively, and 1.2% for the placebo group. It was declared in the Statistical Analysis Plan that stent thrombosis and its sub-categories would be summarised by treatment group since this endpoint was not a formal study endpoint in the study protocol even though it was adjudicated. Furthermore, the TIMI 51 CSR states that the calculations of the relevant hazard ratio and 95% confidence interval for the time to first occurrence of stent thrombosis were not planned and were performed *after* the unblinding of treatment assignments. Finally and probably most importantly, the endpoint of stent thrombosis was not, in any way, positioned or defined in relation to the hierarchical testing strategy applied to the efficacy endpoints. It would be highly inappropriate to allow the inclusion of such an end-point in the indications. Under such circumstances the Delegate would only permit a purely descriptive analysis of the results in the *Clinical Trials* section of the PI.
- The point estimates in the re-analysis of rivaroxaban 2.5 mg bid versus placebo for the primary efficacy endpoint in All Strata and in Stratum 2 for those subjects on "optimal" thienopyridine treatment were found to be consistent with those from the original analysis. However, as pointed out by the Delegate, the point estimates are marginally worse. As previously remarked, with the removal of those not on "optimal" thienopyridine, one would expect better results in the remaining subjects.
- It remains unclear whether alternative, lower dosage regimens, such as 2 mg bid or 1.5 mg bid may have been clinically effective with fewer adverse events. There appear to be no robust data which will resolve this issue.

Indication

In the light of the foregoing discussion regarding the inappropriateness of inclusion of references to stent thrombosis and to use in subjects on concomitant aspirin without thienopyridine, the Delegate proposed the following indication, if this submission were eventually to be approved:

> "*Prevention of cardiovascular death and myocardial infarction in patients after an acute coronary syndrome (ACS) (non-ST elevation or ST elevation myocardial infarction or unstable angina) in combination with acetylsalicylic acid (ASA) plus a thienopyridine (clopidogrel or ticlopidine)"*

Summary

With the adoption of a more conservative benefit-risk assessment (by including some less severe bleeding events), the benefit-risk ratio is approximately 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). In the view of the Delegate this is a very slight benefit compared with risk, particularly when considered in the context of all the concerns expressed above by the Delegate and in the context of so many issues which require clarification. At this stage the Delegate did not have confidence in being able to recommend approval of the submission and so must recommend rejection.

The Delegate proposed to **reject** this submission by Bayer Australia Ltd to register Xarelto® tablets (containing rivaroxaban 2.5 mg) based on the safety and efficacy of the product not having been satisfactorily established for the indication below, for the reasons stated above in the Risk / Benefit Discussion.

> *"Prevention of cardiovascular death, myocardial infarction and stent thrombosis in patients after an acute coronary syndrome (ACS) (non-ST elevation or ST elevation myocardial infarction or unstable angina) in combination with acetylsalicylic acid (ASA) alone or with ASA plus a thienopyridine (clopidogrel or ticlopidine)."*

There are a large number of issues in this submission which require clarification and explanation and to this end the sponsor has been asked a number of questions in this Delegate's overview. All of these issues require resolution. Also required is amendment of the Product Information document to the satisfaction of the TGA as well as resolution of any outstanding matters with regard to the Risk Management Plan.

The Delegate intended to impose the following specific conditions of registration:

1. The European Risk Management Plan identified as Version: 7.2, dated 29 March 2012, and an Australian Specific Annex (ASA) identified as Version 1, dated September 2012, with revised details of a Risk Minimisation Plan within the ASA as agreed with the TGA, must be implemented.
2. Post marketing reports are to be provided in line with the current published list of European Union (EU) reference dates and frequency of submission of periodic safety update reports (PSURs) until the period covered by such reports is not less than three years from the date of this approval letter. The reports are to meet the requirements in accordance with ICH E2C (R2) guideline on Periodic Benefit-Risk Evaluation Reports and Module VII of the EMA Guideline on Good Pharmacovigilance (GPV) Practices relating to PSURs. Submission of the report must be within the 70 days of the data lock point for PSURs covering intervals up to and including 12 months and within 90 days of the data lock point for PSURs covering intervals in excess of 12 months. The submission may be made up of periodic Safety Update Reports each covering six months.

