EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

21 March 2013
EMA/CHMP/794349/2012
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Xarelto

International non-proprietary name: Rivaroxaban

Procedure No. EMEA/H/C/000944/X/00017

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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Product information

Name of the medicinal product:	Xarelto
Marketing Authorisation Holder:	Bayer Pharma AG 13342 Berlin GERMANY
Active substance:	Rivaroxaban
International Nonproprietary Name/Common Name:	Rivaroxaban
Pharmaco-therapeutic group (ATC Code):	rivaroxaban (B01AX06)
Therapeutic indications:	<u>10mg film-coated tablets:</u> Prevention of venous thromboembolism (VTE) in adult patients undergoing elective hip or knee replacement surgery. <u>15mg and 20mg film-coated tablets:</u> Prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation with one or more risk factors, such as congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, prior stroke or transient ischaemic attack. Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults. (See section 4.4 for haemodynamically unstable PE patients.)
Pharmaceutical form(s):	Film-coated tablet
Strength(s):	10 mg, 15 mg, 20 mg
Route(s) of administration:	Oral use
Packaging:	Blister (PP/alu) and blister (PVC/PVDC/alu)
Package size(s):	5 tablets, 10 tablets, 14 tablets, 28 tablets, 30 tablets, 42 tablets, 98 tablets, 10x1 tablets, 100x1 tablets, 100 (10x10x1) tablets

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LIST OF ABBREVIATIONS

ACC	American College of Cardiology
ACS	acute coronary syndrome
AHA	American Heart Association
ARC	Academic Research Consortium
ASA	acetyl salicylic acid
ATLAS ACS	Anti-Xa Therapy to Lower cardiovascular events in addition to Aspirin with or without thienopyridine therapy in Subjects with Acute Coronary Syndrome
CABG	coronary artery bypass graft
CEC	Clinical Events Committee
CHD	coronary heart disease
CHF	chronic heart failure
CI	confidence interval
CNS	central nervous system
CSR	Clinical Study Report
CV	cardiovascular
DVT	deep venous thrombosis
ESC	European Society of Cardiology
HIV	human immunodeficiency virus
HR	hazard ratio
ITT	intent-to-treat
MI	myocardial infarction
mITT	modified Intent-To-Treat
NSTEMI	non-ST-segment elevation myocardial infarction
OASIS	The Organization to Assess Strategies in Acute Ischemic Syndromes Trial
PCI	percutaneous coronary intervention
reMI	repeat myocardial infarction
RRR	Relative risk reduction
SAP	Statistical Analysis Plan
SCD	sudden cardiac death
SRI	severe recurrent ischemia
SRIH	severe recurrent ischemia requiring hospitalization
SRIR	severe recurrent ischemia requiring revascularization
STEMI	ST-segment elevation myocardial infarction
TDD	total daily dose
TIA	transient ischemic attack
TIMI	thrombolysis in myocardial infarction
UA	unstable angina
U.S.	United States

1. Background information on the procedure

1.1. Submission of the dossier

The MAH Bayer Pharma AG submitted on 22 December 2011 an extension application for Marketing Authorisation to the European Medicines Agency (EMA) for Xarelto, through the centralised procedure falling within the Article 19 Commission Regulation (EC) No 1234/2008 and Annex I (point 2 (c) addition of a new strength).

The MAH applied for the following indication:

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).

Information on Paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/171/2011 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/171/2011 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the MAH did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Market exclusivity

Scientific Advice

The MAH seeked advice at the CHMP for this indication:
(EMEA/CHMP/SAWP/110903/2007, Procedure No.: EMEA/H/SA/422/4/2006/II and EMEA/CHMP/SAWP/312004/2008, Procedure No.: EMEA/H/SA/422/4/FU/1/2008/II.

Licensing status

Xarelto has been given a Marketing Authorisation on 30 September 2008.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Bengt Ljungberg Co-Rapporteur: Martina Weise

- The application was received by the EMA on 22 December 2011.
- The procedure started on 25 January 2012.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 16 April 2012 (Annex 1). The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 23 April 2012 (Annex 2).
- During the meeting on 24 May 2012, the CHMP agreed on the consolidated List of Questions to be sent to the MAH. The final consolidated List of Questions was sent to the MAH on 29 May 2012 (Annex 3).
- The MAH submitted the responses to the CHMP consolidated List of Questions on 17 August 2012.
- The Rapporteurs circulated the Joint Assessment Report on the MAH responses to the List of Questions to all CHMP members on 1 October 2012 (Annex 4).
- During the CHMP meeting on 18 October 2012 the CHMP agreed on a list of outstanding issues to be addressed in writing and in an oral explanation by the MAH (Annex 5).
- The MAH submitted the responses to the CHMP List of Outstanding Issues on 12 November 2012.
- During a SAG meeting on 10 January 2013, experts were convened to address questions raised by the CHMP (Annex 6).
- During the CHMP meeting on 14-17 January 2013, outstanding issues were addressed by the MAH during an oral explanation before the CHMP.
- During the CHMP meeting on 14-17 January 2013 the CHMP agreed on 2nd List of Outstanding Issues to be addressed in writing by the MAH (Annex 7).
- The MAH submitted the responses to the CHMP List of Outstanding Issues on 15 February 2013.
- The Rapporteurs circulated the Joint Assessment Report on the MAH responses to the List of Outstanding Issues to all CHMP members on 5 March 2013 (Annex 8).
- During the meeting on 18-21 March 2013, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive scientific opinion to Xarelto.

2. Scientific discussion

2.1. Introduction

Coronary heart disease (CHD) is a common clinical and pathological condition. The incidence and prevalence rates of CHD remain high throughout the world. The estimated number of deaths from CHD is 1.95 million in Europe and 0.7 million within the EU. Whilst overall cardiovascular mortality, incidence and case fatality rates are declining in most Northern, Southern and Western European countries they are not falling as fast or even rising in Central and Eastern European countries. Within Europe, the age-standardized death rates from CHD show geographical variations with lowest rates in Mediterranean countries and highest rates in Eastern Europe.

Following an ACS event, patients are at high risk of another morbid event of ACS or stroke or dying from a CV cause. An important component of the current standard care for post ACS patients is the long term use of antiplatelet agents, principally ASA with or without the addition of a thienopyridine, such as clopidogrel.

Despite the widespread use of antiplatelet agents in the acute and chronic setting, the incidence of CV events such as CV death, MI or stroke in the post-ACS population remains high; the CV event rate was 9.8% at 12 months in patients treated with ticagrelor in the PLATO trial. 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.

The development programme/compliance with CHMP guidance/scientific advice

At the scientific advice meetings held at EMA in 2007 and 2008, the MAH presented the clinical development program for the ACS indication and discussed the phase II program and the design of the single large multicenter, randomized, double-blind, non-inferiority, event-driven phase III study in patients with ACS.

Furthermore in 2008, the MAH presented preliminary results of the phase II study and the next steps in clinical development program (i.e. phase III study) for the “prevention of cardiovascular events in patients with ACS”. At that meeting the program for the conduct of the single large multicenter phase III study in patients with ACS was discussed.

The following topics discussed at that meeting were adhered to and implemented into the development program. These covered 1) single trial concept, 2) choice of dose, 3) inclusion and exclusion criteria, 4) definition of the primary efficacy outcomes, 5) definition of the safety outcomes, 6) statistical plan, 7) PK/PD investigations, 8) streamlined monitoring approach, 9) AE s of special interest, 10) liver monitoring and 11) reporting requirements for efficacy and safety endpoints.

Standard of care treatment was in accordance with the relevant international guideline documents of the relevant international scientific societies.

Overall it can be stated that recommendations given in the scientific advice procedures were followed during the clinical development program.

General comments on compliance with GMP, GLP, GCP

GMP:

GMP Inspections of the drug substance manufacturing and/or the drug product manufacturing sites and / or batch release site are not considered necessary for completion of the module 3 assessment.

GLP:

The MAH stated that all pivotal toxicology studies have been performed under GLP.

GCP:

The company stated that all studies included in this application 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. During the assessment of the submitted clinical data no signal were detected which would raise overall doubts about this statement.

Type of application and other comments on the submitted dossier

This is a line extension application for Xarelto (rivaroxaban) according to article 8(3) according to directive 2001/83/EC for a new proposed indication

“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).”

Rivaroxaban is a potent selective oral direct factor Xa inhibitor. The drug substance is manufactured at Bayer Pharma AG, Wuppertal, Germany, and is micronised at Bayer Pharma AG, Leverkusen, Germany.

Rivaroxaban is a white or yellowish solid. It crystallizes in three modifications with melting points of 230°C (Modification I) and 203°C (Modification II), a transition point of about 127°C (Modification III), furthermore a NMP solvate (= N-methyl-pyrrolidone solvate), a THF inclusion compound, and a hydrate. The amorphous form (glass transition point: about 83°C) can exist at room temperature. From absolute zero (-273°C) to its melting point (230°C) modification I is the thermodynamically stable polymorph. The identity of modification I is controlled by Raman spectroscopy.

Rivaroxaban is practically insoluble in 0.1 and 0.01 M hydrochloric acid, in buffered solutions pH = 3 to pH = 9, water, n-heptane, toluene and in 2-propanol. It is very slightly soluble in ethanol, methanol and ethyl acetate. It is slightly soluble in acetone, acetonitrile, dichloromethane and macrogol 400. Rivaroxaban is soluble in dimethylformamide, N-methylpyrrolidone and dimethylsulfoxide.

In 2008 an immediate-release film-coated tablet containing 10 mg rivaroxaban for oral use was centrally approved in the European Union under the brand name Xarelto. The indication was the prevention of venous thromboembolism (VTE) in adult patients undergoing elective hip or knee replacement surgery. The 15 mg and 20 mg rivaroxaban film-coated tablets, which were approved in 2011, are indicated for the treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE, and prevention of recurrent

DVT and pulmonary embolism (PE) in adults. (See section 4.4 for haemodynamically unstable PE patients.)

The initially applied indication for rivaroxaban 2.5 mg film-coated tablet is for the 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).

2.2. Quality aspects

2.2.1. Introduction

The product is presented as film coated tablets containing 2.5 mg of rivaroxaban (as ethanolate) as active substance.

The composition is described in section 6.1. of the SmPC.

The product is packaged in the same Polypropylene/Aluminium foil blisters as the previously authorised strengths.

2.2.2. Active Substance

Rivaroxaban active substance used for the manufacture of Xarelto 2.5 mg film-coated tablets is of the same quality as that used for the already-marketed Xarelto 10 mg, 15 mg and 20 mg film-coated tablets.

2.2.3. Finished Medicinal Product

Pharmaceutical Development

The new 2.5 mg strength was developed as a small sized film-coated tablet to be used exclusively in a new proposed indication**:** 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).

The 2.5 mg film-coated tablets are manufactured with the currently approved active substance which is already used for the other authorised strengths. The formulation development studies are analogous to those provided for the previously authorised strengths.

Xarelto coated tablets 2.5 mg are manufactured as a standard immediate-release formulation with a standard fluid-bed granulation process followed by tableting and standard film-coating. During development and scale-up, the impact of manufacturing conditions on target properties of the final dosage form such as tablet hardness, disintegration, dissolution, content uniformity and stability were investigated. Tablet hardness, disintegration, content uniformity and stability were determined to be non-critical product properties. Tablet dissolution rate was determined to be influenced by the active substance particle size. Therefore, particle size of rivaroxaban is considered critical and is controlled by appropriate specification limits for the active substance.

The composition of tablets intended for market supply does not change compared to the clinical trials formulation except for the colour of film-coating.

The excipients used in the 2.5 mg strength are the same as those used for the already authorised strengths. All the excipients comply with the Ph. Eur.

The finished product is packaged in polypropylene-aluminium blister. The packaging material used is in compliance with Ph. Eur. requirements. The stability studies indicate that the primary packaging is suitable for maintaining finished product quality.

Adventitious agents

It is confirmed that the lactose is produced from milk from healthy animals in the same condition as those used to collect milk for human consumption and that the lactose has been prepared without the use of ruminant material other than calf rennet according to the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents Via Human and veterinary medicinal products.

Manufacture of the product

The finished product is manufactured as standard immediate-release formulation with a standard fluid-bed granulation process followed by tableting and standard film-coating.

The manufacturing process has been validated by a number of studies for the major steps of the manufacturing process and has been demonstrated to be capable and to be able to reproducibly produce finished product of the intended quality. The in process controls are adequate for this film-coated tablet preparation.

The batch analysis data (n=3) shows that the tablets can be manufactured reproducibly according to the agreed finished product specification, which is suitable for control of this oral preparation.

Product specification

The finished product release specifications are identical to the already authorized strengths and include appropriate tests for appearance (visual inspection), identity (HPLC, TLC/NIR), dissolution (HPLC, UV/vis), degradation products (HPLC), assay (HPLC, 95.0 % - 105.0 %), uniformity of dosage units (HPLC), and microbiological purity (Ph. Eur.).

Batch analysis results in 3 full-scale batches validate consistency and uniformity of manufacture and indicate that the process is capable and under control.

Stability of the product

Stability data was generated for 3 pilot batches stored in the primary packaging intended for use in the marketed product under normal and intermediate conditions (25°C ± 2°C, 60 %RH ± 5 %RH and 30°C ± 2°C, 75 %RH ± 5 %RH) for 24 months and under accelerated conditions (40°C ± 2°C, 75 %RH ± 5 %RH) for 6 months. Additionally the batches were stored for a period of 60 months at 5°C without control of relative humidity. Bulk stability data was also generated for 24 months in 1 batch in a polyethylene bag and tightly closed tin can and stored under climate zone I–IV

conditions. The containers were opened repeatedly to remove one bag for each time point. Data covering a period of 24 months are documented.

Samples of the finished product were stored under thermal and hydrolytic stress in order to investigate the formation of potential degradation products and to assess the influence of temperature and humidity on the physico-chemical properties of the formulation. The thermal stress was projected for 12 months and the humidity stress for 24 months.

Photostability studies were performed according to ICH guideline Q1B, "Photostability Testing of New Drug Substances and Products". The finished product is stable upon exposure to light without immediate packaging.

The parameters studied were appearance (formulation, form, colour), any unspecified degradation product, sum of all degradation products, assay, dissolution after 30 min., and microbial purity. Additionally the tests for hardness, disintegration and water were performed on an informative basis using the pharmacopoeial test methods of the Ph. Eur.. All batches were packaged in the commercial packaging material.

Based on available stability data, the proposed shelf-life as stated in the SmPC is acceptable.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the new 2.5 mg strength Xarelto film-coated tablets has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in the clinic.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.2.6. Recommendation(s) for future quality development

Not applicable

2.3. Non-clinical aspects

2.3.1. Pharmacology

Rivaroxaban, an oxazolidinone derivate, is a potent, selective, orally active small-molecule and direct FXa inhibitor.

The activated serine protease Factor X (FXa) plays a central role in the blood coagulation, as it acts at the convergence point of the intrinsic and extrinsic coagulation pathways. FXa catalyzes the conversion of prothrombin to thrombin; one molecule of FXa results in the generation of more than

1000 thrombin molecules. Inhibition of FXa blocks this burst of thrombin generation, thereby diminishing thrombin-mediated activation of coagulation. Thus, inhibition of FXa is supposed to be an effective strategy for the prevention of both arterial and venous thrombosis.

In addition to previously submitted and assessed studies new in vitro and in vivo investigations have now been performed to further characterize the pharmacological profile of rivaroxaxaban, especially regarding mode of action and interaction potential with inhibitors of platelet aggregation.

In contrast to the direct thrombin inhibitors, rivaroxaban did not increase thrombin generation in the presence of thrombomodulin (which activates the protein C pathway) suggesting that it does not suppress the negative-feedback reaction by inhibition of protein C activation.

Rivaroxaban did not increase a hypercoaguable status; it indirectly reduced thrombin induced platelet aggregation, showed antithrombotic efficacy in preventing arterial thrombosis in hypercholesterolemic atherosclerotic mice and in stent thrombosis in an extracorporeal circuit in pigs. The antithrombotic efficacy was further enhanced in the presence of ASA, P2Y12 receptor blockers (clopidogrel or ticagrelor) and their combinations. In addition, a plaque stabilizing effect of rivaroxaban in atherosclerotic mice was also indicated, as was an inhibitory effect on inflammatory signalling in human atrial slices.

2.3.1. Pharmacodynamics drug interactions

The following pharmacodynamics drug inteactions studies were performed. The summary of he finding is described in the table below.

Effects of Rivaroxaban, Ticagrelor, Acetylsalicylic Acid alone and in Combination on Tissue Factor-Induced Thrombin Generation in vitro (PH-36625)

Effects of Rivaroxaban, Ticagrelor and in Combination on Tissue Factor-Mediated Platelet Aggregation in vitro (PH-36624)

Effects of Rivaroxaban, Acetylsalicylic acid and Clopidogrel Alone and in Combination in a Porcine Model of Stent Thrombosis (PH-36605)

Type of Study	**Test System**	**Study Number**	**Major Findings** (see also presentations below)
Interaction of Rivaroxaban with ticagrelor and acetylsalicylic acid	*In vitro* Thrombin generation, human plasma	(PH-36625)	Rivaroxaban at 60 ng/ml affected the parameters of thrombin generation: mVI, Cmax, lag time, tmax (most potent on the kinetic parameters mVI, lag time and tmax.) Ticagrelor at 1000 ng/ml affected mVI and tmax as well as Cmax. ASA alone had no influence on any parameter. Rivaroxaban + Ticagrelor gave a further reduction in Cmax and mVI and prolonged tmax. ASA had no influence on any parameter in combination with rivaroxaban.

			ASA + rivaroxaban + ticagrelor showed a slight consistent effect on Cmax, mVI, tmax and lag time.
Interaction of Rivaroxaban with ticagrelor	*In vitro* Platelet aggregation, human plasma	(PH-36624)	Rivaroxaban inhibited tissue factor-induced platelet aggregation in a concentration-dependent manner. Rivaroxaban (15 and 30 ng/ml and ticagrelor (1 and 3 µg/ml) synergistically enhanced the inhibition of aggregation compared with either agent alone.
Interaction of Rivaroxaban with clopidogrel and acetylsalicylic acid	Stent thrombosis, porcine Intravenous infusion	(PH-36605)	Rivaroxaban showed dose dependent effects in inhibition of in stent thrombosis. Combination with ASA and the triple combination of rivaroxaban, ASA and clopidogrel was more effective than either treatment alone (the triple therapy reduced in stent thrombus formation to a nearly undetectable limit)

2.3.2. Pharmacokinetics

The pharmacokinetic profile of rivaroxaban is well known. No new data have been submitted in this application except for studies on transporters which are discussed and assessed in the Clinical part.

2.3.3. Toxicology

Rivaroxaban/Xarelto has been approved for other indications in 2008 and 2011, respectively, and a full non-clinical programme has thus been submitted previously. In the present application four additional studies in juvenile animals, two pilot studies and two pivotal studies have been submitted.

The NOAEL of the subchronic repeat-dose studies in juvenile rats was established at 20 mg/kg for males and at 60 mg/kg for females in the first study using the same vehicle throughout the study and at 60 mg/kg in the second study in which the vehicle was changed at day 20 and an increased exposure was achieved. In the first study histopathological examination revealed a slight increase of periinsular alterations (hemorrhage, fibrosis, inflammation) in the pancreas of high dose males. In the thyroid glands of males dosed at 60 mg/kg, a higher incidence of colloidal alteration was seen in the first juvenile study (0-0-1-5 out of 12 animals at 0, 6, 20 and 60 mg/kg, respectively), whereas follicular cell hypertrophy showed no clear-cut treatment-related effect (3-1-2-5 out of 12 animals). In the second juvenile study, in which significantly higher exposures were achieved at the same doses, the incidence of colloidal alteration seen in the thyroid glands of male rats was not different in exposed animals as compared to controls (3-1-3-4 out of 12 animals) and no clear-cut treatment-related effect on follicular cell hypertrophy was neither seen (7-5-8-5 out of 12 animals in males and 1-3-2-1 out of 12 animals in females).

It is concluded that the investigations of rivaroxaban in juvenile rats did not reveal any new toxicity so far unknown from testing adolescent or adult animals and thus that the safety profile in juvenile rats appears to be in line with previous findings. Minor effects on pancreatic peri-insular findings as well as on the thyroid gland seen in the first subchronic toxicity study were not confirmed in the second study showing significantly higher systemic exposure. The numerical

increase in pancreatic peri-insular lesions (hemorrhage, hemosiderin, and fibrosis) and colloid alteration in the thyroids in the first juvenile study was therefore considered to be incidental. Overall, the toxicological profile of rivaroxaban remains unchanged considering the new juvenile toxicity data in rats.

The SmPC section 5.3 was updated accordingly to reflect the results of the juvenile toxicity study.

2.3.4. Ecotoxicity / environmental risk assessment

In the previous submitted ERA for the maximum recommended daily dose of 30 mg (EMEA/H/C/0944/X/10) it was concluded (based on generated experimental data) that no environmental risk for rivaroxaban in surface-, groundwater and waste water treatment plants, respectively, was anticipated.

The conclusion is therefore that the lower daily dose of 5 mg Rivaroxaban applied for in the present application is neither expected to pose a risk to the environment.