The sponsor should address the following issues in the Pre-ACPM response:

a. The sponsor was requested to comment on the issue of the robustness of the results of the dose-finding study TIMI 46.

b. The sponsor was requested to comment on to the apparently high death rate in the 5 mg total daily groups combined in TIMI 46.

c. The sponsor was asked to confirm whether or not there were any confirmed cases of Hy's Law in TIMI 46.

d. The sponsor was requested to provide the precise numbers of subjects in the age group 18-54 years who had diabetes mellitus, a history of MI or both diabetes and a history of MI. The sponsor was also asked to comment on why this younger age group was subject to these extra inclusion criteria and how this may affect the generalisability of the study results.

e. The sponsor was requested to comment on the appropriateness of including a reference to stent thrombosis in the indications.

f. Given the relatively quite small size of the treatment sub-groups in Stratum 1 in TIMI 51 and the consequent results for Stratum 1 which were not statistically significant, the Delegate was of the opinion that these results should not be reflected in the indications. Indications should ideally only ever reflect robustly evidenced primary efficacy endpoints. The sponsor was asked to express its views on the matter.

g. The Delegate has made a number of comments about the individual components of the composite primary efficacy endpoint of the pivotal study TIMI 51. The sponsor was asked to respond to those comments.

h. With regard to the data supplied by the sponsor in response to the questions asked about the high rate of premature withdrawals of subjects in TIMI 51, the sponsor was requested to provide the equivalent of Table 9 in the CER updated with information about the efficacy endpoints known now for 94.9% of subjects, insofar as that is possible.

i. With regard to the data supplied by the sponsor in response to the questions asked about the high rate of premature withdrawals of subjects in TIMI 51, the sponsor was requested to comment on the fact that the up-dated data may still underestimate bleeding adverse events.

j. The sponsor was requested to respond to the issues raised by the Delegate in the assessment of the re-analysis of endpoints conducted in the sub-population of subjects on "optimal" thienopyridine treatment. The sponsor was also requested to carry out the primary efficacy analysis in those 700-800 subjects not on "optimal" thienopyridine treatment.

k. The sponsor was requested to provide the location in the data of the overall number of treatment-emergent anaemia cases as well as all the necessary explanatory tables.

l. The sponsor was requested to justify why alternative, lower dosage regimens such as 2 mg bid or 1.5 mg bid may not be as equally clinically effective as the tested dose 2.5 mg bid but with fewer adverse events.

The Delegate's Overview was at this stage submitted for ACPM advice.

Response from sponsor

Bayer Australia Ltd (the Sponsor) proposed a new indication:

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

The proposed indication for stent thrombosis has now been removed, as has the reference to patients receiving aspirin alone (Stratum 1), in accordance with the Delegate's comments. This is further discussed in the section entitled *Indications*.

Background

Acute coronary syndromes (ACS) are common clinical and pathological conditions. Atherothrombosis is the major pathophysiological process responsible for the occurrence of ACS in patients. The incidence and prevalence rates of ACS remain high throughout the developed world. In Australia, the projected incidence of ACS in 2014 is 82, 660[9]. Dual anti-platelet therapy has become the standard of care for treatment with ACS; nevertheless, the rates of cardiovascular (CV) death and myocardial infarction (MI) remain high in the community.

Anticoagulation is a central and widely accepted part of the standard of care for ACS patients in the acute setting, all parenteral anticoagulants have demonstrated clinical benefit in this setting in large clinical trials. The purpose of the ATLAS ACS program is to investigate whether the long

[9] Estimated based on projected Australian population in 2014 and epidemiological data in "ACS in Perspective: the importance of secondary prevention" commissioned by Deloitte Access Economics in 2011

term use of an anticoagulant can continue to provide clinical benefit as ACS patients continue to be at substantial clinical risk for thrombosis-related events.

By the significant reduction of CV death shown in the ATLAS ACS 2 TIMI 51 study, long term use of rivaroxaban 2.5 mg bid has demonstrated clinical relevance in patients with an ACS in addition to standard of care [HR 0.66 (0.51, 0.86) p=0.002].

The results from TIMI 51 were presented at the European Society of Cardiology (ESC) Congress 2012. Although the application is pending approval in Europe, a recommendation has already been made in the ESC guidelines that "i*n selected patients who receive aspirin and clopidogrel, low-dose rivaroxaban (2.5 mg twice daily) may be considered if the patient is at low bleeding risk*"[10] further supports the role of rivaroxaban in this setting.

Dose-ranging study

The sponsor acknowledged the Delegate's comments regarding the dose-finding study TIMI 46, in that the 2.5 mg bid dosage regimen was the lowest effective regimen tested. It was demonstrated in the VTE prophylaxis studies that the lowest effective dose was 2.5 mg bid, since the 1.25mg bid dose demonstrated no pharmacodynamic effect, therefore this formed the basis for the decision to test 2.5 mg bid and 5 mg once a day (OD) as the lowest doses in the ATLAS ACS TIMI 46. The Delegate has questioned if lower dosage regimens such as 2 mg bid or 1.5 mg bid could be as clinically effective with fewer adverse events. It is acknowledged in the EMA guidance[11] on dose response information that there is the possibility that the lowest dose studied is still greater than needed to exert the drug's maximum effect, however imperfect dose response data is not in itself a reason for rejection provided an acceptable balance of observed undesired effects and beneficial effects has been demonstrated at one of the doses studied.

By demonstrating favourable benefit/risk and acceptable safety with rivaroxaban in the ATLAS ACS program, the sponsor believed an acceptable balance has been achieved for the rivaroxaban 2.5 mg bid dose in use with thienopyridine plus an ASA.

Benefit/risk

Benefit/risk assessment is critical to ascertain that the benefit gained exceeds the harm caused by health interventions. The Delegate ended the discussion on benefit/risk with an adoption of a more conservative benefit-risk assessment with a benefit-risk ratio being approximately 1.3 to 1 (101 non-haemorrhagic CV death, MI and ischaemic stroke events prevented: 77 TIMI major or TIMI life-threatening bleeding events caused) with a remark that this is a very slight benefit compared with risk. This ratio was derived from a subpopulation within the Stratum 2 from the 2.5 mg bid dose arm and those considered on "optimal" thienopyridine therapy.

Calculated benefit/risk ratio is by and large dependent on the type of bleeding chosen for the assessment. As noted by the Delegate, a more conservative approach was adopted by including TIMI major or TIMI life-threatening bleeding. Caution should be exercised when putting into perspective how the laboratory-based TIMI bleeding scale is interpreted into clinically meaningful outcomes. TIMI major bleeding is defined as any symptomatic intracranial haemorrhage or clinically overt signs of haemorrhage (including imaging) associated with a drop in haemoglobin of ≥ 5 g/dL (or when the haemoglobin concentration was not available, an absolute drop in haematocrit of ≥ 15%). In Study TIMI 51, bleeding events such as moderate epistaxis, mild to severe gastrointestinal haematemesis or increased/prolonged menstrual or vaginal bleeding were adjudicated as TIMI major bleeding events by the investigators. Of the identified TIMI major bleeds, approximately 1/3 of these were classified as mild or moderate by

[10] The Task Force on the management of ST-segment elevation acute myocardial infarction of the European Society of Cardiology (ESC) 2012 "ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation" European Heart Journal (2012) 33, 2569–2619

[11] Note For Guidance on Dose Response Information to Support Drug Registration (CPMP/ICH/378/95)

the study investigator. The TIMI major bleeds observed in the studies were manageable with supportive measures in large proportion of cases, the vast majority resolved without sequelae.

It is worth noting that the benefit in this assessment is prevention of events, which could be fatal, irreversible and catastrophic. On the contrary, TIMI major bleeding events are manageable and reversible. In light of this, benefit-risk assessment should focus on comparing events with similar clinical impact.