2.3.5. Discussion on non-clinical aspects

Rivaroxaban is already approved in different indications for prevention and treatment of thrombo-embolic events. The maximum recommended daily dose is 20 mg once daily for chronic use and 30 mg/day (2x15 mg) for short term use. For the indication “Secondary Prevention of Acute Coronary Syndrome” a lower dose of 5 mg (2.5 mg bid) is proposed. Rivaroxaban was investigated in different in vitro and in vivo models to further characterize its pharmacological profile especially regarding mode of action and interaction potential with inhibitors of platelet aggregation and in repeat-dose studies in juvenile rats. The new nonclinical data on primary pharmacodynamics as well as on pharmacodynamic drug-drug interaction and data on juvenile animal toxicity of rivaroxaban do not influence the overall nonclinical risk assessment which thus remains unchanged. In summary, no new safety concerns emerged from the updated non clinical data. The new lower dosage level of Rivaroxaban applied for is not expected to pose a risk to the environment.

2.3.6. Conclusion on the non-clinical aspects

There are no objections to approval from a non-clinical perspective.

2.4. Clinical aspects

2.4.1. Introduction

The rivaroxaban ACS program was a multinational program to evaluate the efficacy and safety of rivaroxaban compared with placebo in addition to standard care antiplatelet therapy in subjects with ACS. The program included:

- 1 supportive global phase II study BAY 59 7939/11898, also known as 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).

- 1 pivotal global phase III study BAY 59 7939/13194, also known as the ATLAS ACS 2 TIMI 51 Trial (The second trial of Anti-Xa Therapy to Lower cardiovascular events in Addition to standard therapy in Subjects with Acute Coronary Syndrome).

Both studies were multicenter, prospective, randomized, parallel group/or sequential parallel-group, placebo controlled, multi-dose, and double-blind studies that compared the efficacy and safety of oral rivaroxaban with placebo in addition to standard care antiplatelet therapy (aspirin or aspirin combined with a thienopyridine) in subjects with a recent ACS event.

GCP

The Clinical trials were performed in accordance with GCP as claimed by the MAH.

The MAH has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

Tabular overview of clinical studies

Overview of Phase II and III Clinical Studies Supporting the Rivaroxaban ACS Program

Study Number Study Name / phase	Rivaroxaban Dose	Control Group and Dose	Number of Randomized Subjects	Scheduled Duration of Treatment
13194 ATLAS ACS 2 TIMI 51 Phase III	2.5 mg b.i.d. 5 mg b.i.d.	Placebo	total: 15,526 All Strata Riva: 2.5 mg b.i.d.: 5,174 5 mg b.i.d.: 5,176 Total: 10,350 Placebo: 5,176 Stratum 1 (ASA): 1,053 Riva: 2.5 mg b.i.d.: 349 5 mg b.i.d.: 349 Total: 698 Placebo: 355 Stratum 2 (ASA+Thienopyridine): 14,473 Riva: 2.5 mg b.i.d.: 4,825 5.0 mg b.i.d.: 4,827 Total: 9,652 Placebo: 4,821	Study duration was event-driven. 30-day follow-up after the last dose of study drug administration For All Strata combined, the mean duration of treatment: total: 393.8 days 2.5 mg b.i.d.: 395.8 days; 5 mg b.i.d.: 385.6 days; Placebo: 399.9 days
11898 ATLAS ACS TIMI 46 Phase II	2.5 mg b.i.d. 5 mg o.d. 5 mg b.i.d. 10 mg o.d. 7.5 mg b.i.d.* 15 mg o.d.* 10 mg b.i.d. 20 mg o.d.	Placebo	total: 3491 All Strata Riva: 2.5 mg b.i.d.: 153 5 mg b.i.d.: 527 Total (all doses & regimens): 2331 Placebo: 1160 Stratum 1 (ASA): 761 Riva: 2.5 mg b.i.d.: 77 5 mg b.i.d.: 97 Total (all doses & regimens): 508 Placebo (combined): 253 Stratum 2 (ASA+Thienopyridine): 2730 Riva: 2.5 mg b.i.d.: 76 5 mg b.i.d.: 430 Total (all doses & regimens): 1823 Placebo (combined): 907	The planned duration of the double-blind treatment period was 180 days. The mean treatment duration: total: 160.6 days; 159.1 days for combined rivaroxaban treatment groups and 163.6 days for combined placebo groups. 30-day follow-up

* Only for subjects in the Stratum 2

2.4.2. Pharmacokinetics

The PK part of the application consists of three parts, the in vivo biopharmaceutical characterization of the new rivaroxaban tablet strength (2.5 mg), some new in vitro transporter studies as well as population PK/PD and exposure-response analyses of rivaroxaban in the target population.

Characterization of the new rivaroxaban tablet strength (2.5 mg) (Study 12361)

Study 12361 was conducted in a single-center, randomized, non-blinded, 3-way cross-over, non placebo controlled design. 24 healthy male subjects aged 20 to 45 years were enrolled. 23 subjects completed the 3 periods of the study according to protocol and were included in the PK analysis set.

The study drug was administered under fasting conditions.

The results are presented below:

Point estimators (LS-means) and exploratory two-sided 95% confidence intervals of selected pharmacokinetic parameters after administration of rivaroxaban [ANOVA results, all subjects valid for PK, n=23], (Study 12361)

Ratio	Parameter	Unit	Estimated Ratio	95% Confidence interval
10 mg / 5 mg	AUC/D	h/L	0.8964	0.8345 – 0.9629
	C_{max}/D	1/L	0.7683	0.6770 – 0.8718
10 mg / 2.5 mg	AUC/D	h/L	0.8636	0.8040 – 0.9277
	C_{max}/D	1/L	0.6640	0.5851 – 0.7535
5 mg / 2.5 mg	AUC/D	h/L	0.9634	0.8969 – 1.035
	C_{max}/D	1/L	0.8642	0.7616 – 0.9807

An exploratory across-study analysis of covariance on 42 Phase 1 trials, covering rivaroxaban single-dose administrations from 1.25 to 80 mg and multiple-dose administrations from 5 to 30 mg, showed that the intake of rivaroxaban tablets with or without food did have a statistically significant effect on AUC and Cmax of rivaroxaban plasma concentrations over all applied doses: AUC was approximately 20% higher and Cmax was approximately 40% higher under fed condition compared to fasting condition. However, this food effect was primarily driven by data obtained with rivaroxaban doses greater than 10 mg. When limiting the across-study analysis to rivaroxaban tablet doses less than or equal to 10 mg, any relevant food effects were less apparent, while for tablet doses equal and above 15 mg food effects became obvious and pronounced.

Based on the results from this pooled analysis and the lack of a relevant food effect observed in a food effect study with a 10 mg rivaroxaban tablet, a dedicated food effect study was not conducted on lower strength formulations, in particular the 2.5 mg tablet strength.

in vitro studies, transport proteins (study PH-36523 and study PH-36522)

In study PH-36523, the uptake of rivaroxaban into human embryonic kidney control cells and cells overexpressing OATP1B1 and OATP1B3 was investigated. No active uptake of rivaroxaban was observed for OATP1B1 and for OATP1B3. Rivaroxaban did not reduce the active uptake of pravastatin into HEK-OATP1B1 cells and HEK-OATP1B3 cells at concentrations of 1 µM and 10 µM.

In study PH-36522, the uptake of rivaroxaban into human embryonic kidney control cells and cells overexpressing OAT1, OAT3 and OCT2 was investigated. Based on this in vitro data, rivaroxaban is neither a substrate nor an inhibitor of OAT1 and OCT2 at clinically relevant concentrations. Rivaroxaban showed an interaction potential in OAT3-expressing HEK cells. The uptake of rivaroxaban was 1.5-fold higher in OAT3-transfected cells than in vector-transfected cells. Further, the OAT probe substrate Estrone 3-sulfate and the OAT-inhibitor probenecid showed a weak inhibition of the uptake of rivaroxaban. In OAT3-transfected cells, 1 µM rivaroxaban caused a significant inhibition of 22% of the OAT3 mediated uptake of estrone 3-sulfate.

In study PH-36581, the inhibitory potential of dronedarone towards P-gp mediated efflux of rivaroxaban was investigated with P-gp-transfected LLC-PK1 cells. The efflux of rivaroxaban in LLC-MDR1 cells was inhibited by dronedarone with an IC50 of 0.37 µM.

Population PK/PD and exposure-response analyses of rivaroxaban in the target population

The pharmacokinetic data from study RIVAROXACS2001 / ATLAS ACS TIMI 46 was evaluated using population pharmacokinetic modelling (PopPK). The PK of rivaroxaban in patients with ACS was adequately described by an oral one-compartment model with first-order absorption and first-order elimination. The patient covariates included in the model, were age and renal function effects on CL/F, and body weight and age effects on V/F. The typical values of CL/F and V/F in patients with ACS at a dose of 2.5 mg were comparable to those in patients with VTE following knee and hip surgery at a 2.5-mg dosing regimen.

The PK/PD analyses of the ATLAS study were conducted in a subgroup of patients where time matched PK and PD samples were collected. The PD measurements include prothrombin time (PT) and prothrombinase induced clotting time (PiCT). Rivaroxaban plasma concentrations showed a close-to-linear relationship with PT in the ACS population. The parameter estimates for the current ACS population are consistent with those reported for the DVT and AF populations.

A statistical analysis of data from the ATLAS study was performed to quantify the influence of rivaroxaban exposure on the hazard of clinically significant bleeding in addition to clinically relevant covariates, and to test if there was a difference in the bleeding hazard between the once daily regimens and twice daily regimens in the exposure-bleeding outcome relationship. A Cox Proportional Hazards model relating AUC24 and rivaroxaban treatment (dichotomous variable) linearly to the hazard of clinically significant bleeding was used to describe the data.

2.4.1. Pharmacodynamics

Mechanism of action

Rivaroxaban is a potent and highly selective direct FXa inhibitor that is orally bioavailable.

In a subgroup of ACS patients from study ATLAS TIMI 46, prothrombin fragment 1 and 2 (F1.2) was measured. Compared to patients receiving placebo, rivaroxaban administration was associated with a significant reduction in F1.2 concentration 8-24 hours after administration which continued throughout the 180 days of treatment, indicating a persisting effect of rivaroxaban on reduction of thrombin generation over time.

2.4.2. Discussion on clinical pharmacology

The pharmacodynamics for rivaroxaban have been well characterised in studies assessed in earlier applications.

2.4.3. Conclusions on clinical pharmacology

There are no objections to approval from a pharmacokinetic or pharmacodynamic perspective.

2.5. Clinical efficacy

2.5.1. Dose response study (study 11898)

The main purpose of the phase II study, ATLAS ACS TIMI 46, study 11898, was to estimate the correct dose of rivaroxaban that should be given to patients with a recent ACS. The secondary purpose was to evaluate the efficacy and safety of rivaroxaban in subjects with acute coronary syndrome who received standard care antiplatelet therapy.

Efficacy and safety endpoints

The primary efficacy endpoint was the composite of all-cause death, MI, stroke, or SRIR (severe recurrent ischemia requiring revascularization).

The key secondary efficacy endpoint was the composite of all-cause death, MI, or stroke.

The primary safety endpoint was the incidence of clinically significant bleeding, a composite of TIMI major bleeding, TIMI minor bleeding, or bleeding requiring medical attention.

For ATLAS ACS TIMI 46 study (11898) the following main inclusion and exclusion criteria were applied.

Key Inclusion Criteria

Subjects who met the following criteria were eligible for enrollment in the study:

- Had symptoms suggestive of ACS that lasted at least 10 minutes at rest occurring within 7 days of randomization;
- Had either a diagnosis of STEMI or a diagnosis of NSTEMI or UA with at least 1 of the following:
  - Elevated cardiac enzyme marker (e.g., creatine kinase isoenzyme, muscle and brain subunit [CK-MB]) or troponin I or T);
  - ≥1 mm ST-segment deviation (i.e., elevation or depression);
  - TIMI risk score ≥3.
- Man or woman between 18 and 75 years of age, inclusive. Subjects older than 75 years of age were allowed to enroll in the 20-mg or lower TDD panels assuming an acceptable safety profile was demonstrated, as determined by the OC in consultation with the IDMC Chair;
- Women must have been surgically sterile or if sexually active, practicing an effective method of birth control (e.g., prescription oral contraceptives, contraceptive injections, intrauterine device, double barrier method, contraceptive patch, male partner sterilization) before entry and throughout the study; Women of childbearing potential must have a negative urine β-human chorionic gonadotropin (β-hCG) pregnancy test at screening.

Key Exclusion Criteria

- Active internal bleeding, clinically significant bleeding, bleeding at a non compressible site, or bleeding diathesis within 30 days of randomization;
- Platelet count <90,000/μL at the screening visit;

- Major surgery, biopsy of a parenchymal organ, eye surgery (including cataract surgery or vision correcting surgery), or serious trauma within 30 days before randomization;
- Clinically significant gastrointestinal bleeding within 6 months before the randomization visit;
- History of hemorrhagic stroke at any time or clinical presentation consistent with intracranial hemorrhage;
- Recent ischemic stroke or transient ischemic attack (TIA) of any etiology within 30 days of randomization;
- Sustained uncontrolled hypertension: systolic blood pressure of ≥180 mmHg or diastolic pressure of ≥100 mmHg that persists for more than 1 hour at time of screening despite treatment;
- The need for continued treatment with anticoagulant drugs (e.g., warfarin);
- Known significant kidney disease with calculated creatinine clearance <30 mL/min at the screening visit;
- Known significant liver disease or alanine aminotransferase (ALT) >3 times the upper limit of normal (ULN) values;
- Anemia (i.e., hemoglobin <10 g/dL) at the screening visit;
- Systemic treatment with a strong inhibitor of cytochrome P450 3A4, such as ketoconazole or protease inhibitors, within 4 days before randomization or planned treatment during the time period of the study;
- Treatment with a strong inducer of cytochrome P450 3A4, such as rifampin/rifampicin within 4 days before randomization or planned treatment during the time period of the study.

Methods

The ATLAS ACS TIMI 46 study was randomized, multicenter, double-blind and placebo-controlled. The study was originally planned in 2 stages: Stage 1 for dose escalation and Stage 2 for dose confirmation. Stage 1 enrollment was expanded obviating the need for Stage 2, which was never performed.

The study consisted of a 6-month double-blind treatment period and a 1-month follow up period and compared once-daily dosing with twice-daily dosing within the same total daily dose (TDD). A total of 3,491 subjects with ACS were randomized to various rivaroxaban dose groups. This included 761 (21.8%) in Stratum 1 (ASA only) and 2730 (78.2%) in Stratum 2 (ASA+thienopyridine); among them, 2,331 subjects were randomly assigned to receive rivaroxaban and 1160 subjects to receive placebo.

Dosage

If the subject received intravenous UFH or bivalirudin, the first dose of study drug was to be administered at the time that the UFH or bivalirudin infusion was stopped. If the subject received subcutaneous UFH, LMWH, or fondaparinux the first dose of study drug was to be administered at the time that the next planned dose of subcutaneous UFH, LMWH, or fondaparinux would have been given (e.g., 12 to 24 hours after the previous dose). If no form of anticoagulation was administered at the time of randomization, dosing may have begun immediately. To minimize time beyond the recommended interval on the first day, it was preferred to begin dosing in the afternoon or evening. If a PCI had been performed, dosing was initiated as described above, but ≥4 hours following PCI. Study drug was taken with or without food. In both strata individual subjects remained on the dose and dosing regimen to which they were randomized, for the 6-month treatment period.

2.5.1.1. Results

The rate of primary composite endpoint of all-cause death, MI, stroke or SRI requiring revascularization was 6.0% (141/2331) for the rivaroxaban combined dose group and 7.2% (83/1160) for the placebo group. A relative risk reduction (RRR) of 16% was observed with a

hazard ratio (HR) of 0.84 (95% CI: 0.64, 1.10), and a Log-rank p-value of 0.213. The rate of key secondary composite endpoint of all-cause death, MI or stroke was 4.3% (101/2331) for the rivaroxaban combined dose group and 5.7% (66/1160) for the placebo group. A RRR of 24% was observed with a HR of 0.76 (95% CI: 0.55, 1.03) and a Log-rank p-value of 0.077. (see below Table E2)

Table E2 : Treatment Effect of Primary, and Key Secondary Efficacy Endpoints

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

K/N: # of events / # of randomized subjects
Intention to treat analysis based on adjudicated events
*: the primary efficacy endpoint: the composite of all-cause death, MI (including reMI), stroke (ischemic, hemorrhagic or unknown), or SRI requiring revascularization;
**: the key secondary efficacy endpoint: the composite of all-cause death, MI (or reMI), or stroke (ischemic, hemorrhagic or unknown)
***: Rivaroxaban all dose groups and dosing regimens combined

Dose response

In Stratum 1, there was an indication of a dose response of rivaroxaban. For the primary efficacy endpoint, the Hazard Ratio (HR) (95% CI) for rivaroxaban 5 mg, 10 mg, and 20 mg TDD groups, as compared with the pooled placebo group were 0.65 (0.35, 1.22), 0.64 (0.36, 1.15), and 0.40 (0.19, 0.84), respectively. For the key secondary efficacy endpoint, the HR (95% CI) for rivaroxaban 5 mg, 10 mg, and 20 mg TDD groups, as compared with the pooled placebo group were 0.78 (0.41, 1.47), 0.62 (0.33, 1.18), and 0.37 (0.16, 0.84), respectively. The trend of the risk reduction over the dose levels for the key secondary efficacy endpoint was statistically significant (p-value = 0.01).

In Stratum 2, MAH found that the primary and key secondary efficacy results showed no clear dose response for rivaroxaban, but rather a similar reduction with all doses. For the primary efficacy endpoint, the HR (95% CI) for rivaroxaban 5 mg, 10 mg, 15 mg, and 20 mg TDD groups, as compared with the pooled placebo group were 1.07 (0.53, 2.19), 0.82 (0.54, 1.26), and 1.43 (0.89, 2.29), and 1.10 (0.69, 1.76), respectively. For the key secondary efficacy endpoint, the HR for rivaroxaban 5 mg, 10 mg, 15 mg, and 20 mg TDD groups, as compared with the pooled placebo group were 0.62 (0.22, 1.73), 0.75 (0.45, 1.23), 1.47 (0.86, 2.51), and 0.80 (0.44, 1.47), respectively. The trend of the risk reduction over the dose levels for the key secondary efficacy endpoint was not statistically significant (p = 0.99).

The detailed results of the primary endpoint and its components are shown in the table E3 below.

Table E3 : Treatment Effect of Primary and Key Secondary Efficacy Endpoints by Dose Level Against Pooled Placebo Group (Study Atlas ACS TIMI 46: Intent-to-Treat Analysis Set

Stratum	Parameter	Pooled Placebo K/N (%)	Rivaroxaban 5 mg K/N (%)	Rivaroxaban 5 mg HR (95% CI)	Rivaroxaban 10 mg K/N (%)	Rivaroxaban 10 mg HR (95% CI)	Rivaroxaban 15 mg K/N (%)	Rivaroxaban 15 mg HR (95% CI)	Rivaroxaban 20 mg K/N (%)	Rivaroxaban 20 mg 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

There was a significant interaction (p=0.04) in the effect of treatment with rivaroxaban on the composite endpoint of death, MI, and stroke, indicating effect modification by background antiplatelet therapy resulting in different risk reduction between the 2 strata. MAH also concluded, that the margin for additional risk reduction by anticoagulants in Stratum 2 with ASA plus a thienopyridine appeared to be narrower than that in Stratum 1 with ASA alone.

Bleedings

The primary safety endpoint was the incidence bleeding events that were classified as major, minor, or bleeding requiring medical attention.

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

The results are summarised in the following table :

Treatment Effect of TE Primary Bleeding Endpoints by Dose Level Against Pooled Placebo as Adjudicated by CEC (Study ATLAS ACS TIMI 46: Safety Analysis Set)

	Placebo	Rivaroxaban			
Endpoint	K/N (%)	5 mg K/N (%)	10 mg K/N (%)	15 mg K/N (%)	20 mg K/N (%)
Combined strata					
Clinical Sig	36/1153 (3.1)	17/307 (5.5)	109/1046 (10.4)	43/353 (12.2)	89/603 (14.8)
TIMI MM	3/1153 (0.3)	2/307 (0.7)	22/1046 (2.1)	9/353 (2.5)	14/603 (2.3)
TIMI Major	1/1153 (<0.1)	1/307 (0.3)	16/1046 (1.5)	6/353 (1.7)	9/603 (1.5)
Stratum 1					
Clinical Sig	4/252 (1.6)	2/154 (1.3)	12/195 (6.2)		16/157 (10.2)
TIMI MM	0/252 (0.0)	0/154 (0.0)	4/195 (2.1)		1/157 (0.6)
TIMI Major	0/252 (0.0)	0/154 (0.0)	4/195 (2.1)		0/157 (0.0)
Stratum 2					
Clinical Sig	32/901 (3.6)	15/153 (9.8)	97/851 (11.4)	43/353 (12.2)	73/446 (16.4)
TIMI MM	3/901 (0.3)	2/153 (1.3)	18/851 (2.1)	9/353 (2.5)	13/446 (2.9)
TIMI Major	1/901 (0.1)	1/153 (0.7)	12/851 (1.4)	6/353 (1.7)	9/446 (2.0)

Clinical Sig: clinically significant bleeds; TIMI MM: TIMI major or minor bleeds. TE=Treatment Emergent.
Safety population based on treatment emergent adjudicated events, occurring between 1st dose and last dose plus 2 days

The overall results for the twice-daily dosing regimen tended to be numerically better than the once-daily dosing regimen results. For the primary efficacy endpoint, the HR (95% CI) was 1.14 (0.82, 1.58) for the once-daily dosing regimen versus the twice-daily dosing regimen.