The sponsor believed that the benefit/risk ratio should reflect the proposed indication, that is, Stratum 2 from the 2.5 mg bid dose arm. The sub population in which any CYP2C19 inhibitors were used concomitantly with thienopyridine thus should be included based on further analyses on this subpopulation where robustness of study finding was established. The benefit/risk ratio for the proposed population as calculated in the original submission is 11.3 (115.18 non-haemorrhagic CV death + MI + stroke events prevented: 10.16 fatal bleeding + symptomatic ICH events caused). The sponsor believed the safety comparison of fatal bleeding + ICH is more appropriate since TIMI major bleeding is manageable and reversible as stated above.

To compare events with similar clinical impact, non-haemorrhagic CV death and fatal bleeding both of which lead to mortality are included. A benefit-risk ratio of 25.9 (95.05 non-haemorrhagic CV death events prevented: 3.67 fatal bleeding events caused) is estimated from Stratum 2 of the 2.5 mg bid dose arm.

Taking it a step further, a more conservative approach is adopted to include irreversible harm in the analysis. A benefit-risk ratio of 9.4 (95.05 non-haemorrhagic CV death events prevented: 10.16 fatal bleeding + symptomatic ICH caused) is estimated from the same population.

In summary, using approaches that compare against several different levels of bleeding severity, rivaroxaban consistently prevented more fatal and irreversible non-haemorrhagic events than bleeding events caused. Thus, the sponsor believed that a favourable benefit-risk has been confirmed with rivaroxaban 2.5 mg bid in addition to thienopyridine plus an ASA in patients with ACS.

Safety

Overall, the rates of the primary safety endpoint (treatment-emergent non-CABG TIMI major bleeding) in the ATLAS ACS 2 TIMI 51 study were low. The addition of rivaroxaban 2.5 mg bid to standard care antiplatelet therapy increased the incidence of the primary safety endpoint compared with placebo. The rates of intracranial bleeding (0.3% in 2.5 mg bid versus 0.1% in placebo) and haemorrhagic stroke (0.3% in 2.5 mg bid versus 0.1% in placebo) were low overall in the Phase III study, but incidence rates were higher in the rivaroxaban treatment groups compared with placebo. However, the incidence rates for those with fatal intracranial bleeding (0.1% in 2.5 mg bid versus 0.1% in placebo) and fatal bleeding events (0.1% in 2.5 mg bid versus 0.2% in placebo) were similar among placebo subjects and rivaroxaban 2.5 mg bid subjects.

Other comments from the delegate

Dose-finding study

ATLAS ACS TIMI 46 was a randomised, double-blind, placebo-controlled, dose-escalation and dose-confirmation study to evaluate the safety and efficacy of rivaroxaban in combination with aspirin alone or with aspirin and a thienopyridine in subjects with Acute Coronary Syndromes (ACS). This study was designed to be conducted in two stages;

1. Dose escalation and
2. Dose confirmation.

Stage 1 was powered to look at safety outcomes rather than efficacy. Stage 2 was not conducted for the reasons stated by the Delegate in the Overview above. The primary intent of this study was to allow for a preliminary estimate of the bleeding rate for each treatment and stratum. TIMI 46 was not powered for assessing treatment effects for individual doses, dose regimens or stratum specific outcomes.

Comparisons of the results for the 2.5 mg bid dose in the primary composite endpoint (CV Death/MI/Stroke) in studies ACS TIMI 46 with ACS TIMI 51 shows that these are comparable despite the difference in subject numbers [ATLAS ACS TIMI 46 (CV-D/MI/St) - 18/308 (5.8%) versus ATLAS ACS TIMI 51 Primary endpoint 313/5114 (6.1%)], and should provide TGA some reassurance regarding the robustness of the results for the proposed dose.

The Delegate raised concerns about the apparent high death rate in the pooled 5 mg arm of the study, which appears (as a percentage) to be more than double the deaths in the placebo arm of trial TIMI 46 [3.6% (11/308) versus 1.6% (18/1160)]. The Delegate pointed out the numbers in the pooled 5 mg arm are significantly smaller than the numbers in the placebo arm and has questioned if this result can be attributed to chance.

The sponsor notes that Stage 1 of the ATLAS ACS TIMI 46 was not powered to determine efficacy outcomes but rather designed to determine safety outcome versus dose, and extrapolating mortality results in such a small population group should be done with a degree of caution.

A review of a similar endpoint in ATLAS ACS TIMI 51 (refer CV/Death rates; Table 21 Delegate's Overview) provides results in a larger and better balanced population and these results demonstrates a statistically significant reduction in the CV/Death endpoint for the 2.5 mg strength (2.5 mg (94/5114) versus placebo 143/5113). The sponsor believed that consideration of the results as a whole is more appropriate.

As requested by the Delegate, the sponsor confirmed that no cases of Hy's Law were observed in either ATLAS ACS TIMI 46 or TIMI 51.The cases with elevated alanine transaminase (ALT) + total bilirubin (TB) were assessed by the LAP (Liver Advisory Panel) independently. Three subjects in the placebo group as opposed to none in the rivaroxaban group had post-baseline concurrent elevations of ALT >3x ULN and bilirubin >2x ULN. Reported adverse events and detailed narratives for these subjects were provided. The LAP for these cases excluded or considered the causality as "unlike".

Special inclusion criteria in phase III study

The ATLAS ACS 2 TIMI 51 study was designed to evaluate the efficacy and safety of rivaroxaban in subjects with a recent ACS (STEMI, NSTEMI, or UA) who were receiving standard care. Subjects who had been hospitalised for symptoms suggestive of ACS that lasted at least 10 minutes at rest, and occurred 48 hours or less before hospital presentation or who developed ACS while being hospitalised for an indication other than ACS, and had a diagnosis of UA, NSTEMI or STEMI were eligible for the study.

As noted by the Delegate, special inclusion criteria were applied to subjects who were 18 to 54 years of age. These patients had to have either diabetes mellitus or a prior MI in addition to the presenting ACS event.

The decision to require subjects 18 to 54 years of age, inclusive, to have either diabetes mellitus or a previous MI to be eligible for the study was based on a preliminary analysis of the TIMI database, consisting of 44,500 subjects with recent ACS enrolled in the TIMI clinical studies, and an analysis of results from the Phase II study, ATLAS ACS TIMI 46 (ATLAS ACS TIMI 46 CSR, section 6.6.4. Subject Population Selected for Inclusion in the Phase III Study), demonstrating that this subject group is at high risk and likely to derive benefit from anticoagulant therapy in this disease state.

The results of this analysis revealed that the incidence of the composite death/Ml/stroke endpoint in patients aged less than 55 years was 7.37% compared to 11.9% in patients of the same age group with a prior MI or 9.69% in patients < 55 years of age with diabetes mellitus.

Scientific Advice from EMA was sought; this specific inclusion criterion was considered acceptable.

Overall, 4,964 (32%) subjects had a history of diabetes and 4,181 (26.9%) subjects had a prior MI in the Atlas ACS TIMI 51 study. In the age group of 18-54 years (n = 2647), 1536 (58%) had diabetes mellitus, 1302 (49.2%) had prior MI and 347 (13.1%) had both diabetes and prior MI.

The generalisability of the results seen in this patient subgroup (18-54) relates specifically to the clinical use of rivaroxaban in high risk patients. Patients below the age of 55 years who experience an infarct are considered at high risk. Therefore, the patient enrichment in the 18-54 years sub-group of mainly high risk patients, is directly applicable to patients <55 years most likely to receive treatment in a clinical setting, irrespective of the prior risk factor required for the study.

Premature withdrawal

In the original submission, the sponsor reported in the clinical study report (CSR) that of the 15,526 subjects randomised in ATLAS ACS 2 TIMI 51, 13,124 (84.5%) subjects completed the study alive, and 537 (3.5%) subjects died during the study. The remaining 1,865 (12.0%) subjects were categorised as having "incomplete follow-up". Of the 1,865 subjects categorised as having incomplete follow-up, some already 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 censoring date. When the primary censoring method, mITT, is applied, 698 subjects had missing vital status and 799 subjects had incomplete primary efficacy endpoint follow-up. By the ITT censoring method, 1,338 subjects had missing vital status and 1,509 had incomplete primary efficacy endpoint follow-up. The smaller number in the mITT set is to be expected since some subjects dropped out of the study more than 30 days after study drug had been discontinued, and were considered as completers for the mITT approach.