Stratum 1, once-daily dosing was slightly better than twice-daily dosing [HR (95% CI), 0.91(0.49, 1.70)]; whereas, for Stratum 2, once-daily dosing was worse than twice-daily dosing [HR (95% CI), 1.24(0.84, 1.84)].

Similar results were observed for the individual rivaroxaban dose level compared with the pooled placebo group, or compared with each placebo dose level. Comparison of the effect of the rivaroxaban 5 mg and 10 mg TDD groups (administered as either 5 mg, and 10 mg once-daily or 2.5 mg, and 5 mg twice-daily) on the key secondary efficacy endpoint showed a greater RRR with the twice-daily dosing regimen. Across strata, rivaroxaban at doses of 2.5 mg and 5 mg twice-daily resulted in 46% and 37% relative reductions in risk for the key secondary efficacy endpoint while rivaroxaban doses of 5 mg and 10 mg administered once-daily resulted in 8% and 24% RRR in the same endpoint. This was observed in both Stratum 1 and Stratum 2.

The MAH concluded, that rivaroxaban TDD of 5 and 10 mg appeared to have an acceptable safety profile, had less bleeding than the higher doses, and within these 2.5 mg and 5 mg twice daily were numerically more efficacious than the once-daily doses, and offered a more favorable net clinical benefit. Higher doses of rivaroxaban were not associated with increased efficacy in subjects receiving rivaroxaban in addition to dual antiplatelet therapy. This led to the selection of rivaroxaban 2.5 mg and 5 mg twice-daily doses for testing in the phase III ATLAS ACS2-TIMI 51 study.

For the secondary goal of evaluating the efficacy of rivaroxaban in subjects with ACS in addition to standard care antiplatelet therapy, MAH concluded that although the phase II study was not powered to identify differences between individual dose groups, the results suggested that rivaroxaban may meaningfully reduce major CV events with an acceptable incremental bleeding risk in addition to ASA or ASA plus a thienopyridine in ACS patients.

2.5.1.2. Discussion

The study was a well-designed dose-escalating and dose-finding study planned to be performed in two sequentially stages. According to the MAH, due to that enrollment proceeded quickly in Stage 1, additional dose panels were tested and previously tested dose panels repeated. The increased size of Stage 1 lead to that the planned confirmation stage was never initiated and the efficacy and safety analyses planned in Stage 2 was performed within Stage 1. The study was however not powered for assessing treatment effects for individual doses or dose regimens.

However, some important patient groups, and patients with a recent ischemic stroke or transient ischemic attack (TIA) were excluded from the study.

There was no prominent difference between the doses for the primary and key secondary efficacy results in Stratum 2 and there was no clear indication for a reduction in any dose group.

The twice-daily rivaroxaban dosing regimen had a numerically greater effect on the primary and key secondary endpoints than the once-daily regimen.

It is important to note, that the margin for additional risk reduction appeared to be less when the patient is treated with dual antiplatelet therapy. A clear dose-response relationship with regard to bleedings was demonstrated. The bleeding pattern was consistent with what has been recorded for rivaroxaban in other indications with a predominance for mucosal bleedings.

There was a significant interaction (p=0.04) in the effect of treatment with rivaroxaban on the composite endpoint of death, MI, and stroke, indicating effect modification by background antiplatelet therapy resulting in different risk reduction between the 2 strata. MAH concluded, that the margin for additional risk reduction by anticoagulants in Stratum 2 with ASA plus a thienopyridine appeared to be narrower than that in Stratum 1 with ASA alone.

Thus the margin for additional risk reduction appeared to be less when the patient is treated with dual antiplatelet therapy.

The reasons for the twice daily dosing regimen in the phase III study and the safety profile appeared to be somewhat more advantageous in the phase II trial as highlighted by the MAH appear acceptable by the CHMP.

2.5.2. Main study (study 13194)

The main study is the ATLAS ACS2-TIMI 51 study (The Second Trial of Anti-Xa Therapy to Lower Cardiovascular Events in Addition to Aspirin with or without Thienopyridine Therapy in Subjects with Acute Coronary Syndrome), study number 13194. The ATLAS ACS2-TIMI 51 study was a randomized, multicenter, double-blind, event-driven and placebo-controlled phase III study.

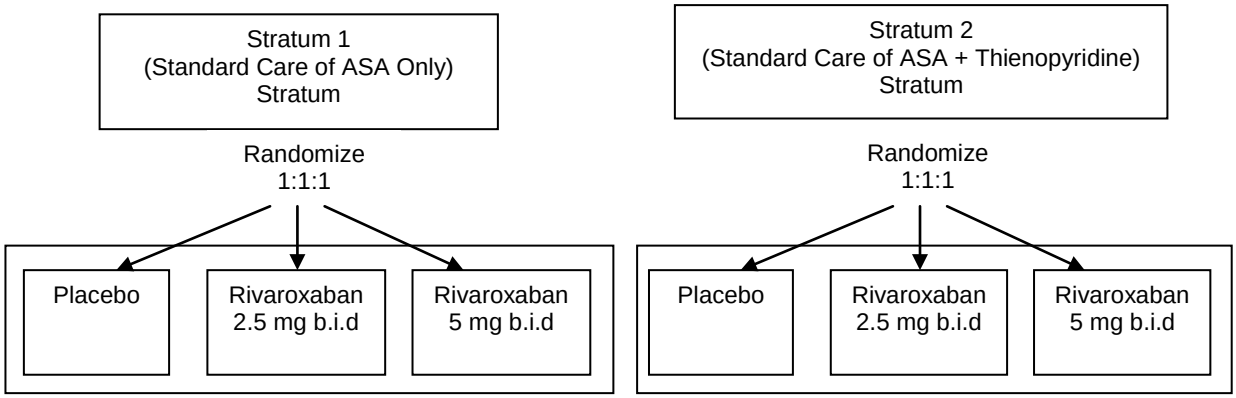
15526 patients were included at 766 centers in 44 countries.

The study was designed to determine whether rivaroxaban in addition to standard care antiplatelet therapy reduces the risk of the composite of CV death, MI, or stroke in subjects with a recent ACS event compared with placebo.

Methods

Figure E1

Design of ATLAS ACS 2 TIMI 51(study 13194)



- **Study participants**

The study ATLAS ACS2-TIMI 51 enrolled adult subjects who had been hospitalized for symptoms suggestive of ACS or developed ACS while being hospitalized, and who were receiving ASA therapy (75 to 100 mg/day) alone or in combination with a thienopyridine (clopidogrel or ticlopidine, per the national or locally indicated dosage). This population was chosen as the company considered it representative of those patients with a recent ACS who were at moderate to high risk for thromboembolic CV complications. About 50% of all randomized subjects had STEMI. NSTEMI and unstable angina comprised about 25% each of the ACS index events for admitting diagnosis.

- **Key Inclusion Criteria**

Subjects had to satisfy the following criteria to be enrolled in the study:

- Man or woman, 18 years of age or older
- Currently receiving ASA therapy (75 to 100 mg/day) alone or in combination with a thienopyridine (clopidogrel or ticlopidine per national dosing recommendation)
- Had been hospitalized for symptoms suggestive of ACS that lasted at least 10 minutes at rest, and occurred 48 hours or less before hospital presentation or who developed ACS while being hospitalized for an indication other than ACS, and have a diagnosis of:
  - STEMI:
  - NSTEMI:
  - UA with at least 1 of the following:
    - transient or persistent ST-segment deviation 0.1 mV or greater in 1 or more ECG leads
    - TIMI risk score of ≥4.
- 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.

Patients with STEMI had to have elevated biomarkers of myocardial necrosis (CK-MB or troponin).

- **Key Exclusion Criteria**

Potential subjects who met any of the following criteria were to be excluded from participating in the study:

Bleeding risk:

- Any condition that, in the opinion of the investigator, contraindicated anticoagulant therapy or would have an unacceptable risk of bleeding, such as, but not limited to, the following:
    - active internal bleeding, clinically significant bleeding, bleeding at a noncompressible site, or bleeding diathesis within 30 days of randomization
    - platelet count <90,000/µL at screening
    - history of intracranial hemorrhage
    - major surgery, biopsy of a parenchymal organ, or serious trauma (including head trauma) within 30 days before randomization
    - clinically significant gastrointestinal bleeding within 12 months before randomization
    - have an International Normalized Ratio (INR) known to be >1.5 at the time of screening
    - abciximab bolus or infusion within the 8 hours prior to randomization, or an eptifibatide or tirofiban bolus or infusion within the past 2 hours before randomization
    - any other condition known to increase the risk of bleeding

Severe concomitant diseases such as:

- Cardiogenic shock at the time of randomization
- Ventricular arrhythmias refractory to treatment at the time of randomization
- Calculated creatinine clearance <30 mL/min at screening
- Known significant liver disease (e.g., acute hepatitis, chronic active hepatitis, cirrhosis), or liver function test (LFT) abnormalities (confirmed with repeat testing) which would require study drug discontinuation, i.e., alanine aminotransferase (ALT) >5x upper limit of normal (ULN) or ALT >3x ULN plus total bilirubin >2x ULN
- A prior ischemic stroke or transient ischemic attack (TIA) in subjects who the investigator planned to include in Stratum 2 (ASA plus thienopyridine). (Note: subjects with a prior ischemic stroke or TIA were eligible for inclusion in the study only if they intended to be treated with ASA only). Subjects with a prior hemorrhagic stroke were excluded completely from the study.
- Anemia (i.e., hemoglobin <10 g/dL) at screening
- Known clinical history of human immunodeficiency virus (HIV) infection at screening
- Substance abuse (drug or alcohol) problem within the previous 6 months
- Any severe condition that would limit life expectancy to less than 6 months

Atrial fibrillation was also an exclusion criterion, except for subjects younger than 60 years of age who had no clinical or echocardiographic evidence of cardiopulmonary disease and who had only a single episode of atrial fibrillation that occurred more than 2 years ago.

Patients with a prior ischemic stroke or transient ischemic attack, TIA, were excluded from inclusion in the group that were supposed to receive both ASA and a thienopyridine.

- **Treatments**

Patients were randomized to rivaroxaban 2.5 mg or 5 mg, or placebo, twice daily in addition to conventional therapy (ASA + clopidogrel or ticlopidine). The conventional therapy (ASA+clopidogrel or ticlopidine) was given per national dosing recommendation.

Differences regarding the loading dose of the thienopyridine or with respect to the duration of dual antiplatelet treatment might have occurred in the study. Currently these issues cannot be sufficiently clarified from the information available and more information is needed to exclude a relevant impact on study outcome.

The duration of dual antiplatelet treatment was at the discretion of the investigator and could have varied depending on the subject's diagnosis or whether a bare metal stent or drug eluting stent was implanted. Thus, upon CHMP request the MAH provided further clarification on the duration of dual antiplatelet treatment which in conclusion, did not raise further concern by the CHMP as having no impact on the results.

Subjects were randomly assigned to study drug up to 7 calendar days after the subject had beenhospitalized for the index ACS event, when parenteral anticoagulant therapy would normally be discontinued. Enrollment was to occur as soon as possible after the initial treatments for the index ACS event, including revascularization procedures, but could not occur during the first 24 hours following hospitalization.

Subjects returned to the study center every 12 weeks until the global treatment end date; the projected date of accrual of approximately 983 primary efficacy endpoint events anticipated to be adjudicated as mITT events. The Executive Committee (EC) notified sites in advance of the global treatment end date via written communication, and study sites scheduled subjects for EOT visits as soon as possible on or after the date. Subjects were instructed not to discontinue their study drugs on the global treatment end date, but rather at the EOT visit; therefore, some subjects were treated with study drug after the global treatment end date. Thirty days after their last dose of study drug, subjects were to complete the final end-of-study (EOS) contact (either in person or by telephone) to assess efficacy and safety data.

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

- **Objectives**

Based on time from randomization to the first occurrence of the primary efficacy endpoint, the objective of the primary efficacy analysis was to determine whether rivaroxaban is superior to placebo, in addition to standard care, in the reduction of primary efficacy endpoint events in subjects with a recent ACS.

- **Outcomes/endpoints**

The primary efficacy endpoint in the phase III ATLAS ACS 2 TIMI 51 study was the composite of CV death, MI, or stroke.

The secondary efficacy endpoints were:

1. The composite of all-cause death, MI, or stroke
2. Net clinical outcome, defined as the composite of CV death, MI, ischemic stroke, or TIMI major bleeding event not associated with coronary artery bypass graft (CABG) surgery (non-CABG TIMI major bleeding)
3. The composite of CV death, MI, stroke, or severe recurrent ischemia requiring revascularization (SRIR)
4. The composite of CV death, MI, stroke, or severe recurrent ischemia leading to hospitalization (SRIH)

In addition the individual components of the composite primary and major secondary endpoints were to be analyzed.

Safety Evaluations

The primary safety endpoint in this study was the occurrence of non-CABG TIMI major bleeding events. Other safety evaluations included all reported bleeding events, serious adverse events, adverse events leading to discontinuation of study drug, adverse events of special interest and clinical laboratory tests.

- **Sample size**

This was an event-driven study to be stopped when at least 983 adjudicated primary efficacy endpoints had accrued across both strata, with at least 728 adjudicated primary efficacy endpoints in Stratum 2. The total sample size estimation was based on the predicted number of adjudicated events required and the following assumptions:

- Enrollment projection and placebo event rates (12% at 1 year in Stratum 1; 6% at 1 year in Stratum 2) similar to those for the Phase 2 ATLAS ACS TIMI 46 study
- Total enrollment period of approximately 27 months
- Total treatment duration of approximately 33 to 34 months
- Yearly dropout (e.g., withdrawal of consent, lost to follow-up, premature discontinuation of study drug) rate of 10% in each treatment group.

A total of 983 primary efficacy endpoint events were estimated to have approximately 96% power to detect a 22.5% relative reduction (i.e., hazard ratio=0.775) between pooled doses of rivaroxaban and placebo arms pooled across Stratum 1 and 2, with a 2-sided type I error rate of 0.05. It was also based on the sum of the events required at approx. 90% power in each stratum, to detect a 35% relative reduction in Stratum 1 (255 primary events) and a 22.5% relative reduction in Stratum 2 (728 primary events) comparing combined rivaroxaban doses and placebo arms within each strata.

Each individual dose arm, pooled across Stratum 1 and 2, was powered at approx. 90% for an overall relative risk reduction of 22.5%, within each individual dose arm, and within each individual stratum the study was powered at approx. 80% for the assumed relative risk reduction of 35% in Stratum 1 and 22.5% in Stratum 2.

Originally, approximately 13,570 subjects (2,079 subjects in Stratum 1 and 11,491 subjects in Stratum 2) were estimated to be needed to reach the expected number of primary efficacy endpoint events and the targeted study power. The protocol allowed for the sample size to be increased to 16,000 subjects if planning assumptions were modified based on a blinded data review; since Stratum 1 enrollment was slower than originally projected, the final sample size was increased to approximately 15,500.

- **Randomisation**

Randomization was to occur as soon as possible after the initial treatments or revascularization procedures for the index ACS event had been performed, up to 7 days after the hospitalization for the index ACS event.

Randomization was stratified by the intention to use thienopyridine (yes, stratum 2; or no, stratum 1) as standard care, in addition to low-dose ASA therapy 75 to 100 mg/day. Within each stratum, subjects was randomly assigned in a 1:1:1 ratio to receive rivaroxaban 2.5 mg twice daily, rivaroxaban 5 mg twice daily, or placebo twice daily.

- **Blinding (masking)**

In addition to the double-blind design, a central Clinical Events Committee (CEC) adjudicated and classified all efficacy and primary safety endpoint events while blinded to treatment assignment.

- **Statistical methods**

The study was stopped based on the estimated accrual of 983 primary efficacy endpoints anticipated to be adjudicated as mITT events. A formal interim review of efficacy and safety data was performed when approximately 70% (688) of the required total number (983) of primary efficacy events, had occurred, in order to assess whether the study should be stopped for overwhelming superiority. However, the study continued unaltered following that analysis.

Two simultaneous evaluation strategies were selected on the basis of advice from health authorities in different regions. The primary strategy was based on data combined across both strata. A second evaluation strategy was based on the FDA-recommended approach of combined analyses across both dose regimens in subjects in Stratum 2 (ASA+Thienopyridine) only. The use of simultaneous evaluation strategies based on the total population and stratum 2 only due to different regulatory requirements above described is considered acceptable although it may raise concerns regarding multiplicity.

The statistical methods for efficacy and safety analyses are appropriate. The stratified randomization was taken into account in the analysis.

For the primary endpoint, a closed hierarchical testing procedure was applied, which adequately controls the type 1 error for the tests of superiority of the combination of the dose groups and the single dose groups. As the hierarchical testing procedure for the secondary endpoints was performed independently for the two dose groups using a 0.05 significance level, the family-wise type 1 error was not strongly controlled at the 0.05 level. Nevertheless, it is agreed that a strong control of type 1 error may not be needed considering the high correlation of primary and secondary endpoints.

The sensitivity analyses are appropriate. However, for the analyses based on the ITT and Total-ITT population, it has to be taken into account that information on occurrence of endpoint events for the time after discontinuation of study drug was not available for all subjects who discontinued study drug prematurely. However, the MAH has collected vital data on patients that discontinued the trial prematurely. The results of these analyses are judged to support the conclusions made on the basis of the primary efficacy analyses.

The conclusion of consistent treatment effect across subgroups in case of lack of significant interaction between treatment group and subgroup variable is not acceptable because the study was not powered to show significant interactions. However, the consistency of the treatment effect across subgroups can be evaluated based on the hazard ratios that were provided for each of the subgroups.

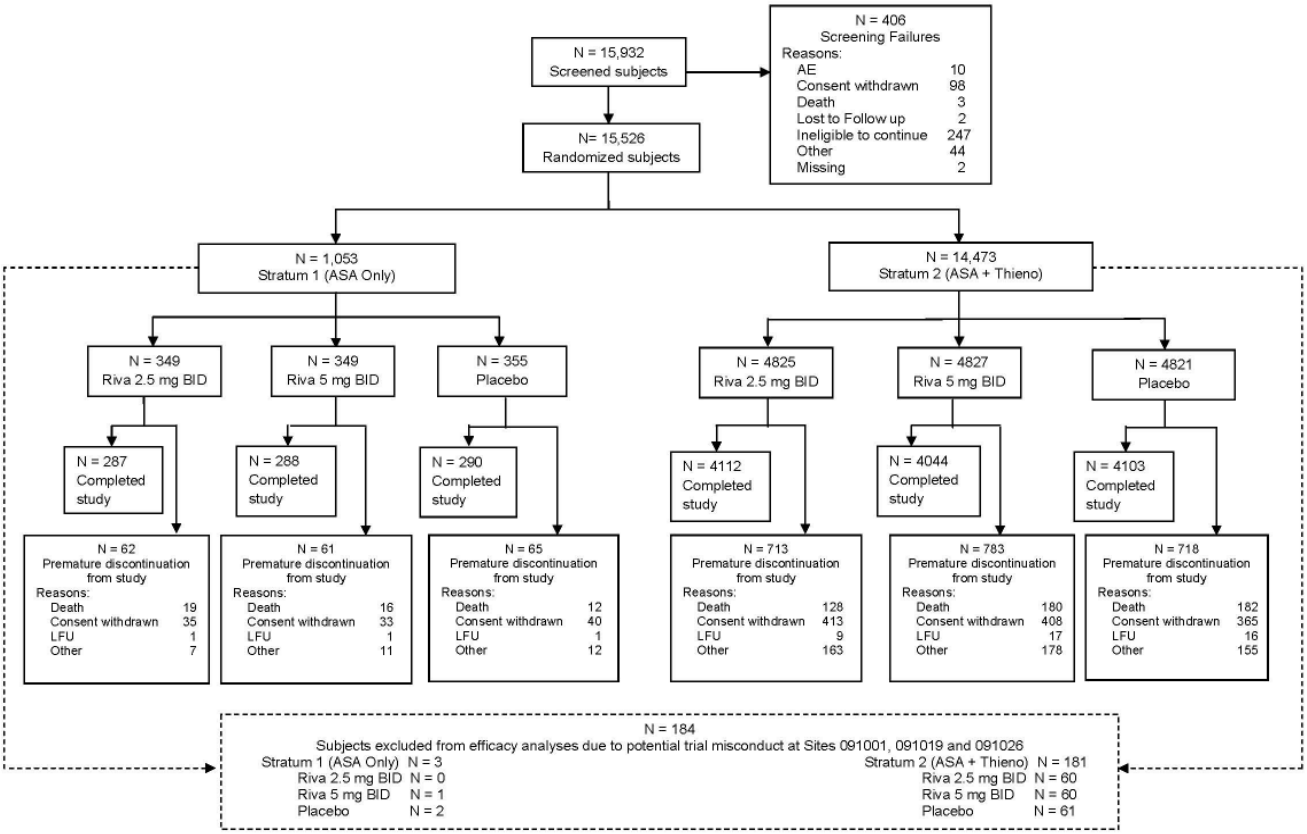
At the planning stage, stent thrombosis was not considered a formal study endpoint and was only to be summarized.