Efforts by Bayer to obtain vital status information for missing patients resulted in additional outcomes for 1,025 (76.6%) of the 1,338 subjects with missing vital status at the global treatment end date, and vital status for 843 of them was confirmed.

The sponsor noted that the Delegate has requested this data to be presented in the same format as Table 9 of the CER (Attachment 1), however this was not possible as only vital status data was collected because patients had ceased drug therapy at this point.

After incorporating the newly obtained vital status information, analyses of all cause death in the mITT analysis set and in the ITT analysis set were performed and compared with the original study results reported in the CSR.

The analyses based on the mITT analysis set show that the HRs (95% CI) for all cause death were 0.69 (0.54, 0.88) for rivaroxaban 2.5 mg bid, 0.95 (0.76, 1.19) for rivaroxaban 5 mg bid, and 0.82 (0.67, 1.00) for combined doses in All Strata, essentially unchanged from the original findings and continuing to strongly favour rivaroxaban treatment for the 2.5 mg bid dose. A similar pattern was also observed in Stratum 2. The analysis in the ITT analysis set shows results consistent with the mITT analysis, with HRs (95% CI) for all cause death of 0.74 (0.60, 0.92) for rivaroxaban 2.5 mg bid, 0.98 (0.81,1.20) for rivaroxaban 5 mg bid, and 0.86 (0.72,1.03) for combined doses in All Strata, also minimally changed from the original findings. Similar results are also observed in Stratum 2.

In only 116 subjects, discontinuation of study drug and withdrawal of consent occurred on the same day, in 151 subjects consent withdrawal occurred 15-30 days after the last dose of study drug and 402 subjects withdrew consent more than 30 days after discontinuation of study drug. Additionally, in 307 subjects, as a result of the initiative to obtain vital status on or after the

global treatment end date (GTED) in as many subjects who withdrew consent as possible, vital status was available on or after the GTED of 3 Jun 2011.

This is important because in the majority of subjects, information regarding subject outcome was available during the vulnerable and uncertain period following discontinuation of study drug.

A comparison of baseline demographic and disease characteristics for those subjects who prematurely discontinued from the study and in those subjects included in the efficacy analysis was provided. The results show that the subjects with missing vital status more closely resemble subjects who were alive at the global treatment end date. Importantly, in terms of age, prior MI, baseline PCI for index event, creatinine clearance (all of which are well established predictors for adverse outcome in ACS patients), subjects with missing vital status were similar in these characteristics to those subjects who were alive at the global treatment end date.

Internal consistency of the primary efficacy results

ATLAS ACS 2 TIMI 51 was designed with sufficient power to evaluate the effects of combined and individual rivaroxaban doses on the composite primary endpoint of CV death, MI and stroke.

The significantly higher risk of fatal bleeding and the numerically higher incidences of death due to CHF/cardiogenic shock and MI in the 5 mg bid group compared with the 2.5 mg bid dose partially contributed to the diminished effect of this dose on the reduction of CV death.

The difference in the reduction of CV death between the 2 rivaroxaban dose groups may be partially explained by the higher dose of rivaroxaban (5 mg bid) increasing the rate of major bleeding, which while not being immediately fatal, may predict a fatal outcome due to medical complications within the following 30 days.

One possible explanation for the increased mortality after a major bleeding event may be that discontinuation of study medication, thienopyridine and/or ASA treatment due to the major bleeding event results in adverse cardiovascular events with fatal outcome in the subsequent period.

In summary, both doses of rivaroxaban reduce the risk of CV death. This is clearly apparent at a dose of 2.5 mg bid (HR: 0.66, 95% CI: 0.51, 0.86), however, at the 5 mg bid dose, the effect of rivaroxaban on mortality is weakened (HR: 0.94, 95% CI: 0.75, 1.20) by the increased risk of serious bleeding that carries its own hazard for adverse outcome.