Study results

- **Participant flow**

As the study was event-driven, subjects were exposed to the study drug for varying lengths of time, depending on when they were randomized. The median total duration of treatment was 397 days in the rivaroxaban 2.5 mg twice daily group. Across all treatment groups, more than 75% of subjects were exposed to study drug for ≥6 months, more than half for ≥12 months, and almost one-third were exposed for ≥18 months.

Figure E2 : Subject disposition (Study RIVAROXACS3001)



- **Conduct of the study**

The study was initiated in November 2008 and was completed in September 2011. In total 766 sites in 44 countries worldwide randomized subjects in this study. The majority of subjects were white (73.5%). The highest enrolling region was Eastern Europe (6074 [39.1%]), followed by Asia (3195 [20.6%]) and Western Europe (2241 [14.4%]); and 874 subjects enrolled in the North America region (5.6%)

A formal interim review of efficacy and safety data was performed when approximately 70% (688) of the required total number (983) of primary efficacy events, best available or adjudicated by the Clinical Events Committee, had occurred, in order to assess whether the study should be stopped for overwhelming superiority. The data cut-off for the interim analysis was November 29, 2010, based on 704 total primary efficacy events. The IDMC met on January 12, 2011 to review the data. The study continued unaltered following that analysis.

In summary, the study was well designed and the amendments improved the quality of the study. Subjects from 3 sites (i.e, 091001, 091019, and 091026) were excluded from the efficacy population due to potential trial misconduct. The MAH has clarified and justified the exclusion of these sites in response to the CHMP which was considered to be acceptable. This concerned a minor percentage of the total study population (1.2%), equally distributed between treatment groups and was also decided prior to the unblinding of the study.

- **Baseline data**

The majority of all randomized subjects had CV risk factors, such as hypertension (67.4%), diabetes mellitus (32.0%) or history of MI (26.9%). There were 60.5% subjects who had a revascularization procedure for the index event; the vast majority of these procedures were percutaneous coronary intervention, PCI (99.3%).

A relatively low proportion of the subjects were women (25.3%), and only a few were elderly (36.5% of patients were older than 65 years old, and 9.0% of patients were older than 75 years old). Mean age was 61.8 years. Approximately 74 % of the subjects were white, and 0.7% of the patients were black or African-American.

Table E5 Prior Medications of Interest

Subject Stratum Type Of Medications	Rivaroxaban 2.5 mg BID (N=5174) n (%)	Rivaroxaban 5 mg BID (N=5176) n (%)	Rivaroxaban Combined (N=10350) n (%)	Placebo (N=5176) n (%)	Total (N=15526) n (%)
All Strata	5174	5176	10350	5176	15526
Aspirin	5105 (98.7)	5099 (98.5)	10204 (98.6)	5108 (98.7)	15312 (98.6)
Thieno	4790 (92.6)	4812 (93.0)	9602 (92.8)	4811 (92.9)	14413 (92.8)
Beta-Blocker	3426 (66.2)	3394 (65.6)	6820 (65.9)	3444 (66.5)	10264 (66.1)
ACE-I or ARB	2022 (39.1)	1977 (38.2)	3999 (38.6)	2050 (39.6)	6049 (39.0)
Statin	4304 (83.2)	4342 (83.9)	8646 (83.5)	4321 (83.5)	12967 (83.5)
CCB	820 (15.8)	742 (14.3)	1562 (15.1)	764 (14.8)	2326 (15.0)
ASA	349	349	698	355	1053
Aspirin	347 (99.4)	347 (99.4)	694 (99.4)	352 (99.2)	1046 (99.3)
Thieno	77 (22.1)	73 (20.9)	150 (21.5)	82 (23.1)	232 (22.0)
Beta-Blocker	220 (63.0)	210 (60.2)	430 (61.6)	206 (58.0)	636 (60.4)
ACE-I or ARB	144 (41.3)	142 (40.7)	286 (41.0)	155 (43.7)	441 (41.9)
Statin	250 (71.6)	238 (68.2)	488 (69.9)	241 (67.9)	729 (69.2)
CCB	78 (22.3)	66 (18.9)	144 (20.6)	80 (22.5)	224 (21.3)
ASA + Thieno	4825	4827	9652	4821	14473
Aspirin	4758 (98.6)	4752 (98.4)	9510 (98.5)	4756 (98.7)	14266 (98.6)
Thieno	4713 (97.7)	4739 (98.2)	9452 (97.9)	4729 (98.1)	14181 (98.0)
Beta-Blocker	3206 (66.4)	3184 (66.0)	6390 (66.2)	3238 (67.2)	9628 (66.5)
ACE-I or ARB	1878 (38.9)	1835 (38.0)	3713 (38.5)	1895 (39.3)	5608 (38.7)
Statin	4054 (84.0)	4104 (85.0)	8158 (84.5)	4080 (84.6)	12238 (84.6)
CCB	742 (15.4)	676 (14.0)	1418 (14.7)	684 (14.2)	2102 (14.5)

Note: Percentages calculated with the number of subjects in each subject stratum and treatment group as denominator.
Note: ACE-I indicates angiotensin converting enzyme inhibitors.
Note: ARB indicates angiotensin receptor blocker.
Note: CCB indicates calcium channel blocker.
Note: Prior medication includes the medications subjects took before the randomization date.
Note: ASA = Acetylsalicylic acid; Thieno = Thienopyridine.
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The most common medication used prior to randomization was ASA (15,312 [98.6%]). The vast majority (14181 [98.0%]) of subjects in Stratum 2 were receiving a thienopyridine prior to randomization compared with only 232 (22.0%) of 1,053 randomized subjects in Stratum 1.

There were no important imbalances or relevant asymmetries in characteristics across treatment groups and strata in baseline demographic or disease characteristics at time of randomisation. However, as a high discontinuation rate was observed demographic and disease characteristics were reanalysed in the patients that discontinued and compared with the overall study population. It was found that the characteristics of the patients that discontinued were more similar to the patients that survived than to those that died.

- **Numbers analysed**

Of the 15,526 subjects randomized in the study, 15,342 (98.8%) subjects (5,114 in the 2.5 mg b.i.d. group, 5,115 in the 5 mg b.i.d. 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 b.i.d. group, 5,110 in the 5 mg b.i.d. group, and 5,125 in the placebo group) received at least 1 dose of study drug and were included in the safety population.

The reasons for premature discontinuation are displayed in table E7 below:

Table E7 : Primary Reasons for Premature Discontinuation From Double-Blind Treatment Period (Study RIVAROXACS3001: Safety Analysis Set)

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

Note: Percentages calculated with the number of subjects in each treatment group as denominator.
Note: ASA = Acetylsalicylic acid; Thieno = Thienopyridine.

In summary, the efficacy population included all randomized subjects except subjects randomised at one of three sites excluded due to potential study misconduct. They were however included in the Safety population. Overall it was about 1% in each of the treatment groups that never started treatment with study drug. Regarding the different analysis populations used for efficacy they differed only in the censoring rules for determining evaluable efficacy and safety events respectively, i.e. the number of subjects in each of the mITT, ITT and ITT-Total population respectively was 5114, 5115, and 5113 in the 2.5 mg BID, 5 mg BID and the placebo group

respectively. The only exception was for the per protocol population used in one sensitivity analysis of the primary efficacy endpoint.

- **Summary of main efficacy results**

Table E8 : Effect of Rivaroxaban Compared with Placebo on the Primary Efficacy Endpoint

	---------- 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.
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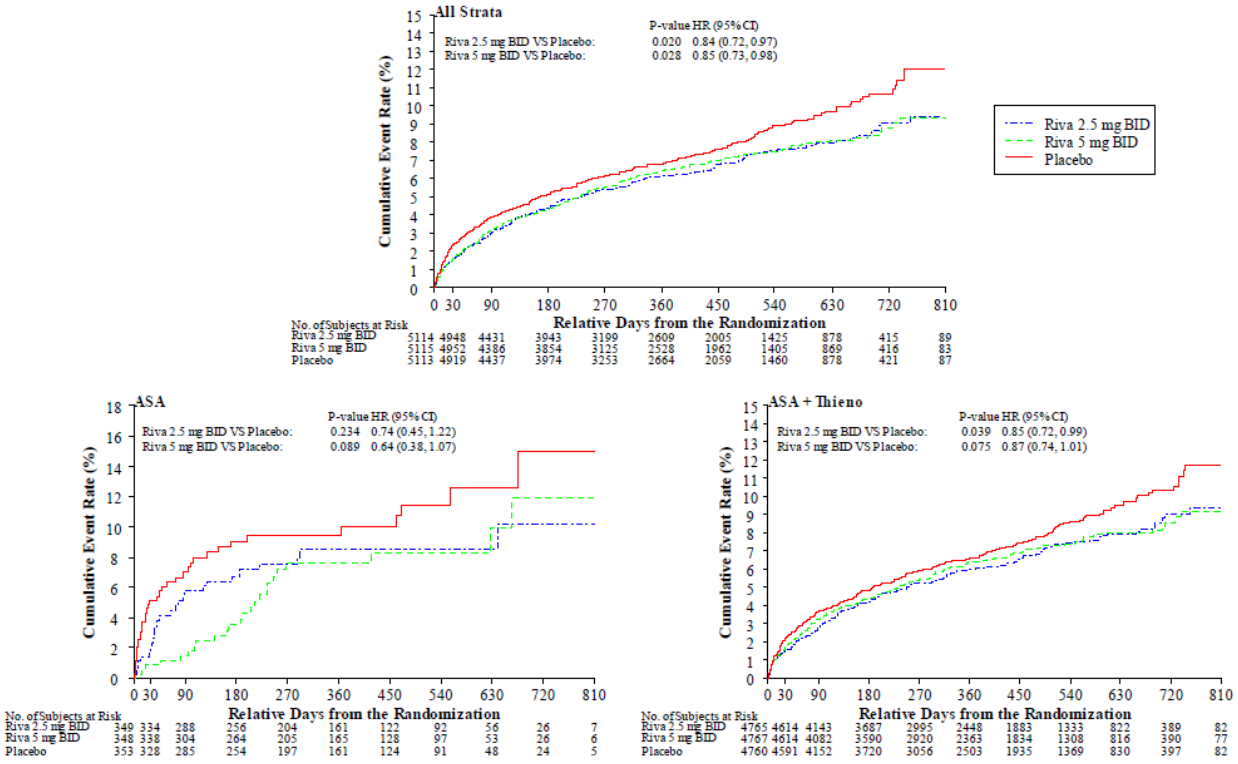
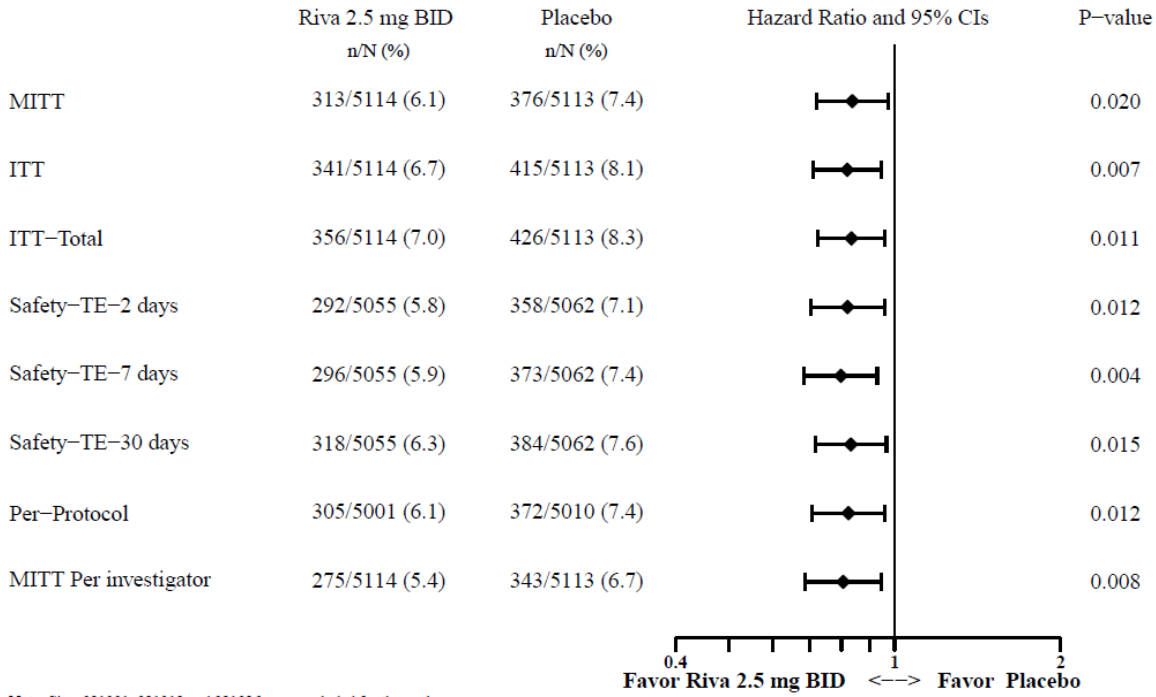
Figure E3 : Kaplan-Meier Estimates of the Primary Efficacy Endpoint (Cardiovascular Death, MI, Stroke)

mITT (Excluding Sites 091001, 091019 and 091026)



The MITT-, ITT-, and safety-TE analyses were all consistent.

Figure E4 : Effect of Rivaroxaban 2.5 mg BID Compared with Placebo on the Primary Efficacy Endpoint (First Occurrence of Cardiovascular Death, MI, Stroke) in All Strata (Study RIVAROXACS3001)



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

The sensitivity analyses supported the conclusions in the primary analysis. Due to the overall low incidence rates different censoring rules lead to that although more events were included in the analyses, the number of additional events were low and seems also to have been similar in each of the treatment group (2.5 mg vs. placebo). This lead to that there was almost no or only small differences between the analyses based on the different analysis sets, including the PP analysis. The latter probably due also to how the censoring rules was defined in the primary mITT analysis (censoring data or events occurring 30 days following treatment discontinuation and 30 days after randomization for those subjects who were randomized but not treated).

Hierarchical Testing – Event rate, Hazard Ratio and 95% Confidence Interval for Time to the First Occurrence of Efficacy Endpoints

Subject Stratum: All Strata

Parameter / Treatment Group	n/N	(%)	Event Rate (100 pt-yr)	--- Comparison to Placebo --- HR (95% CI)	Log-Rank P-value	Significant? Y/N
Primary Efficacy Endpoint						
Combined Riva	626/10229	6.1	5.97	0.84 (0.74,0.96)	0.008	Yes
Placebo	376/5113	7.4	7.04			
Primary Efficacy Endpoint						
Riva 2.5 mg BID	313/5114	6.1	5.92	0.84 (0.72,0.97)	0.020	Yes
Placebo	376/5113	7.4	7.04			
Secondary Efficacy Endpoint 1						
Riva 2.5 mg BID	320/5114	6.3	6.05	0.83 (0.72,0.97)	0.016	Yes
Placebo	386/5113	7.5	7.23			
Secondary Efficacy Endpoint 2						
Riva 2.5 mg BID	361/5114	7.1	6.85	0.93 (0.81,1.07)	0.320	No
Placebo	391/5113	7.6	7.32			
Secondary Efficacy Endpoint 3						
Riva 2.5 mg BID	437/5114	8.5	8.44	0.92 (0.80,1.04)	0.185	No
Placebo	481/5113	9.4	9.15			
Secondary Efficacy Endpoint 4						
Riva 2.5 mg BID	372/5114	7.3	7.12	0.84 (0.73,0.96)	0.011	No
Placebo	447/5113	8.7	8.47			
Primary Efficacy Endpoint						
Riva 5 mg BID	313/5115	6.1	6.03	0.85 (0.73,0.98)	0.028	Yes
Placebo	376/5113	7.4	7.04			
Secondary Efficacy Endpoint 1						
Riva 5 mg BID	321/5115	6.3	6.18	0.84 (0.73,0.98)	0.025	Yes
Placebo	386/5113	7.5	7.23			
Secondary Efficacy Endpoint 2						
Riva 5 mg BID	366/5115	7.2	7.07	0.95 (0.83,1.10)	0.508	No
Placebo	391/5113	7.6	7.32			
Secondary Efficacy Endpoint 3						
Riva 5 mg BID	421/5115	8.2	8.24	0.89 (0.78,1.01)	0.081	No
Placebo	481/5113	9.4	9.15			
Secondary Efficacy Endpoint 4						
Riva 5 mg BID	388/5115	7.6	7.55	0.88 (0.77,1.01)	0.070	No
Placebo	447/5113	8.7	8.47			

Note: Primary Efficacy Endpoint: first occurrence of cardiovascular death including unknown death, MI or stroke;
Secondary Efficacy Endpoint 1: first occurrence of all cause death, MI or stroke;
Secondary Efficacy Endpoint 2 (Net Clinical Outcome): first occurrence of cardiovascular death including unknown death, MI, ischemic stroke or TIMI major bleeding not associated with CABG surgery;
Secondary Efficacy Endpoint 3: first occurrence of cardiovascular death including unknown death, MI, stroke or severe recurrent ischemia requiring revascularization;
Secondary Efficacy Endpoint 4: first occurrence of cardiovascular death including unknown death, MI, stroke or severe recurrent ischemia leading to hospitalization.
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: 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: Statistical significance is based on per-specified hierarchical testing procedure according to the protocol.
Note: ASA = Acetylsalicylic acid; Thieno = Thienopyridine; CABG = Coronary artery bypass grafting; MI = Myocardial infarction.

Primary efficacy endpoint events (composite of CV death, MI or stroke)

In All Strata, the effect of rivaroxaban 2.5 mg b.i.d. on the primary efficacy endpoint was largely driven by the reduction in CV deaths (HR: 0.66, 95% CI: 0.51, 0.86), including a numerical reduction in fatal MIs. The result in the 5 mg b.id group was primarily driven by a reduction in MIs, even though a small numerical reduction in CV deaths was observed in this group.

The described numerical inconsistencies between the two dose groups for the components of the composite efficacy endpoint have been extensively discussed in the responses to the CHMP LoQ:s. One explanation for the inconsistency observed provided by the MAH is that patients in the 5 mg bid dose group had more bleedings putting them at increased risk also for ischemic events. There is also some external support for such an association from other trials within this area

Further, for All Strata, the combined rivaroxaban doses were superior to placebo, in addition to standard care, in reducing the occurrence rate of primary efficacy endpoint events (i.e., composite of CV death, MI or stroke) in subjects with a recent ACS in the mITT analysis set (HR: 0.84, 95% CI: 0.74, 0.96; p=0.008).

Within Stratum 1 (ASA only) there was no statistically significant difference between any of the rivaroxaban dose groups vs. placebo. The relatively small number of patients on ASA only also precludes any firm conclusions on the efficacy to be expected in this subgroup, however, the overall trend for the composite primary endpoint was consistent with the overall results.

No reduction of the stroke incidence was seen and the differences for the other components of the primary endpoint was somewhat inconsistent between dose groups and strata as discussed further below.

As the high discontinuation rate with slightly imbalances between the groups was observed, a bias from risk differences between the treatment arms might have had an impact on the study outcome. Therefore, the MAH has provided comparisons of demographic and disease characteristics at time of randomisation and in those subjects included in the efficacy analysis.

The MAH, upon CHMP request, has performed extensive analyses on the patients that discontinued early and has also made efforts to retrieve vital data for these patients and in conclusion, the results supported the primary efficacy analysis.

Cardiovascular deaths

In all Strata, the combined rivaroxaban doses were superior to placebo in reducing the incidence of CV deaths (HR: 0.80, 95% CI: 0.65, 0.99; nominal p value=0.038). The incidence of CV death was 1.8% in the 2.5 mg b.i.d. group and 2.6% in the 5 mg b.i.d. group, compared with 2.8% in the placebo group. Rivaroxaban 2.5 mg b.i.d. was superior to placebo in reducing CV deaths (HR: 0.66, 95%CI: 0.51, 0.86; nominal p value=0.002); the incidence of CV deaths in the rivaroxaban 5 mg b.i.d. group was not significantly different compared with placebo (HR: 0.94, 95%CI 0.75, 1.20).

In Stratum 2, the results were consistent with those seen in All Strata. The combined rivaroxaban doses were superior to placebo in reducing the incidence of CV deaths (HR: 0.78, 95% CI: 0.63, 0.97; nominal p value=0.028). Notably, the largest reduction in CV deaths compared with placebo was observed in the 2.5 mg b.i.d. group (HR: 0.62, 95% CI: 0.47, 0.82; nominal p value=<0.001), while the incidence of CV deaths in the 5 mg b.i.d. and placebo groups were not significantly different (HR: 0.95, 95% CI 0.74, 1.21).

In All Strata, death due to MI in the 2.5 mg b.i.d. group was similar to that of placebo group (18 [0.4%] versus 23 [0.4%]) and was numerically higher in the 5 mg b.i.d. group (30 [0.6%]). CHF/cardiogenic shock as cause of death was lowest in the 2.5 mg b.i.d. group (8 [0.2%]), followed the placebo group (17 [0.3%]), and highest in the 5 mg b.i.d. group (19 [0.4%]).

The reduction in death observed in the 2.5 mg twice daily group was due to a reduction in sudden or un witnessed deaths and deaths due to congestive heart failure/ cardiogenic shock. In the 5 mg

twice daily group, no reduction was seen on death due to heart failure/ cardiogenic shock, and there was a higher number observed in the deaths due to MI and non-intracranial hemorrhagic deaths compared with placebo.

Bleeding-related causes of death, whether due to intracranial hemorrhage (ICH) or not, were balanced between the 2.5 mg b.i.d. group and placebo; however, extracranial hemorrhage as cause of death was numerically higher in the 5 mg b.i.d. group than that in placebo group (5/5115 versus 1/5113).

In conclusion, the 2.5 mg b.i.d dose showed a reduction in CV death, which was not shown with the 5 mg b.i.d dose.
The somewhat higher frequency in death due to CHF/cardiogenic shock, MI, and extracranial haemorrhage in the 5 mg b.i.d. group may have contributed to the diminished effect of the 5 mg b.i.d. dose on reducing CV death. In stratum 2 (ASA+Thienopyridine), there is a slight tendency to a higher number of deaths due to infection in the 5 mg group (0.2%) than in the 2.5 mg group (<0.1%) and the placebo group (<0.1%). The MAH has reviewed all available safety data on infection rates in clinical studies and the incidence rates of treatment-emergent adverse events in the System Organ Class Infections and Infestations were overall comparable between the rivaroxaban and the control group. In conclusion, there is no clear signal for increased infection rates.

Table E11 : Summary of Cardiovascular Deaths by Primary Cause

Subject Stratum: All Strata

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

Note: Percentages calculated with the number of subjects in each treatment group as denominator.
Note: Death events occur at or after randomization and the earliest date of the global treatment end date, 30 days after study drug was prematurely discontinued and 30 days after randomization for those subjects who were randomized but not treated.
Note: ASA = Acetylsalicylic acid; Thieno = Thienopyridine; CABG = Coronary artery bypass grafting.

Myocardial infarctions

In all Strata, 29 of the 179 (16.2%) subjects with MIs in the 5 mg b.i.d. group had a fatal outcome as reported by the investigators, compared to 16 of the 205 (7.8%) subjects with MIs in the 2.5 mg b.i.d. group and 18 of 229 (7.9%) in the placebo group. Similarly, in Stratum 2, 27 of the 169 (15.9%) subjects with MIs in the 5 mg b.i.d. group had a fatal outcome as reported by the investigators, compared to 15 of the 189 (7.9%) subjects with MIs in the 2.5 mg b.i.d. group and 18 of 207 (8.7%) in the placebo group.

A greater reduction in the incidence of MIs was observed with rivaroxaban 5 mg b.i.d. compared with the 2.5 mg b.i.d. dose; however, a numerically higher percentage of MIs in the 5 mg b.i.d. group were fatal.

It is striking that the frequency of MI with fatal outcome is approximately doubled when doubling the dose. However, the numbers are small and it is agreed with the MAH that these may have been due to chance.

Stroke

In All Strata and Stratum 2, subjects in rivaroxaban treatment groups had numerically more strokes than the placebo group. The incidence of stroke in All Strata was 0.9% in the 2.5 mg b.i.d. group and 1.1% in the 5 mg b.i.d. group, compared with 0.8% in the placebo group.

In Stratum 2, the results were similar to All Strata, with the lowest incidence occurring in the placebo group. The incidence of stroke was 0.9% in the 2.5 mg b.i.d. group and 1.0% in the 5 mg b.i.d. group, compared with 0.7% in the placebo group.

Interestingly, subjects in Stratum 1 treated with rivaroxaban 2.5 mg b.i.d had numerically fewer strokes (0.6% in the 2.5 mg b.i.d. group and 2.3% in the 5 mg b.i.d. group) compared with subjects in the placebo group (2.0%). However, the number of stroke events was small in both groups.

Secondary Efficacy endpoint Events 1 (composite of all-cause death, MI or stroke)

The secondary efficacy endpoint 1 events consisted of the composite of all-cause death, MI and stroke. For All Strata, both the 2.5 mg b.i.d. and the 5 mg b.i.d. doses of rivaroxaban were individually superior to placebo, in addition to standard care, in reducing the occurrence of Secondary Efficacy Endpoint 1 events (i.e., composite of all-cause death, MI or stroke).

In stratum 2, rivaroxaban 2.5 mg was superior to placebo in reducing the occurrence of Secondary Efficacy Endpoint 1 events. This was driven by a statistically significant reduction in all-cause mortality. Since rivaroxaban 5 mg b.i.d was not significantly different compared with placebo in the primary efficacy analysis, it was not formally tested in the secondary endpoint analyses.

However, in stratum 2 (ASA+Thienopyridine), there is a tendency to a higher number of deaths due to infection in the 5 mg group (0.2%) than in the 2.5 mg group (<0.1%) and the placebo group (<0.1%).

Table E12 : Summary of All Cause Deaths by Primary Cause (Stratum 2) (safety analysis set)

Subject Stratum: ASA + Thieno

	Rivaroxaban			
	2.5 mg BID (N=4772) n (%)	5 mg BID (N=4768) n (%)	Combined (N=9540) n (%)	Placebo (N=4773) n (%)
All Cause Death	126 (2.6)	178 (3.7)	304 (3.2)	181 (3.8)
Cardiovascular Deaths	102 (2.1)	147 (3.1)	249 (2.6)	153 (3.2)
Non-hemorrhagic stroke	1 (<0.1)	5 (0.1)	6 (0.1)	3 (0.1)
Intracranial hemorrhage	6 (0.1)	7 (0.1)	13 (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	11 (0.2)	24 (0.5)	35 (0.4)	17 (0.4)
Directly related to revascularization (CABG or PCI)	3 (0.1)	2 (<0.1)	5 (0.1)	4 (0.1)
Cardiac arrhythmia	1 (<0.1)	4 (0.1)	5 (0.1)	6 (0.1)
Pulmonary embolism	0	0	0	2 (<0.1)
Sudden or unwitnessed death	58 (1.2)	67 (1.4)	125 (1.3)	91 (1.9)
Hemorrhage, not intracranial	1 (<0.1)	5 (0.1)	6 (0.1)	1 (<0.1)
Myocardial infarction	20 (0.4)	30 (0.6)	50 (0.5)	22 (0.5)
Other vascular	0	0	0	0
Non-Cardiovascular Deaths	20 (0.4)	28 (0.6)	48 (0.5)	23 (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	15 (0.3)	12 (0.3)	27 (0.3)	13 (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	4 (0.1)	3 (0.1)	7 (0.1)	5 (0.1)

Secondary Efficacy endpoint Events 2 (composite of CV death, MI, ischemic stroke, or non-CABG TIMI major bleeding) = Net clinical outcome

For the net clinical outcome (the Secondary Efficacy Endpoint 2, defined as the composite of CV death, MI, ischemic stroke, or non-CABG TIMI major bleeding) neither the combined doses, the 2.5 mg b.i.d. nor the 5 mg b.i.d. dose of rivaroxaban significantly decreased the occurrence of events (in All Strata and Stratum 2) compared with placebo. The rate of non-CABG TIMI major bleeding was nominally significantly increased in all rivaroxaban groups (combined rivaroxaban: HR: 3.40, 95%CI: 2.19, 5.26; p<0.001; 2.5 mg b.i.d.: HR: 2.99, 95%CI: 1.86, 4.80; p<0.001; 5 mg b.i.d.: HR: 3.81, 95%CI: 2.40, 6.04; p<0.001).

As a result, the hierarchical testing for the rest of the secondary endpoints in All Strata was stopped.

Secondary Efficacy endpoint Events 3 and 4

Table E13 Effect of Rivaroxaban Compared With Placebo on Secondary Efficacy Endpoints

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

Note: The data shown are for all randomized subjects and the endpoint events occurring at or after randomization and the earliest date of the global treatment end date, 30 days after study drug was prematurely discontinued and 30 days after randomization for those subjects who were randomized but not treated.
Note: A subject could have more than one component event.
Note: n = number of subjects with events; N = number of subjects at risk; % = 100 * n / N.
Note: Dth/MI/St: first occurrence of all cause death, MI or stroke;
Net Clin. Outcome: first occurrence of cardiovascular death including unknown death, MI, ischemic stroke or TIMI major bleeding not associated with CABG surgery;
CV_Dth/MI/St/SRIR: first occurrence of cardiovascular death including unknown death, MI, stroke or severe recurrent ischemia requiring revascularization;
CV_Dth/MI/St/SRIH: first occurrence of cardiovascular death including unknown death, MI, stroke or severe recurrent ischemia leading to hospitalization;
NonCABG TIMI Maj.: TIMI major bleeding event not associated with CABG surgery;
SRI_Revas: severe recurrent ischemia requiring revascularization; SRI_Hosp: severe recurrent ischemia leading to hospitalization.
Note: HR (95% CI): Hazard ratios (95% confidence interval) as compared 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; MI = Myocardial infarction.

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

The additional secondary efficacy endpoints are the composite of CV death, MI, stroke, or severe recurrent ischemia requiring revascularization (SRIR) (Secondary Efficacy Endpoint 3) and the composite of CV death, MI, stroke, or severe recurrent ischemia leading to hospitalization (SRIH) (Secondary Efficacy Endpoint 4). Overall, rivaroxaban treatment did not reduce the occurrence of Secondary Efficacy Endpoint 3 events, but rivaroxaban 2.5 mg b.i.d. reduced the occurrence of Secondary Efficacy Endpoint 4 events compared with placebo, both in All Strata (HR: 0.84, 95% CI: 0.73, 0.96) and in Stratum 2 (HR: 0.85, 95% CI: 0.73, 0.98).

According to the pre-specified hierarchical testing strategy, if an individual test during any step was not statistically significant, further testing could continue but significance could not be claimed.

Due to the end of the pre-specified formal statistical testing on the secondary efficacy endpoints 3 and 4 according the SAP, it is not possible to draw further conclusion with respect to the results regarding these endpoints. Although the significant result for the 2.5 mg group (p<0.011, HR 0.85, 95%CI: 073, 0,98) is noted.

Stent thrombosis

For all CV deaths and cardiac ischemic events requiring adjudication, the possibility of stent thrombosis was assessed by ARC (Academic Research Consortium) definitions. In All Strata, 61 (1.2%) subjects in the rivaroxaban 2.5 mg b.i.d. group and 61 subjects (1.2%) in the 5 mg b.i.d. group had stent thrombosis defined as “definite”, “probable” or “possible” by ARC definitions, compared to 87 (1.7%) subjects in the placebo group. In Stratum 2, a similar reduction in stent thrombosis was observed in the rivaroxaban treatment groups compared with placebo. In the ITT-Total analysis set, the incidence of stent thrombosis observed in the 2.5 mg b.i.d. group (58 [1.2%]) was significantly lower than that observed with placebo (85 [1.8%]) (HR: 0.68, 95% CI: 0.49, 0.95). Similarly, in the 5 mg b.i.d. group, 60 (1.3%) subjects had stent thrombosis compared to 85 (1.8%) subjects in the placebo group (HR: 0.71, 95% CI: 0.51, 0.99).

Regarding the analyses of the occurrence of stent thrombosis the comparisons between rivaroxaban and placebo were post-hoc. It is agreed that nominally statistically significant difference have been showed. It is however not clear on what grounds it was decided not only to summarize this outcome but also to perform analyses comparing the rivaroxaban dose groups with the placebo group. These analyses were no part of the hierarchical testing procedure and hence, nor the initially planned confirmatory strategy. Formally this may be a false positive finding, and, strictly, no claims should be made as a part of the indication.

Clinical studies in special populations

There was no significant interaction in the primary efficacy endpoint results by region; subjects across all regions benefitted from treatment with rivaroxaban compared with placebo. The benefit of rivaroxaban was also consistently demonstrated irrespective of whether subjects had STEMI, NSTEMI or unstable angina as their index event. For further information, please see the clinical assessment report.

In the Follow-Up Scientific Advice dated 26 June 2008, it was also pointed out that standard treatment in ACS patients is very different depending if the patients are candidates for reperfusion therapy or not (fibrinolysis or a catheter-based treatment). It was also pointed out, that subgroup analysis should be performed based on the use of fibrinolytic, IIb-IIIa antagonist. Such analyses have been provided and the differences between the treatment groups are consistent with the overall efficacy findings.

From a biostatistical point of view, the conclusion of consistent treatment effect across subgroups in case of lack of significant treatment by subgroup interaction is not acceptable, because the study was not powered to show significant interactions. However, the consistency can be evaluated descriptively based on the provided hazard ratios for the subgroups.

Supportive study

No supportive study in addition to the ATLAS ACS TIMI 46 study has been provided.

2.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies

The design and the size of the clinical programme are judged to be largely adequate for an assessment of the efficacy to be expected in ACS patients at high risk for future cardiovascular events. The studies have been well performed. The included population, concomitant medication and background therapy seems to be essentially representative for a European ACS population although a somewhat low proportion of women (25%) is noted. However, the results in the subgroup of women was consistent with the overall results.

Efficacy data and additional analyses

From an efficacy perspective the choice of doses to be brought forward was not easily defined based on the dose-finding study. Actually, there was no indication of a reduction of the primary composite endpoint (all-cause death, MI, stroke, or severe recurrent ischemia) in stratum II (patients on a combination of ASA and thienopyridin) which can be regarded as the most relevant stratum in the current clinical setting. Of primary importance for dose selection were obviously the safety outcomes that seem to have formed the basis for the final decision of what doses to take forward to the phase III study.

Considering the efficacy results of all dose groups in the dose finding study twice daily dosing had a slightly larger reduction as compared to placebo than od dosing, the choice of the twice daily dosing appears reasonable, but is inconsistent with the approved dosing regimens for other indications. However, in light of the available clinical evidence, these differences in dosing intervals for the different indications can be accepted.

In the pivotal three-arm study, rivaroxaban 2.5 mg bid and 5 mg bid was compared to placebo in addition to standard care in patients with ACS after the initial treatment. The included population represents a population where treatment for cardiovascular disease was frequent already at baseline. In addition patients under the age of 55 were required to have diabetes or hypertension to be included.

Overall high rate of subjects who discontinued prematurely was observed. Premature discontinuation was more often observed in the rivaroxaban groups (all strata) than in the placebo group [28.2 % (n=2880/10225) for the combined riovaroxaban versus (26.4 % (n=1351/5125)].

The composite primary endpoint of cardiovascular death, myocardial infarction or stroke was reduced in the 2.5 mg bid group in the over-all population with event rates/100 patient-years of 7.04 vs. 5.92 (HR 0.84, 95% CI 0.72; 0.97, p=0.020) in the rivaroxaban and placebo groups respectively approximately corresponding to an absolute reduction of one percent events/year. The results were driven by stratum II (ASA and thienopyridin) as the proportion of patients in stratum 1 (only ASA for platelet inhibition) was small (6.8%), but where a consistent trend was observed.

In the 5 mg bid dose group a similar reduction was seen with event rates/100 patient-years of 7.04 vs 6.03 (HR 0.85; 95% CI 0.73, 0.98, p=0.028). Also these results were driven by stratum II.

The hazard ratios for stratum I were consistent with the overall results in both dose groups and actually numerically somewhat lower than in stratum II but as the proportion of patients treated with ASA only was small no firm conclusions can be drawn. It could, however, be speculated based

on the phase II and III study results that the additional benefit is larger if rivaroxaban is added to less intensive platelet inhibition.

In summary, the outcome with regard to the components of the primary efficacy end-point was inconsistent.

In All Strata, the effect of rivaroxaban 2.5 mg b.i.d. on the primary efficacy endpoint was largely driven by the reduction in CV deaths, including a reduction in fatal MIs. A numerical non-significant reduction in MIs reduction was noted in that dose group as compared to placebo, but no reduction of strokes was seen. Rather, a small numerical increase of strokes was observed.

In the 5 mg bid dose group no significant reduction of CV deaths in comparison with placebo was seen but rather a weak numerical trend. In this dose group the significant results were driven by a significant reduction of MIs. However, in All Strata as well as in Stratum 2, a higher percentage of MIs in the 5 mg b.i.d. group were fatal compared to the 2.5 mg b.i.d group and the placebo group.

All-cause deaths in the 2.5 mg b.i.d. group was reduced in consistency with the reduction of CV deaths (HR: 0.68, 95%CI: 0.53, 0.87, p=0.002). In the 5 mg bid group no such reduction was seen (HR 0.95; 0.76,1.19, p=0.662.

It is also noteworthy that the pre-defined net clinical outcome endpoint (Secondary Efficacy Endpoint 2 where primary efficacy results were balanced with TIMI major bleedings) did not improve with rivaroxaban treatment.

The most important finding in support for the proposed 2.5 mg bid rivaroxaban regimen is the reduction of all-cause deaths. The numerically inconsistency between the two dose groups with regard to the components of the composite primary endpoint has been extensively discussed and it is recognized that the trends observed are consistent. The MAH has also brought forward the explanation that the increased bleeding tendency in the 5 mg b.i.d dose group could partially explain the apparently less pronounced effect on mortality as compared with the 2.5 mg b.i.d. group. It is accepted that this explanation provided some external support. (see further discussion in the report).

Additional Expert consultation

Before reaching its final opinion, the CHMP asked the view of the Cardiovascular Scientific Advisory group (CV-SAG) in order to further discuss the benefit/risk in the targeted indication. The outcome of the CV-SAG consultation is mentioned below:

1. **Is the benefit shown for 2.5 mg rivaroxaban in the ATLAS studies regarding the composite primary endpoint (cardiovascular deaths, myocardial infarction or stroke) clinically relevant and large enough to balance the increase in bleedings observed in the pivotal study?**

The SAG was of the view that the benefit of 2.5 mg bid rivaroxaban with reference to the composite primary endpoint was relevant and sizable, and in the enrolled population outweighed the occurrence of clinically relevant bleedings. Nevertheless, as the enrolled population is not fully representative of the general European population of Patients with ACS and the bleeding risk of enrolled patients was not high, the real net benefit of its widespread use in the ACS population cannot be predicted based on the available data. In particular the patients in the trial were relatively young, with little co-morbidity when compared with other studies and European registries. In this regard, some specific points were raised and emphasised by the SAG:

a/ In Europe, the use of PCI is extensive. However, in ATLAS TIMI 51 only approximately 60% of the Patients underwent early PCI, and the absolute risk reduction with reference to

the primary endpoint was low in the subgroup of patients having undergone baseline PCI and consequently the benefit/risk balance remains questionable in these patients that have high a risk of bleeding.

b/ ATLAS TIMI 51 investigated only the association of rivaroxaban and either clopidogrel or ticlopidine. However, the benefit/risk profile of its association with newer anti-platelet agents Ticagrelor and Prasugrel has not been investigated and co-administration should therefore be avoided since it could possibly be harmful.

c/ In the currently proposed indication, rivaroxaban should not be used in patients with a platelet count of less than 90,000/µL, anaemia (i.e. haemoglobin level of less than 10 g/dL), a creatinine clearance of less than 30 mL/minute, clinically significant gastrointestinal bleeding within 12 months, or in patients with previous intracranial haemorrhage, stroke or transient ischaemic attack while already on aspirin and thienopyridines, since a positive benefit/risk profile in these conditions has not been demonstrated.

2. Is the increased bleeding risk, as reported in the ATLAS studies, manageable in daily practice where often patients with a relative high bleeding risk are being treated, in particular elderly patients and patients with comorbidities such as renal dysfunction?

The SAG was of the view that in ATLAS TIMI 51 bleeding risk was manageable although quite substantial (TIMI bleeding requiring medical attention: 12.9% in the 2.5 mg bid group vs. 7.5% in the placebo group). Further, the experts agreed that the management of bleedings should be possible also in a similar population in real clinical practice. However, concerning patients at higher risk of bleeding, with multiple complex co-morbidities (in particular renal dysfunction) and elderly patients, as these groups were underrepresented in the pivotal study, no information on the impact and management of bleeding can be derived from this study.

3. Is there a subset of ACS patients, where long term rivaroxaban in addition to aspirin and clopidogrel can be recommended in particular taking into account literature data (including data with other oral anticoagulants), clinical experience, results of the pivotal study and the MAH proposal for a target population?

Based on the data obtained with rivaroxaban in the ATLAS TIMI 51 study, the SAG members agreed that it is not possible to clearly define a subset of ACS patients that would benefit more from long-term rivaroxaban treatment in addition to aspirin and/or clopidogrel/ticlopidine. The decision for treatment has to be taken on an individual basis taking into account the absolute thrombotic risk and the specific bleeding risk of the individual patient.

Further, the SAG members were of the view that the use of markers of myocardial necrosis should be further validated by prospective evaluation before introduction as a guide for rivaroxaban treatment in ACS patients as proposed by the MAH.

CHMP discussion following the SAG consultation

The CHMP considered that a significant reduction of the primary composite endpoint events being consistent in the two dose groups had been demonstrated. A highly relevant reduction of CV-mortality and total mortality in the 2.5 mg bid dose group, corresponding to the dose recommended for approval.

With regards to bleeding complications, they are considered manageable in the vast majority of patients, although it is recognised that the patients included in the ATLAS TIMI51 study represented a group with lower risk of bleeding to what is anticipated in the daily practice.

Thus the representativeness of the study population of the EU population was extensively discussed given the low risk patients included in this study and the risk of bleeding anticipated to be higher when considering daily practice, older patients with more comorbidities.

It was however recognised that patients included in clinical trials are selected patients with lower risk and the ALTAS TIMI51 study in this respect could be considered comparable with other recent clinical studies in this population with acute coronary syndrome.