Lack of efficacy in stroke

As stated above ATLAS ACS 2 TIMI 51 was designed to determine efficacy in the composite endpoint (CV Death/MI/Stroke). Analysis of the components of the composite endpoint demonstrated that stroke was not statistically and clinically significant and appeared slightly worse for the 2.5 mg bid active arm (0.9% versus 0.8%). It is noted that the patient population for ATLAS ACS 2 TIMI 51 was primarily an ACS population, meaning that the next event would likely be an ACS event and not stroke. Therefore, the sponsor was of the opinion that no conclusions should be drawn from the ATLAS ACS 2 TIMI 51 study regarding the prevention of stroke as the population was not configured to provide definitive outcomes for prevention of secondary stroke alone.

Further confirmation of this can be seen when comparing the results for stroke in TIMI 51 to the results for stroke in TIMI 46 (Table 18), where it can be seen that the pooled 5 mg versus pooled placebo showed a positive trend for the active arm (0.3% versus 0.6%). The sponsor therefore reiterated that the composite endpoint should be the focus rather than attempting to draw conclusion from one component of the composite endpoint.

When comparing the results for stroke to other products also used in the treatment of ACS (such as ticagrelor (AstraZeneca), prasugrel (Lily) and clopidogrel (Sanofi), a similar non-statistically

significant outcome can be seen in the stroke sub-group analysis. The clopidogrel PI in particular demonstrates that the sub-group analysis for clopidogrel versus placebo was equivalent (0.6%) in the non-fatal stroke population.

Lack of efficacy in fatal MI

The Delegate noted that the rates of fatal MI in study ATLAS ACS TIMI 51 showed no advantage conferred by either active rivaroxaban treatment regimen compared with placebo. One hypothesis that may explain the difference in the degree of the effect of the 2.5 mg bid on myocardial infarction is that although this dose prevents coronary thrombotic events including myocardial infarction, these events may be manifest and categorised in the trial as other fatal complications of myocardial ischemia, such as a sudden death, fatal cardiogenic shock/CHF, or a fatal arrhythmia. Supportive evidence from the literature suggests that two-thirds of sudden deaths in patients with ischaemic heart disease may be associated with intraluminal coronary thrombus formation leading to a fatal myocardial infarction.

An analysis performed by the TIMI organisation, shows that when serious ischaemic events are considered more broadly (fatal and non-fatal MI as well as fatal complications of ischemia taken together), both doses of rivaroxaban were associated with a similar event reduction compared with placebo. The table below shows the cumulative number of fatal and non-fatal events that could be considered to be related to an MI and when all events are considered together, the 2.5 mg dose reduces events related to myocardial infarction to a similar degree as the 5 mg dose.

Table 25. Cumulative number of fatal and non-fatal events that could be considered to be related to an MI

	Rivaroxaban		
	2.5mg BID (N=5114)	5mg BID (N=5115)	Placebo (N=5113)
		<--------P = NS------->	
All cause Death	103	142	153
	<----------P = 0.002---------->		
[a] Non-fatal MI	186	144	202
Fatal MI	18	30	23
Other Fatal Complications of Ischemic Heart Disease	64	82	103
Fatal Sudden or Unwitnessed Event	55	59	81
Fatal CHG/Cardiogenic Shock	8	19	17
Fatal Arrhythmic Event	1	4	5
		<-------P = 0.01------->	
TOTAL: Non-fatal MI + Fatal MI + Other Fatal Complications of Ischemic Heart Disease	268	256	328
	<----------P = 0.02---------->		

Note: Non-fatal MI shown above = [values for *MI* from Table 24 of the CSR study 13194] minus [values for *"a fatal complication of ischemic heart disease per CEC"* from Table 29 of the CSR study 13194]

In conclusion, both doses are more similar than they are different at reducing important clinical events in ACS patients. Both doses reduce the risk of the primary efficacy endpoint, as well as fatal and non- fatal MI to a very similar degree. The robust reduction in CV death drives the effects of 2.5 mg bid of rivaroxaban on the primary efficacy endpoint.