The external support for the efficacy of anticoagulant treatment in this population (support also when added to dual antiplatelet therapy) was discussed and several views considered.

Taking into account the APPRAISE1 dose finding study performed on apixaban and although limited data are available at present, it is considered that the concept to add a low dose of an anticoagulant to the antiplatelet therapy appears attractive in a selected group of patients and can be justified also from what is known of the pathogenetic mechanisms. The MAH provided also further clarification during the Oral Explanation regarding possible external support from other studies in term of population studied which helped to reinforced the issue related to external validity raised by the CHMP.

The problem has always been with regards to bleeding risks and it is noted that a clearly higher dose was used in the apixaban phase III study equivalent to the dose given in AF, bleeding outweighed the beneficial effects.

For rivaroxaban, two lower 2 doses were compared with placebo in a double blind manner and the dose proposed (2.5 bid) represents only one quarter of the dose approved in atrial fibrillation. It is also considered by the CHMP that the twice daily regimen is probably an additional advantage with the proposed regimen taking the PK characteristics into account.

As shown below, it is recognised that the results for the patients that underwent PCI were less impressive in absolute terms which has been discussed in the responses to the CHMP questions. However, the relative reduction in CV-mortality and all-cause mortality in this subgroup was consistent with the overall results.

For patients who underwent PCI and had elevated cardiac biomarkers who underwent PCI and had elevated cardiac biomarkers showed a nominally statistically significant reduction of CV death (HR 0.57; 95% CI: 0.34, 0.94; p = 0.027) and stent thrombosis (HR 0.64; 95% CI: 0.42, 0.96; p = 0.028) compared with reduction of CV death (HR 0.54; 95% CI: 0.33, 0.89; p = 0.013) and stent thrombosis (HR 0.64; 95% CI: 0.43, 0.95; p = 0.026) in the overall population.

Table 1-1 Effect of Rivaroxaban 2.5 mg bid on Primary Efficacy Endpoint, its components and stent thrombosis (Modified Intent-to-Treat (Excluding Sites 091001, 091019 and 091026)) for PCI patients, All Strata

	Subjects with PCI in overall study population				Subjects with PCI and with elevated biomarkers excl. prior stroke / TIA			
Subject Stratum	2.5 mg BID (N=3114)	Placebo (N=3096)	-- 2.5 mg BID vs. Placebo --		2.5 mg BID (N=2757)	Placebo (N=2759)	-- 2.5 mg BID vs. Placebo --	
Parameter	n(%)	n(%)	HR (95% CI)	Log-Rank P-value	n(%)	n(%)	HR (95% CI)	Log-Rank P-value
Primary	153 (4.9)	165 (5.3)	0.94 (0.75,1.17)	0.572	142 (5.2)	153 (5.5)	0.94 (0.75,1.18)	0.611
CV_Dth	24 (0.8)	45 (1.5)	0.54 (0.33,0.89)	0.013	23 (0.8)	41 (1.5)	0.57 (0.34,0.94)	0.027
MI	115 (3.7)	113 (3.6)	1.03 (0.79,1.33)	0.829	106 (3.8)	106 (3.8)	1.02 (0.78,1.33)	0.911
Stroke	27 (0.9)	21 (0.7)	1.30 (0.74,2.31)	0.360	24 (0.9)	18 (0.7)	1.36 (0.74,2.51)	0.320
Stent Thrombosis (definite, probable, possible)	40 (1.3)	63 (2.0)	0.64 (0.43,0.95)	0.026	38 (1.4)	60 (2.2)	0.64 (0.42, 0.96)	0.028

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 Cox proportional hazards model.
Note: Log-Rank P-value: P-values (two-sided) as compared to placebo arm are based on the stratified log rank test.

Table 1-2 Effect of Rivaroxaban 2.5 mg bid on Primary Safety Endpoint (Treatment-Emergent Safety) for PCI patients, All Strata

	Subjects with PCI in overall study population				Subjects with PCI and with elevated biomarkers excl. prior stroke / TIA			
Subject Stratum	2.5 mg BID (N=3076)	Placebo (N=3059)	-- 2.5 mg BID vs. Placebo --		2.5 mg BID (N=2725)	Placebo (N=2726)	-- 2.5 mg BID vs. Placebo --	
Parameter	n(%)	n(%)	HR (95% CI)	Log-Rank P-value	n(%)	n(%)	HR (95% CI)	Log-Rank P-value
Non-CABG TIMI major bleeding	52 (1.7)	16 (0.5)	3.30 (1.88,5.78)	<0.001	46 (1.7)	13 (0.5)	3.60 (1.95,6.67)	<0.001

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: HR (95% CI): Hazard ratios (95% confidence interval) as compared to placebo arm are based on the stratified Cox proportional hazards model.
Note: Log-Rank P-value: P-values (two-sided) as compared to placebo arm are based on the stratified log rank test.

In summary, the proportion of patients treated with ASA only (stratum 1) was small, thus no firm conclusions can be drawn for that stratum. It could, however, be speculated based on the hazard ratios observed in the phase II and III study results that the additional benefit is larger if rivaroxaban is added to less intensive platelet inhibition. Therefore, the CHMP considered reasonable and acceptable to include ACS patients treated with ASA only in the target population.

Considering the CV-SAG concerns raised related to the ad hoc retrospective analysis of elevated cardiac biomarkers and the recommendation for the proposed indication, the CHMP considering the published results with cardiac biomarkers and its use in practice was nevertheless further reassured and agreed with the MAH revised proposal for the use in the prevention of atherothrombotic events in adult patients after an acute coronary syndrome (ACS) with elevated cardiac biomarkers.

It is also emphasised that other platelet function inhibitors have been approved recently in ACS patients, e.g. ticagrelor that has an approved indication similar to the one now requested for rivaroxaban. Nothing can be said about the effects of adding rivaroxaban to such treatment.

2.5.4. Conclusions on the clinical efficacy

The reduction in the composite primary endpoint is judged to be sufficiently well demonstrated with consistent results in the two dose groups. The reduction of CV mortality and all cause mortality has been demonstrated in the 2.5 mg dose group which is the dose proposed for approval. The less impressive reduction of mortality in the 5 mg dose group could partly be explained by the higher bleeding rate in that dose group and it could partly be a chance finding in light of the overall results.

In summary the overall results appear sufficiently convincing in the targeted subgroup of patients after an acute coronary syndrome (ACS) with elevated cardiac biomarkers (post hoc analysis).

Summary of main study (study 13194)

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 2. Summary of Efficacy for trial 13194 ATLAS ACS 2 TIMI 51 Trial

Title: A Randomized, Double-Blind, Placebo-Controlled, Event-Driven Multicenter Study to Evaluate the Efficacy and Safety of Rivaroxaban in Subjects With a Recent Acute Coronary Syndrome The ATLAS ACS 2 TIMI 51 Trial (The Second Trial of Anti-Xa Therapy to Lower Cardiovascular Events in Addition to Standard Therapy in Subjects With Acute Coronary Syndrome)			
Study identifier	RIVAROXACS3001 (BAY59-7939/13194) EudraCT Number: 2008-002708-25		
Design	Randomized, double-blind, placebo-controlled, event-driven, multicenter study The study was conducted in 3 phases: a 6-day screening phase, a double-blind treatment phase, and a follow up phase. Two oral doses of rivaroxaban (2.5 mg twice daily and 5 mg twice daily) were studied in comparison with placebo twice daily (on top of ASA alone or ASA plus a thienopyridine (clopidogrel or ticlopidine)). Randomization was stratified by the intention to use thienopyridine (yes [Stratum 2] or no [Stratum 1]) as standard care, in addition to low-dose aspirin/acetylsalicylic acid (ASA) therapy (75 to 100 mg/day). Within each stratum, subjects were randomly assigned in a 1:1:1 ratio to receive rivaroxaban 2.5 mg twice daily, rivaroxaban 5 mg twice daily or placebo twice daily.		
	Duration of main phase:		Event driven; Across all treatment groups, more than 75% of subjects were exposed to study drug for ⩾6 months, more than half for ⩾12 months, and almost one-third were exposed for ⩾18 months; The median time on treatment was 13 months and overall treatment duration was up to 31 month.
Hypothesis	Superiority		
Treatments groups	All Strata		Rivaroxaban 2.5 mg BID. 5174 patients randomized Rivaroxaban 5.0 mg BID. 5176 patients randomized Rivaroxaban combined. 10350 patients randomized Placebo. 5176 patients randomized
	All Strata biomarker positive excl. prior stroke patients		Rivaroxaban 2.5 mg BID. 4142 patients randomized Rivaroxaban 5.0 mg BID. 4125 patients randomized Rivaroxaban combined. 8267 patients randomized Placebo. 4197 patients randomized
Endpoints and definitions	Primary endpoint	Primary Efficacy Endpoint	composite of cardiovascular death, MI or stroke (ischaemic and haemorrhagic)
	Secondary endpoint	Secondary Efficacy EP 1	composite of all cause death, MI or stroke (ischaemic and haemorrhagic)
		Secondary Efficacy EP2 (Net Clinical Outcome)	composite of cardiovascular death, MI, ischemic stroke or TIMI major bleeding not associated with CABG surgery

		Secondary Efficacy EP3	composite of cardiovascular death, MI, stroke (ischaemic and haemorrhagic) or severe recurrent ischemia requiring revascularization				
		Secondary Efficacy EP4	Composite of cardiovascular death, MI, stroke (ischaemic and haemorrhagic) or severe recurrent ischemia leading to hospitalization				
	Other endpoint	Primary safety endpoint	Non-CABG TIMI major bleeding				
Database lock	24 September 2011						
Results and Analysis							
Analysis description	**Primary Analysis**						
Analysis population and time point description	Modified Intent-to-Treat All randomized subjects (Excluding Sites 091001, 091019 and 091026) 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.						
Descriptive statistics and estimate variability		Treat-ment group	Rivaroxaban combined	Rivaroxaban 2.5 mg BID	Rivaroxaban 5.0 mg BID	Placebo	
	All Strata Pre-specified	Number of subjects	10229	5114	5115	5113	
		Primary Efficacy Endpoint	Incidence rate: 6.1%	Incidence rate: 6.1%	Incidence rate: 6.1%	Incidence rate: 7.4%	
	All Strata bio-marker positive excl. prior stroke patients Post-hoc	Number of subjects	8193	4104	4089	4160	
		Primary Efficacy EP	Incidence rate: 6.2%	Incidence rate: 6.2%	Incidence rate: 6.1%	Incidence rate: 7.9%	
Effect estimate per comparison	All Strata Pre-specified	Primary Efficacy Endpoint	Comparison groups	Rivaroxaban combined vs. Placebo	Rivaroxaban 2.5 mg BID vs. Placebo	Rivaroxaban 5.0 mg BID vs. Placebo	
			Hazard Ratio	0.84	0.84	0.85	
			95% CI	0.74 – 0.96	0.72 – 0.97	0.73 – 0.98	
			Log-Rank p-value	P = 0.008	P = 0.020	P = 0.028	
	All Strata bio-marker positive excl. prior stroke patients Post-hoc	Primary Efficacy Endpoint	Comparison groups	Rivaroxaban combined vs. Placebo	Rivaroxaban 2.5 mg BID vs. Placebo	Rivaroxaban 5.0 mg BID vs. Placebo	
			Hazard Ratio	0.79	0.80	0.79	
			95% CI	0.69 – 0.91	0.68 – 0.94	0.67 – 0.93	
			Log-Rank p-value	P = 0.001	P= 0.007	P = 0.004	
Analysis description	**Primary Analysis (components)**						
Analysis population and time point description	Modified Intent-to-Treat All randomized subjects (Excluding Sites 091001, 091019 and 091026) 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.						
Descriptive statistics and estimate variability		Treatment group	Rivaroxaban combined	Rivaroxaban 2.5 mg BID	Rivaroxaban 5 mg BID	Placebo	
	All Strata Pre-specified	Number of subjects	10229	5114	5115	5113	
		Cardiovascular death	Incidence rate: 2.2%	Incidence rate: 1.8%	Incidence rate: 2.6%	Incidence rate: 2.8%	
		MI	Incidence rate: 3.8%	Incidence rate: 4.0%	Incidence rate: 3.5%	Incidence rate: 4.5%	
		Stroke (ischaemic andhaemorrhagic)	Incidence rate: 1.0%	Incidence rate: 0.9%	Incidence rate: 1.1%	Incidence rate: 0.8%	
	All Strata bio-marker positive excl. prior stroke patients Post-hoc	Number of subjects	8193	4104	4089	4160	
		Cardiovascular death	Incidence rate: 2.1%	Incidence rate: 1.7%	Incidence rate: 2.6%	Incidence rate:3.1 %	
		MI	Incidence rate: 3.9%	Incidence rate:4.3%	Incidence rate: 3.6%	Incidence rate: 4.9%	

		Stroke (ischaemic andhaemorrhagic)	Incidence rate: 0.9%	Incidence rate:0.9%	Incidence rate: 0.9%	Incidence rate: 0.7%
Effect estimate per comparison	All Strata Pre-specified	Cardiovascular death	Comparison groups	Rivaroxaban combined vs. Placebo	Rivaroxaban 2.5 mg BID vs. Placebo	Rivaroxaban 5.0 mg BID vs. Placebo
			Hazard Ratio	0.80	0.66	0.94
			95% CI	0.65 – 0.99	0.51 – 0.86	0.75 – 1.20
			Log-Rank p-value	P = 0.038	P = 0.002	P = 0.633
		MI	Comparison groups	Rivaroxaban combined vs. Pbo	Rivaroxaban 2.5 mg BID vs. Pbo	Rivaroxaban 5.0 mg BID vs. Pbo
			Hazard Ratio	0.85	0.90	0.79
			95% CI	0.72 – 1.00	0.75 – 1.09	0.65 – 0.97
			Log-Rank p-value	P = 0.047	P = 0.270	P = 0.020
		Stroke (ischaemic and haemorrhagic)	Comparison groups	Rivaroxaban combined vs. Placebo	Rivaroxaban 2.5 mg BID vs. Placebo	Rivaroxaban 5.0 mg BID vs. Placebo
			Hazard Ratio	1.24	1.13	1.34
			95% CI	0.86 – 1.78	0.74 – 1.73	0.90 – 2.02
			Log-Rank p-value	P = 0.246	P = 0.562	P = 0.151
	All Strata bio-marker positive excl. prior stroke patients Post-hoc	Cardiovascular death	Comparison groups	Rivaroxaban combined vs. Placebo	Rivaroxaban 2.5 mg BID vs. Placebo	Rivaroxaban 5.0 mg BID vs. Placebo
			Hazard Ratio	0.72	0.55	0.89
			95% CI	0.57 – 0.90	0.41 – 0.74	0.69 – 1.15
			Log-Rank p-value	P = 0.004	P = <0.001	P = 0.360
		MI	Comparison groups	Rivaroxaban combined vs. Placebo	Rivaroxaban 2.5 mg BID vs. Placebo	Rivaroxaban 5.0 mg BID vs. Placebo
			Hazard Ratio	0.81	0.88	0.75
			95% CI	0.68 – 0.97	0.72 – 1.08	0.61 – 0.92
			Log-Rank p-value	P = 0.021	P = 0.215	P = 0.007
		Stroke (ischaemic and haemorrhagic)	Comparison groups	Rivaroxaban combined vs. Placebo	Rivaroxaban 2.5 mg BID vs. Placebo	Rivaroxaban 5.0 mg BID vs. Placebo
			Hazard Ratio	1.30	1.23	1.38
			95% CI	0.85 – 2.01	0.75 – 2.02	0.85 – 2.24
			Log-Rank p-value	P = 0.225	P = 0.403	P = 0.190
Analysis description	**Secondary Analyses**					
Analysis population and time point description	Modified Intent-to-Treat All randomized subjects (Excluding Sites 091001, 091019 and 091026) 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.					
Descriptive statistics and estimate variability		Treatment group	Rivaroxaban combined	Rivaroxaban 2.5 mg BID	Rivaroxaban 5.0 mg BID	Placebo
	All Strata Pre-specified	Number of subjects	10229	5114	5115	5113
		Secondary Efficacy Endpoint 1	Incidence rate: 6.3%	Incidence rate: 6.3%	Incidence rate:6.3%	Incidence rate:7.5%
		Secondary Efficacy Endpoint 2 (Net Clinical Outcome)	Incidence rate: 7.1%	Incidence rate: 7.1%	Incidence rate:7.2%	Incidence rate:7.6%
		Secondary Efficacy Endpoint 3	Incidence rate: 8.4%	Incidence rate: 8.5%	Incidence rate:8.2%	Incidence rate:9.4%

		Secondary Efficacy Endpoint 4	Incidence rate: 7.4%	Incidence rate: 7.3%	Incidence rate:7.6%	Incidence rate:8.7%
	All Strata biomarker positive excl. prior stroke patients Post-hoc	Number of subjects	8193	4104	4089	4160
		Secondary Efficacy Endpoint 1	Incidence rate: 6.3%	Incidence rate: 6.4%	Incidence rate: 6.2%	Incidence rate: 8.1%
		Secondary Efficacy Endpoint 2 (Net Clinical Outcome)	Incidence rate: 7.2%	Incidence rate: 7.2%	Incidence rate: 7.2%	Incidence rate: 8.1%
		Secondary Efficacy Endpoint 3	Incidence rate: 8.2%	Incidence rate: 8.5%	Incidence rate: 7.9%	Incidence rate: 9.8%
		Secondary Efficacy Endpoint 4	Incidence rate: 7.2%	Incidence rate: 7.1%	Incidence rate: 7.4%	Incidence rate: 8.9%
Effect estimate per comparison	All Strata Pre-specified	Secondary Efficacy Endpoint 1	Comparison groups	Rivaroxa-ban combined vs. Placebo	Rivaroxa-ban 2.5 mg BID vs. Placebo	Rivaroxa-ban 5.0 mg BID vs. Pbo
			Hazard Ratio	0.84	0.83	0.84
			95% CI	0.74 – 0.95	0.72 – 0.97	0.73 – 0.98
			Log-Rank pvalue	P = 0.006	P = 0.016	P = 0.025
		Secondary Efficacy Endpoint 2 (Net Clinical Outcome)	Comparison groups	Rivaroxaban combined vs. Placebo	Rivaroxaban 2.5 mg BID vs. Placebo	Rivaroxaban 5.0 mg BID vs. Placebo
			Hazard Ratio	0.94	0.93	0.95
			95% CI	0.83 – 1.06	0.81 – 1.07	0.83 – 1.10
			Log-Rank pvalue	P = 0.337	P = 0.320	P = 0.508
		Secondary Efficacy Endpoint 3	Comparison groups	Rivaroxaban combined vs. Placebo	Rivaroxaban 2.5 mg BID vs. Placebo	Rivaroxaban 5.0 mg BID vs. Placebo
			Hazard Ratio	0.90	0.92	0.89
			95% CI	0.81 – 1.01	0.80 – 1.04	0.78 – 1.01
			Log-Rank pvalue	P = 0.074	P = 0.185	P = 0.081
		Secondary Efficacy Endpoint 4	Comparison groups	Rivaroxaban combined vs. Placebo	Rivaroxaban 2.5 mg BID vs. Placebo	Rivaroxaban 5.0 mg BID vs. Placebo
			Hazard Ratio	0.86	0.84	0.88
			95% CI	0.76 – 0.97	0.73 – 0.96	0.77 – 1.01
			Log-Rank pvalue	P = 0.011	P = 0.011	P = 0.070
	All Strata biomarker positive excl. prior stroke patients Post-hoc	Secondary Efficacy Endpoint 1	Comparison groups	Rivaroxaban combined vs. Placebo	Rivaroxaban 2.5 mg BID vs. Placebo	Rivaroxaban 5.0 mg BID vs. Placebo
			Hazard Ratio	0.79	0.80	0.79
			95% CI	0.69 – 0.91	0.68 – 0.94	0.67 – 0.93
			Log-Rank pvalue	P = <0.001	P = 0.007	P = 0.004
		Secondary Efficacy Endpoint 2 (Net Clinical Outcome)	Comparison groups	Rivaroxaban combined vs. Placebo	Rivaroxaban 2.5 mg BID vs. Placebo	Rivaroxaban 5.0 mg BID vs. Placebo
			Hazard Ratio	0.90	0.90	0.90
			95% CI	0.78 – 1.03	0.77 – 1.05	0.77 – 1.05
			Log-Rank pvalue	P = 0.110	P = 0.166	P = 0.184
		Secondary Efficacy Endpoint 3	Comparison groups	Rivaroxaban combined vs. Placebo	Rivaroxaban 2.5 mg BID vs. Placebo	Rivaroxaban 5.0 mg BID vs. Placebo
			Hazard Ratio	0.84	0.87	0.81
			95% CI	0.75 – 0.95	0.76 – 1.01	0.70 – 0.94

			Log-Rank pvalue	P = 0.006	P = 0.059	P = 0.006
		Secondary Efficacy Endpoint 4	Comparison groups	Rivaroxaban combined vs. Placebo	Rivaroxaban 2.5 mg BID vs. Placebo	Rivaroxaban 5.0 mg BID vs. Placebo
			Hazard Ratio	0.82	0.80	0.84
			95% CI	0.72 – 0.93	0.68 – 0.93	0.72 – 0.98
			Log-Rank pvalue	P = 0.002	P = 0.004	P = 0.026
Analysis description	**Safety Analysis**					
Analysis population and time point description	Treatment–Emergent Safety 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.					
Descriptive statistics and estimate variability		Treatment group	Rivaroxaban combined	Rivaroxaban 2.5 mg BID	Rivaroxaban 5.0 mg BID	Placebo
	All Strata Pre-specified	Number of subjects	10225	5115	5110	5125
		Primary safety endpoint	Incidence rate: 1.4%	Incidence rate: 1.3%	Incidence rate:1.6%	Incidence rate: 0.4%
	All Strata biomarker positive excl. prior stroke patients Post-hoc	Number of subjects	8168	4096	4072	4157
		Primary safety endpoint	Incidence rate: 1.5%	Incidence rate: 1.3%	Incidence rate:1.6%	Incidence rate: 0.4%
Effect estimate per comparison	All Strata Pre-specified	Primary safety endpoint	Comparison groups	Rivaroxa-ban combined vs. Placebo	Rivaroxaban 2.5 mg BID vs. Placebo	Rivaroxaban 5.0 mg BID vs. Placebo
			Hazard Ratio	3.96	3.46	4.47
			95% CI	2.46 – 6.38	2.08 – 5.77	2.71 – 7.36
			Log-Rank p-value	P = <0.001	P = <0.001	P = <0.001
	All Strata biomarker positive excl. prior stroke patients Post-hoc	Primary safety endpoint	Comparison groups	Rivaroxaban combined vs. Placebo	Rivaroxaban 2.5 mg BID vs. Placebo	Rivaroxaban 5.0 mg BID vs. Placebo
			Hazard Ratio	3.91	3.44	4.40
			95% CI	2.32 – 6.59	1.97 – 6.01	2.55 – 7.60
			Log-Rank pvalue	P = <0.001	P = <0.001	P = <0.001

2.6. Clinical safety

Patient exposure

Overall exposure in ACS patients

The total rivaroxaban treated safety population in support of the ACS indication consisted of 15,350 subjects.