Optimal use of thienopyridine

The Delegate refers to the use of sub-optimal thienopyridine (clopidogrel or ticlopidine) therapy in patients who may have been on concomitant CYP2C19 inhibitors, thereby lowering the efficacy of the thienopyridine therapy.

A re-analysis was conducted from the mITT analysis set removing patients who were not considered to be on 'optimal' thienopyridine therapy and the resulting analysis demonstrated a

marginally worse outcome for patients considered to be receiving 'optimal' therapy. A loss in statistical significance also occurred. The re-analyses resulted in a decrease in patient numbers of approximately 700-800. This censoring meant a loss of approximately one third of events since the event numbers were higher in the sub-optimal group even though numerically this was smaller. This shift in numbers resulted in the primary endpoint HR values remaining relatively constant for both pre and post censored analysis [HR 0.84 (0.72, 0.97) p=0.02 versus HR 0.86 (0.71, 1.03) p=0.09) demonstrating the benefit of using rivaroxaban in both 'optimal' and sub-optimal groups.

Event rate of anaemia reported in adverse effects section

The sponsor was requested to explain how the anaemia event rate reported in the proposed PI was derived. The location in the data of the overall number of treatment emergent anaemia cases as well as all the necessary explanatory tables were provided as appendices to this response.

Indication

The new proposed indication is representative of the composite endpoint of the pivotal Study TIMI 51, and is in accordance with TGA adopted guideline CPMP/EWP/570/98[12] which states that a triple composite endpoint is acceptable if it includes all-cause mortality and new MI as components. The proposed wording is:

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

The sponsor agreed to remove the proposed indication for stent thrombosis.

The Delegate has raised the issue of the size of Stratum 1 and appropriateness of it being included in the indication.

Although it is recommended in the AHA, ACC and ESC guidelines that the standard of care for subjects with ACS to use thienopyridine plus aspirin, nevertheless, not all subjects are suitable for thienopyridine therapy for reasons such as intolerability, allergy or previous AE attributable to a thienopyridine.

Stratum 1 was designed to accommodate patients who could not tolerate thienopyridine treatment, but who still required access to alternate treatment therapy in addition to aspirin. As expected, patient numbers for this were small, and statistical significance was therefore not reached, however the HR point estimates were the most favourable for the study [HR 0.69 95% CI 0.45 – 1.05. p=0.084]. Nevertheless, the sponsor agreed to remove reference to Stratum 1 from the proposed indication.

The new indication wording aligns with the approved indications for prasugrel and ticagrelor, products currently used in the treatment of ACS.

The sponsor believed that approval should be based on this composite endpoint, which clearly demonstrates the benefit of rivaroxaban in ACS, rather than based on individual subgroup analysis.

Conclusion

Drawing on the favourable benefit/risk and proven safety profile provided with this submission, an acceptable balance of observed undesired effects and beneficial effects has been demonstrated with rivaroxaban 2.5 mg bid dose in Stratum 2.

[12] CPMP/EWP/570/98. Points to Consider on the Clinical Investigation of New Medicinal Products in the Treatment of Acute Coronary Syndrome (ACS) Without Persistent ST-Segment Elevation. Effective: 19 April 2001.

Advisory Committee Considerations

The Advisory Committee on Prescription Medicines (ACPM) (which has succeeded ADEC), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, advised the following:

The ACPM, taking into account the submitted evidence of quality, safety and efficacy agreed with the Delegate that a positive benefit-risk profile has not been established for the proposed indication.

In making this recommendation the ACPM advised that:

- The overall study design and data analysis is incomplete and inadequate and has not established dose response efficacy with either clarity or confidence.
- The clearly identified safety issues, principally haemorrhage are not balanced with a correspondingly reliable level of efficacy in the proposed population.
- There are many shortcomings in the proposed PI and CMI, particularly in relation to the precautions for use in patients with compromised renal function and the irreversibility of the drug's effect in the context of haemorrhage.

Outcome

The sponsor withdrew their application (on 31 May 2013) before a decision had been made by the TGA.

Attachment 1. Extract from the Clinical Evaluation Report

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