In the dose finding ATLAS ACS TIMI 46 a total of 3,491 subjects were randomized and received at least 1 dose of study drug. The mean treatment duration was 167 days and 158 days in the rivaroxaban 2.5 mg b.i.d. and 5 mg b.i.d. groups, respectively, and 164 days for the placebo group.

A total of 15,526 subjects were randomized in the pivotal ATLAS ACS 2 TIMI 51 study. The mean total duration of treatment for All Strata combined, was 396 days and 386 days in the rivaroxaban 2.5 mg b.i.d. and 5 mg b.i.d. groups, respectively, and 400 days in the placebo group.

In the pivotal ATLAS ACS 2 TIMI 51 study the time of exposure was as follows:

Table S1 Cumulative Duration of Treatment Including Any Study Drug Interruption (ATLAS ACS 2 TIMI 51 Study 13194) - Safety Analysis Set

	---------- Rivaroxaban ----------				
	2.5 mg BID (N=5115)	- 5 mg BID - (N=5110)	- Combined - (N=10225)	-- Placebo - (N=5125)	--- Total -- (N=15350)
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)

Adverse events

The primary safety endpoint in the Phase II Clinical ATLAS ACS TIMI 46 was the incidence bleeding events that were classified according to the TIMI scale as major, minor, or bleeding requiring medical attention

The overall bleeding rates in this study is summarised under the dose finding discussion above.

The incidence rates of non-bleeding adverse events in the phase II study, including treatment-emergent adverse events/SAEs, adverse events and serious adverse events with an onset greater than 2 days after discontinuation of study drug had similar patterns across treatment groups and strata.

In the pivotal phase III study 13194 safety was assessed by evaluation of adverse events, bleeding events, clinical laboratory tests including liver-related laboratory tests, electrocardiograms, vital signs, and physical examinations. Serious adverse events, adverse events leading to discontinuation of study drug, and adverse events of special interest were recorded in the case report form (CRF) and followed by the investigator throughout the study; other non serious adverse events were not routinely recorded in the CRF.

Adverse events of special interest were defined in the protocol as:

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

Three bleeding event scales were used. The TIMI scale was the primary bleeding scale for this study with categories of major, minor, requiring medical attention, and insignificant bleeding events. Two additional bleeding scales were used to provide additional information on bleeding. The ISTH major bleeding event classification has categories of major bleeding events, clinically relevant non-major bleeding events, and minimal bleeding events. Bleeding events associated with CABG were adjudicated independently with the TIMI, ISTH, or GUSTO scales in order to allow for more sensitive bleeding assessments since CABG surgery is associated with excessive transfused blood volume. For detailed definitions, see the clinical AR.

Hepatic Events

- Hepatic events meeting any of the selection criteria listed below were assessed by the Hepatic Event Assessment Committee (HEAC):
- Any ALT > 8xULN (includes symptomatic and asymptomatic cases)

- All deaths with ALT >3x ULN within 30 days of death
- Combined ALT >3xULN with Total bilirubin >2x ULN
- Concurrent elevations (concurrent refers to laboratory analyses drawn from the same sample)
- Non-concurrent elevations if the ALT elevation is followed by a Total bilirubin elevation within 30 days,
- Other (includes cases of possible concern not meeting any of the 3 categories listed above).

Visits occurred at screening, baseline, Weeks 4, 12, and then every 12 weeks thereafter for the duration of the double-blind treatment period until the specified number of primary efficacy endpoint events had been reached.

The overall incidences of treatment-emergent adverse events are given in the table below. With the exception of bleedings there were no differences in treatment emergent adverse events between the three groups.

Table S2. Treatment emergent adverse events in at least 1% of subjects in study 3001

Subject Stratum: All Strata				
	---------- Rivaroxaban ----------			
Body System Or Organ Class Preferred Term	2.5 mg BID (N=5115) n (%)	5 mg BID (N=5110) n (%)	Combined (N=10225) n (%)	Placebo (N=5125) n (%)
Total no. subjects with treatment-emergent adverse events	2769 (54.1)	2898 (56.7)	5667 (55.4)	2694 (52.6)
Cardiac Disorders	905 (17.7)	934 (18.3)	1839 (18.0)	973 (19.0)
Angina Pectoris	295 (5.8)	307 (6.0)	602 (5.9)	340 (6.6)
Angina Unstable	246 (4.8)	269 (5.3)	515 (5.0)	248 (4.8)
Acute Myocardial Infarction	94 (1.8)	91 (1.8)	185 (1.8)	114 (2.2)
Myocardial Infarction	66 (1.3)	59 (1.2)	125 (1.2)	68 (1.3)
Cardiac Failure	75 (1.5)	47 (0.9)	122 (1.2)	56 (1.1)
Atrial Fibrillation	60 (1.2)	56 (1.1)	116 (1.1)	68 (1.3)
Gastrointestinal Disorders	543 (10.6)	685 (13.4)	1228 (12.0)	478 (9.3)
Gingival Bleeding	104 (2.0)	192 (3.8)	296 (2.9)	63 (1.2)
Rectal Haemorrhage	63 (1.2)	59 (1.2)	122 (1.2)	41 (0.8)
Respiratory, Thoracic and Mediastinal Disorders	496 (9.7)	582 (11.4)	1078 (10.5)	387 (7.6)
Epistaxis	268 (5.2)	350 (6.8)	618 (6.0)	141 (2.8)
Cough	63 (1.2)	58 (1.1)	121 (1.2)	74 (1.4)
Dyspnoea	56 (1.1)	65 (1.3)	121 (1.2)	79 (1.5)
Surgical and Medical Procedures	497 (9.7)	448 (8.8)	945 (9.2)	450 (8.8)
Percutaneous Coronary Intervention	249 (4.9)	247 (4.8)	496 (4.9)	240 (4.7)
Coronary Artery Bypass	82 (1.6)	76 (1.5)	158 (1.5)	77 (1.5)
Coronary Revascularisation	61 (1.2)	47 (0.9)	108 (1.1)	46 (0.9)
General Disorders and Administration Site Conditions	374 (7.3)	410 (8.0)	784 (7.7)	389 (7.6)
Chest Pain	113 (2.2)	99 (1.9)	212 (2.1)	90 (1.8)
Non-Cardiac Chest Pain	86 (1.7)	98 (1.9)	184 (1.8)	99 (1.9)
Injury, Poisoning and Procedural Complications	290 (5.7)	356 (7.0)	646 (6.3)	225 (4.4)
Contusion	75 (1.5)	92 (1.8)	167 (1.6)	53 (1.0)
Vascular Disorders	297 (5.8)	318 (6.2)	615 (6.0)	291 (5.7)
Haematoma	103 (2.0)	125 (2.4)	228 (2.2)	79 (1.5)
Hypertension	86 (1.7)	59 (1.2)	145 (1.4)	75 (1.5)
Infections and Infestations	291 (5.7)	323 (6.3)	614 (6.0)	360 (7.0)
Nasopharyngitis	45 (0.9)	33 (0.6)	78 (0.8)	52 (1.0)
Skin and Subcutaneous Tissue Disorders	262 (5.1)	275 (5.4)	537 (5.3)	228 (4.4)
Ecchymosis	82 (1.6)	89 (1.7)	171 (1.7)	53 (1.0)

A higher incidence of discontinuation due to bleedings, primarily mucosal bleedings, was observed in the rivaroxaban groups.

Table S3 Treatment-emergent adverse events in study 3001 resulting in permanent discontinuation of study drug in at least 0.25 % of subjects in any treatment group in the safety analysis set

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

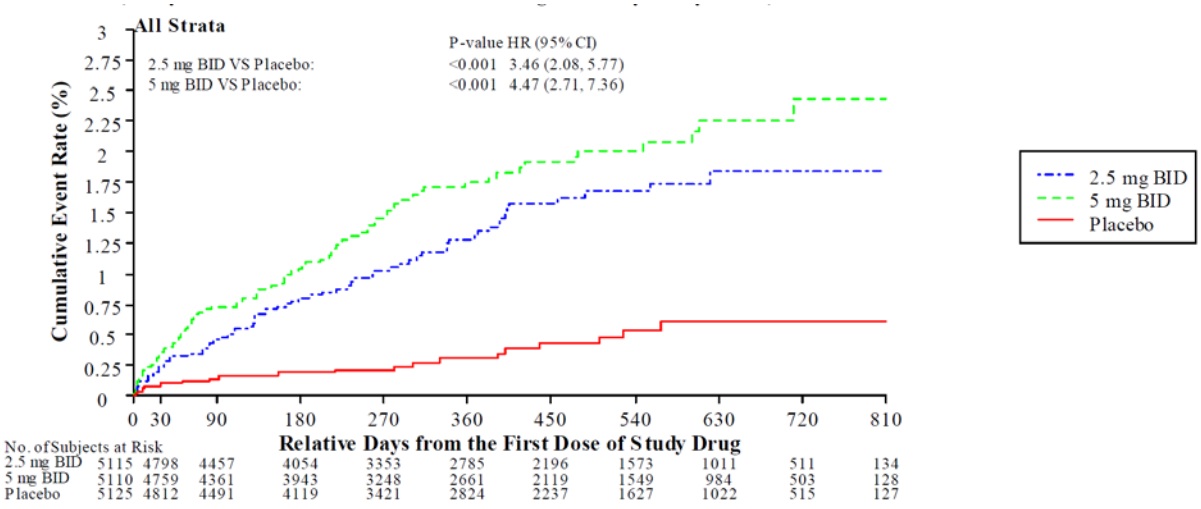
The primary safety endpoint, bleedings according to the TIMI scale, are given in the table below. As expected a dose response relationship with regard to all bleeding categories is observed. The hazard ratios for bleedings in comparison with placebo were higher for stratum 2 than for stratum 1 which could be due to more intense platelet function inhibition. Analyses of bleeding rates according to the two additional bleeding scales that were used gave similar results.

Table S4: Effect of Rivaroxaban Compared with Placebo on Treatment-Emergent Bleeding using TIMI scale as Adjudicate 51 Study 13194) - Safety Analysis Set)

Subject Stratum Parameter	Rivaroxaban 2.5 mg BID (N=5115) n(%)	Rivaroxaban 5 mg BID (N=5110) n(%)	Rivaroxaban Combined (N=10225) n(%)	Placebo (N=5125) 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-Ra P-valu
All Strata	5115	5110	10225	5125				
N-CABG TIMI Ma	65(1.3)	82(1.6)	147(1.4)	19(0.4)	3.46 (2.08,5.77)	<0.001	4.47 (2.71,7.36)	<0.001
Clinical Sig.	586(11.5)	748(14.6)	1334(13.0)	327(6.4)	1.84 (1.61,2.11)	<0.001	2.43 (2.13,2.76)	<0.001
TIMI Ma or Mi	100(2.0)	132(2.6)	232(2.3)	46(0.9)	2.20 (1.55,3.11)	<0.001	2.96 (2.12,4.14)	<0.001
TIMI Major	68(1.3)	85(1.7)	153(1.5)	27(0.5)	2.55 (1.63,3.98)	<0.001	3.25 (2.11,5.02)	<0.001
TIMI Minor	32(0.6)	49(1.0)	81(0.8)	20(0.4)	1.62 (0.92,2.82)	0.090	2.52 (1.50,4.24)	<0.001
TIMI Med. Attent.	492(9.6)	637(12.5)	1129(11.0)	282(5.5)	1.79 (1.55,2.07)	<0.001	2.39 (2.08,2.75)	<0.001
Stratum 1: ASA	343	342	685	352				
N-CABG TIMI Ma	2(0.6)	4(1.2)	6(0.9)	0		0.154		0.046
Clinical Sig.	19(5.5)	23(6.7)	42(6.1)	11(3.1)	1.77 (0.84,3.71)	0.128	2.10 (1.02,4.31)	0.038
TIMI Ma or Mi	3(0.9)	4(1.2)	7(1.0)	2(0.6)	1.53 (0.26,9.16)	0.638	2.00 (0.37,10.94)	0.413
TIMI Major	2(0.6)	4(1.2)	6(0.9)	2(0.6)	1.02 (0.14,7.22)	0.987	2.00 (0.37,10.94)	0.413
TIMI Minor	1(0.3)	0	1(0.1)	0		0.308		
TIMI Med. Attent.	16(4.7)	19(5.6)	35(5.1)	9(2.6)	1.82 (0.81,4.13)	0.144	2.13 (0.96,4.70)	0.056
Stratum 2: ASA + Thieno	4772	4768	9540	4773				
N-CABG TIMI Ma	63(1.3)	78(1.6)	141(1.5)	19(0.4)	3.35 (2.01,5.60)	<0.001	4.26 (2.58,7.03)	<0.001
Clinical Sig.	567(11.9)	725(15.2)	1292(13.5)	316(6.6)	1.84 (1.61,2.12)	<0.001	2.44 (2.14,2.78)	<0.001
TIMI Ma or Mi	97(2.0)	128(2.7)	225(2.4)	44(0.9)	2.23 (1.56,3.18)	<0.001	3.01 (2.13,4.23)	<0.001
TIMI Major	66(1.4)	81(1.7)	147(1.5)	25(0.5)	2.67 (1.68,4.23)	<0.001	3.35 (2.14,5.25)	<0.001
TIMI Minor	31(0.6)	49(1.0)	80(0.8)	20(0.4)	1.56 (0.89,2.74)	0.116	2.52 (1.50,4.24)	<0.001
TIMI Med. Attent.	476(10.0)	618(13.0)	1094(11.5)	273(5.7)	1.79 (1.54,2.07)	<0.001	2.40 (2.08,2.77)	<0.001

Note: The data shown are for all subjects who received at least one dose of study drug and the endpoint events occurring betwee study drug administration and 2 days after the last study drug administration, inclusive.
Note: A subject could have more than one component event.

Fig S1 Kaplan-Meier Estimates of First Occurrence of Treatment-Emergent Non-CABG-Related TIMI Major Bleeding Events as Adjudicated by the CEC (Study 13194) - Safety Analysis Set



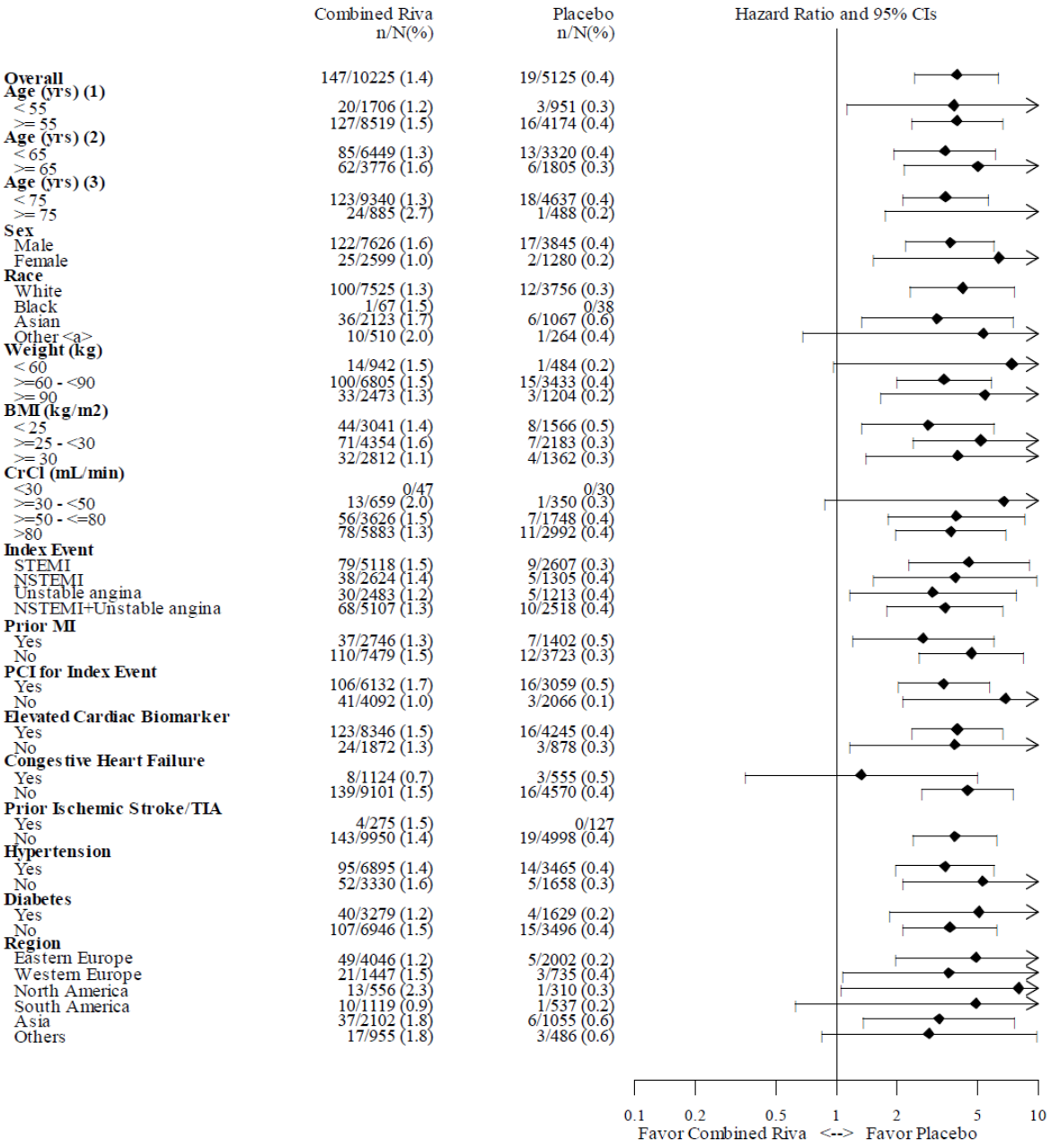
The most frequently reported sites of treatment-emergent TIMI major bleeding were gastrointestinal and intracranial. See Table S5.

Table S5 Treatment emergent TIMI major bleedings by location reported by the CEC (study

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

The increased bleeding rates in among the rivaroxaban treated patients were consistent over different subgroups, Fig S2.

Fig S2 Hazard ratios and rates of first occurrence of non-CABG related TIMI major bleeding events by subgroup for combined rivaroxaban dose groups compared with placebo, study 3001



The hepatic laboratory and clinical adverse events were carefully recorded and in line with the clinical studies in other indications no increased risk could be found among the rivaroxaban treated patients.

Liver-Related Laboratory Values

In All Strata, ALT, AST and total bilirubin post baseline and treatment emergent values >3x ULN were balanced across the 2.5 mg b.i.d. and 5 mg b.i.d. rivaroxaban and placebo groups (post baseline ALT: >3x ULN combined rivaroxaban 136 [1.4%], placebo 73 [1.5%]; treatment emergent ALT >3x ULN: combined rivaroxaban 92 [1.1%], placebo 49 [1.1%]). Balance between treatment groups was also seen at higher ALT levels of >5x, 8x, 10x and 20x ULN.

Based on central laboratory data, means and mean changes from baseline over time for ALT AST, Total (Direct, Indirect) Bilirubin and Alkaline Phosphatase were similar across the treatment groups.

Hepatic Disorder Serious Adverse Events

There were no liver-related deaths considered to be associated with study drug observed in this study.

The incidence of hepatic disorder treatment emergent serious adverse events was 0.8% (combined rivaroxaban 83/10225, placebo 40/5125) in both the combined rivaroxaban and placebo treatment groups.

A total of 92 liver events in 90 subjects were identified and sent for HEAC review.

There were no cases with a majority probable causality assessment based on the composite criteria causality assessment by the HEAC.

Clinical Laboratory Evaluation

Overall there were no noteworthy changes in clinical laboratory test results between any of the rivaroxaban dose groups or placebo. Creatinine, haemoglobin, WBC, platelet numbers, alkaline phosphatises were followed in the majority of patients.

Serious adverse events and deaths

Treatment-emergent serious adverse events occurred at similar rates in the three treatment groups, see table below.

Treatment emergent serious adverse events in at least 1% of subjects, study 3001

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

The table below presents the all cause deaths.

Table **Summary of All Cause Deaths by Primary Cause as Adjudicated by the CEC (ATLAS ACS 2 TIMI 51 Study 13194) - 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)
Sudden or unwitnessed death	69 (1.3)	74 (1.4)	143 (1.4)	96 (1.9)
Myocardial infarction	22 (0.4)	34 (0.7)	56 (0.5)	23 (0.4)
Congestive heart failure / cardiogenic shock	12 (0.2)	27 (0.5)	39 (0.4)	19 (0.4)
Intracranial hemorrhage	7 (0.1)	7 (0.1)	14 (0.1)	6 (0.1)
Non-hemorrhagic stroke	2 (<0.1)	5 (0.1)	7 (0.1)	4 (0.1)
Hemorrhage, not intracranial	1 (<0.1)	5 (0.1)	6 (0.1)	1 (<0.1)
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)
Atherosclerotic vascular disease (excluding coronary)	1 (<0.1)	3 (0.1)	4 (<0.1)	1 (<0.1)
Pulmonary embolism	0	0	0	3 (0.1)
Dysrhythmia	0	0	0	0
Other vascular	0	0	0	0
Non-cardiovascular deaths	22 (0.4)	29 (0.6)	51 (0.5)	24 (0.5)
Malignancy	17 (0.3)	13 (0.3)	30 (0.3)	14 (0.3)
Infection	2 (<0.1)	10 (0.2)	12 (0.1)	2 (<0.1)
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)
Suicide	0	1 (<0.1)	1 (<0.1)	1 (<0.1)
Other non-vascular	0	1 (<0.1)	1 (<0.1)	0
Liver failure	0	0	0	0
Renal failure	0	0	0	1 (<0.1)
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.

2.6.1. Discussion on clinical safety

In terms of number of patients the exposure of rivaroxaban in the proposed indication is considered sufficient for a qualified assessment of the safety characteristics of the proposed regimen. The incidences of non-bleeding adverse events were similar in the rivaroxaban groups as compared to placebo and there were no signals for an increased incidence of non-bleeding hepatic, renal, laboratory adverse events which is in line with earlier experience in other indications. The primary safety end-point, TIMI major bleeding was higher in the rivaroxaban 2.5 mg bid group as compared to placebo with a hazard ratio of 3.46 (95% CI; 2.1, 5.8) corresponding to an absolute rate of 1.3% compared with 0.4% or approximately an increase of 1%. The corresponding figures for the 5 mg bid dose group was an HR of 4.47 (95% CI; 2.7, 7.4) or approximately an increase of 1.2% from 0.4 % to 1.6%. Increased bleeding rates in the acute clinical setting have been shown to have major impact on the long-term risk for cardiovascular complications in ACS patients. However, the data provided by the MAH demonstrate that the benefit obtained seem to persist over time during the follow up. Fatal bleeding events or total mortality was not increased in the 2.5 mg group as compared with placebo during the study observation period.

It is highlighted that clinically relevant haemorrhage at critical sites including intracranial bleedings with potential long-term consequences of long-term functional incapacity is of concern but it is considered to be adequately addressed in the SmPC (section 4.4). However, the bleeding pattern is consistent with what has been shown for rivaroxaban in other indications with a large proportion of mucosal bleedings.

In summary, the long-term cardiovascular consequences of the clearly increased bleeding rates when rivaroxaban is added to platelet function inhibitors for secondary cardiovascular prophylaxis in ACS patients are of concern and these uncertainties must be taken into account in the overall benefit/risk evaluation.

Upon CHMP request, the MAH proposed a post marketing non-interventional study (XA 1301/16773) of Xarelto in combination with antiplatelet therapy or standard dual antiplatelet therapy for secondary prevention of major cardiovascular events in patients with acute coronary syndrome (ACS) with elevated cardiac biomarkers.

11,000 patients are planned for enrollment and the study would end 12 months after enrollment of the last patient. This study will provide further information on the use of rivaroxaban in routine clinical practice especially in elderly patients and in patients with co-morbidities. This is particularly important in view of the limited external data supporting the use of anticoagulants on top of antiplatelet agents.

2.6.2. Conclusions on the clinical safety

In summary the exposure of rivaroxaban in the proposed indication is considered sufficient for assessment of the safety characteristics of the proposed regimen. The incidences of non-bleeding adverse events were similar in the rivaroxaban groups as compared to placebo and there were no signals for an increased incidence of non-bleeding hepatic, renal, laboratory adverse events which is in line with earlier experience in other indications.

In summary, the long-term cardiovascular consequences of the clearly increased bleeding rates when rivaroxaban is added to platelet function inhibitors for secondary cardiovascular prophylaxis in ACS patients are of concern and must be taken into account in the overall benefit/risk evaluation.

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics.

The CHMP considered the need for update of the PSUR cycle as a result of the approval of this new indication. Thus the MAH should submit 6 monthly PSURs and then follow the standard PSUR cycle as set out in the EURD list.

The post marketing non-interventional study (XA 1301/16773) will provide further information on the use of rivaroxaban in routine clinical practice especially in elderly patients and in patients with co-morbidities. Given the limited external data supporting the use of anticoagulants on top of antiplatelet agents, this study is considered key to monitor the benefit/risk in the post authorization setting and will provide further support to the daily use of rivaroxaban to adequately monitor the benefit risk in daily practice, through regular interim analysis reports provided on a yearly basis and at specified milestones (such as 5000 patients followed for at least 3 months). Thus, this post authorization study is a condition to the marketing authorisation in this new indication.

2.7 Pharmacovigilance

Detailed description of the pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the MAH fulfils the legislative requirements and provides adequate evidence that the MAH has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

Risk management plan

Summary of the risk management plan (updated version 7.10):

Safety issues	Agreed pharmacovigilance activities (routine and additional)	Agreed risk minimization activities (routine and additional)
Important identified risks		
Haemorrhage	Routine pharmacovigilance activities Additional information from clinical trials Drug utilization and specific outcome studies Modified Prescription Event Monitoring Study Specialist Cohort Event Monitoring Studies Post-marketing non-interventional cohort studies (XALIA/15915, XANTUS/15914, XA 1301/ 16773) Prescriber/patient surveys will be performed in order to measure effectiveness of additional risk minimization activities	Contraindication in SmPC section 4.3 "*Contraindication*" Warning in SmPC section 4.4 "*Special warnings and precautions for use*" Warning in SmPC section 4.5 "*Interaction with other medicinal products and other forms of interactions*" • Cyp 3A4 and P-gp inhibitors • Anticoagulants • NSAIDS/platelet aggregation inhibitor • Warfarin Haemorrhage is listed in SmPC section 4.8 "*Undesirable effect*" Additional Risk Minimisation Activities for DVT-T, PE-T, SPAF and ACS • Prescriber Guide • Patient Alert Card
Important potential risks		
Embryo-fetal toxicity	Routine pharmacovigilance activities Drug utilization database studies Drug utilization and specific outcome studies Modified Prescription Event Monitoring Study Specialist Cohort Event Monitoring Studies Post-marketing non-interventional cohort studies (XALIA/15915, XANTUS/15914)	SmPC section 4.3 "*Contraindication*" SmPC section 4.6 "*Fertility, pregnancy, and breast feeding*"
Important missing information		
Patients undergoing major orthopaedic surgery other than elective hip or knee replacement surgery	Routine pharmacovigilance activities Drug utilization database studies	SmPC (10 mg) section 4.1 "*Therapeutic indications*" and section 4.4. "*Special warnings and precautions for use*"
Patients with severe renal impairment (CrCl < 30 mL/min	Routine pharmacovigilance activities Drug utilization and specific outcome studies Modified Prescription Event Monitoring	SmPC section 4.2 "*Posology and method of administration*" (Renal impairment) and section

Safety issues	Agreed pharmacovigilance activities (routine and additional)	Agreed risk minimization activities (routine and additional)
	Study Specialist Cohort Event Monitoring Studies Post-marketing non-interventional cohort studies (XALIA/15915, XANTUS/15914, XA 1301/ 16773)	4.4 "*Special warnings and precaution for use*" (Renal impairment)
Remedial procoagulant therapy for excessive haemorrhage	Routine pharmacovigilance activities Additional information from clinical trials Post-marketing non-interventional cohort studies (XALIA/15915, XANTUS/15914, XA 1301/ 16773)	SmPC section 4.9 "*Overdose*"
Patients receiving systemic treatment with Cyp3A4 and P-gp inhibitors other than azole antimycotics (e.g. ketoconazole) and HIV-protease inhibitors (e.g. ritonavir)	Routine pharmacovigilance activities Drug utilization and specific outcome studies Modified Prescription Event Monitoring Study Specialist Cohort Event Monitoring Studies Post-marketing non-interventional cohort studies (XALIA/15915, XANTUS/15914, XA 1301/ 16773)	SmPC section 4.5 "*Interaction with other medicinal products and other forms of interaction*"
Pregnant or breast-feeding women	Routine pharmacovigilance activities Drug utilization and specific outcome studies Modified Prescription Event Monitoring Study Specialist Cohort Event Monitoring studies Post-marketing non-interventional cohort studies (XALIA/15915, XANTUS/15914)	SmPC section 4.3 "*Contraindication*" SmPC section 4.6 "*Fertility, pregnancy and breast feeding*"
Patients with AF and prosthetic valve	Routine pharmacovigilance activities	SmPC (15/20 mg) section 4.4 "Special warnings and precaution for use" (Patients with prosthetic valves)
Long-term therapy for treatment of DVT, PE, SPAF and ACS in real-life setting	Routine pharmacovigilance activities Drug utilization and specific outcome studies Modified Prescription Event Monitoring Study Specialist Cohort Event Monitoring Studies For DVT-T. SPAF, and ACS: Post-marketing non-interventional cohort studies (XALIA/15915, XANTUS/15914 , XA 1301/ 16773)	All safety concerns mentioned in this chapter which may occur during long-term therapy in a real-life setting for treatment of DVT, PE, SPAF and ACS indications are addressed in the SmPC in the relevant sections
Patients with significant liver diseases (severe hepatic impairment/Child Pugh C)	Routine pharmacovigilance activities Drug utilization and specific outcome studies Modified Prescription Event Monitoring Study Specialist Cohort Event Monitoring Studies For DVT-T, SPAF, and ACS: Post-marketing non-interventional cohort studies (XALIA/15915, XANTUS/15914, XA 1301/ 16773)	Section 4.2 Posology and method of administration "Hepatic impairment" Section 4.3 "*Contraindication*"
Patients < 18 years	Routine pharmacovigilance activities Additional information from clinical trials (For 'Treatment of thromboembolic events': PIP EMEA-000430-PIP01-08-M03) Drug utilization and specific outcome studies Modified Prescription Event Monitoring Study Specialist Cohort Event Monitoring Studies	SmPC section 4.2 "*Posology and method of administration*" (Paediatric population)

The RMP has been updated (version 7.10) to include the new proposed indication of ACS [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)].

Upon CHMP request, the MAH has proposed a post marketing non-interventional study (XA 1301/16773), of Xarelto in combination with antiplatelet therapy or standard dual antiplatelet therapy for secondary prevention of major cardiovascular events in patients with acute coronary syndrome (ACS) with elevated cardiac biomarkers. 11,000 patients are planned for enrollment, and the study would end 12 months after enrollment of the last patient.
As discussed above, this study is considered of key importance to continue monitoring the use of xarelto in this new indication. Regular interim analysis are planned with yearly reporting and additional reporting after 5000 patients prior to final study report is submitted.

The MAH should ensure that the sample is collected as quickly as possible (e.g. by including more centers from various countries) and within the agreed timelines.

A study concept has been included in the updated RMP. The concept submitted is endorsed provided that an updated protocol is submitted by June 2013 for final review.

This PASS should be a condition of Marketing Authorisation and therefore is to be inserted in Annex II of the RMP. The RMP has been be updated in line with the CHMP requests.

The ongoing risk minimisation activities aimed at increasing awareness about the potential risk of bleeding during treatment with Xarelto and providing guidance on how to manage that risk are extended to the new proposed indication in order to target all physicians and patients who are expected to prescribe/use Xarelto.

3. BENEFIT RISK ASSESSMENT

Benefits

Beneficial effects

The design and the size of the clinical programme are considered to be adequate for an assessment of the efficacy to be expected in Acute Coronary Syndrome patients with the proposed dose regimen. The large pivotal three arm study had an attractive design comparing two doses of rivaroxaban against placebo and it is considered well performed.

From an efficacy perspective, the choice of doses was not easily defined based on the dose-finding study (ATLAS ACS TIMI 46). Actually, there was no indication of a reduction of the primary composite endpoint (all-cause death, MI, stroke, or severe recurrent ischemia) in stratum II (patients on a combination of ASA and thienopyridin) which can be regarded as the most relevant stratum in the current clinical setting. Of primary importance for dose selection were obviously the safety outcomes that have formed the basis for the final decision of what doses to take forward to the phase III study (2.5mg and 5 mg).

Considering the efficacy results of all dose groups in the dose finding study, twice daily dosing showed a non-significant trend for a larger reduction as compared to placebo than once daily dosing. Based on the phase II study, the choice of the twice daily dosing appears reasonable, but is inconsistent with the dosing frequency for other approved indications. A bid regimen was also considered by the MAH to be potentially safer in the target population expected to have a comparatively high bleeding tendency.

In the pivotal study, three-arm rivaroxaban 2.5 mg bid and 5 mg bid was compared to placebo in addition to standard care in patients with ACS after the initial treatment. The included population, concomitant medication and background therapy seems to be essentially representative for a European ACS population although a somewhat low proportion of women (25%) is noted. However, the results in the subgroup of women was consistent with the overall results.

The composite primary endpoint of cardiovascular death, myocardial infarction or stroke was reduced in the 2.5 mg bid group in the over-all population with event rates/100 patient-years of 7.04 vs. 5.92 (HR 0.84, 95% CI 0.72; 0.97, p=0.020) in the rivaroxaban and placebo groups respectively approximately corresponding to an absolute reduction of one percent events/year. The results were driven by stratum II (ASA and thienopyridin) as the proportion of patients in stratum 1 (only ASA for platelet inhibition) was small (6.8%), but where a consistent trend was observed.

In the 5 mg bid dose group a similar reduction was seen with event rates/100 patient-years of 7.04 vs 6.03 (HR 0.85; 95% CI 0.73, 0.98, p=0.028). Also these results were driven by stratum II.

As the proportion of patients treated with ASA only (stratum 1) was small, no firm conclusions can be drawn for that stratum. It could, however, be speculated based on the hazard ratios observed in the phase II and III study results that the additional benefit is larger if rivaroxaban is added to less intensive platelet inhibition. Based on the data submitted, the CV-SAG recommendation and further discussion with the MAH during the oral explanation, it is finally considered acceptable to approve Xarelto for patients with ASA only and taking into account the more restricted indication in patients with elevated cardiac biomarkers.

The effect of rivaroxaban 2.5 mg b.i.d. on the primary efficacy endpoint was largely driven by the reduction in CV deaths, including a reduction in fatal MIs. A numerical non-significant reduction in MIs was noted in that dose group as compared to placebo, but no reduction of strokes was seen. On the contrary, a small numerical increase of stroke rate was observed.

In the 5 mg bid dose group no significant reduction of CV deaths in comparison with placebo was seen but rather a weak numerical trend. In this dose group the significant results were driven by a significant reduction of MIs.

In conclusion, the observed numerical differences between the dose groups for the components of the composite endpoints have been sufficiently well explained by the MAH.

All-cause deaths in the 2.5 mg b.i.d. group was reduced in consistency with the reduction of CV deaths (HR: 0.68, 95%CI: 0.53, 0.87, p=0.002). In the 5 mg bid group no such reduction was seen (HR 0.95; 0.76, 1.19, p=0.662).

It is also noteworthy that the pre-defined net clinical outcome endpoint (Secondary Efficacy Endpoint 2 where primary efficacy results were balanced with TIMI major bleedings) did not improve with rivaroxaban treatment.

Uncertainty in the knowledge about the beneficial effects

The addition of an anticoagulant to antiplatelet therapy for long term treatment after an ACS event has external support with regard to a reduction of cardiovascular ischemic events but these benefits has been outweighed by an increased bleeding tendency. Thus the external support for a positive benefit/risk balance for the proposed regimen where an anticoagulant is added to dual antiplatelet therapy is difficult in this proposed indication. This application is essentially supported by one pivotal study in a controversial area where other studies have failed. Thus the confirmatory study has to be compelling and the robustness of the findings has been challenged during the assessment. However, in light of the sensitivity analyses performed, the consistency of the primary efficacy endpoint between the two dose groups, and the external support for a reduction in ischemic events by the proposed strategy, the CHMP accepted that a reduction of the primary composite end-point has been demonstrated.

Of all randomised patients (n=15526) 500 (3.2%) had died, 13728 (88,4%) were alive and for 1298 (8.4%) vital status was unknown at the global treatment end day. When baseline parameters judged to be of prognostic relevance were compared the group with missing data was more similar with the group of survivors than with those that died. It is however difficult to if establish if events during or after the acute ACS episode may have rendered the patients with missing data to be at higher risk. In order to reverse the overall primary efficacy results to being non-significant for stratum 2 in the 2.5 mg group the incidence rate in the group with missing data would need to increase from 5.6% in the patients followed to 8.7% in those with missing data. Such a difference is not considered to be plausible. Furthermore, the retrieved vital data of patients that had discontinued the trial prematurely provided further reassurance.

The stroke rates were numerically increased among the rivaroxaban treated patients, primarily due to an increase in haemorrhagic strokes. Patients with an earlier history of TIA or stroke were not to be included in stratum II and there is a clear indication that treatment may be harmful with regard to risk for recurrent stroke in such patients. It should be recognised that earlier episodes of TIA are often difficult to establish retrospectively. However the exclusion of patients with stroke/TIA from the target population has been appropriately addressed in the SPC.

The MAH has accepted to not include a claim for a reduction of stent thrombosis in SPC section 4.1. However it accepted that they are included in section 5.1 together with the overall results in the important subgroup of patients who underwent PCI for the primary ACS-event.

The results for the primary composite end-point in the subgroup of patients that underwent PCI were less impressive which has been discussed in the responses to the CHMP questions. However, the reduction in CV-mortality and all-cause mortality in that subgroup was consistent with the overall results. A summary of the efficacy outcome data as well as bleeding incidences in the patients with elevated biomarkers who underwent PCI was also provided.

It is noteworthy that other platelet function inhibitors have been approved recently in ACS patients, e.g. ticagrelor that has an approved indication similar to the one now requested for rivaroxaban. Nothing can be said about the effects of adding rivaroxaban to such treatment.

Risks

Unfavourable effects

In terms of number of patients the exposure of rivaroxaban in the proposed indication is considered sufficient for a qualified assessment of the safety characteristics of the proposed regimen.

The incidences of non-bleeding adverse events were similar in the rivaroxaban groups as compared to placebo and there were no signals for an increased incidence of non-bleeding hepatic, renal, laboratory adverse events which is in line with earlier experience in other indications.

The bleeding pattern is consistent with what has been shown for rivaroxaban in other indications with a large proportion of mucosal bleedings.

The primary safety end-point, TIMI major bleeding was higher in the rivaroxaban 2.5 mg bid group as compared to placebo with a hazard ratio of 3.46 (95% CI; 2.1, 5.8) corresponding to an absolute rate of 1.3% compared with 0.4% or approximately an increase of 1%. The corresponding figures for the 5 mg bid dose group was an HR of 4.47 (95% CI; 2.7, 7.4) or approximately an increase of 1.2% from 0.4 % to 1.6%. In a Kaplan-Meier analysis the risk for a clinically significant bleeding was 11.6% in the rivaroxaban 2.5 mg big group, 15.3% in the 5 mg bid group and 6.3% in the placebo group. Furthermore the number of intracranial bleeds were 14, 18 and 5 in the three groups, respectively.

The increased bleeding rates are of concern. They were mirrored in the lack of demonstrated effect in the predefined secondary efficacy end-point “net clinical benefit”. The observation that fatal bleeding events or total mortality was not increased in the 2.5 mg dose group as compared with placebo during the study observation period are to some extent reassuring and the results indicate that the overwhelming majority of bleedings could be managed clinically.

Uncertainty in the knowledge about the unfavourable effects

The study population in the pivotal study is on average somewhat younger than what is known for the European target population although it is noticed that 9% of the included patients were above the age of 75. It could also be expected that more patients with complicating co-morbidities will be treated in clinical routine. Thus the study population may not be fully representative for the population that will be treated in the post-marketing setting. This was highlighted and discussed by the CV-SAG and CHMP during the assessment. Taking also into account the CV-SAG recommendations and argumentations provided during the Oral Explanation, reassurance regarding the study population baseline compared with other studies, was provided. Nevertheless, it is highlighted that further information is needed to be collected in the post authorisation setting under routine clinical practice.

Upon request by CHMP, the MAH has agreed to perform a post marketing observational safety study enrolling 11000 patients. This will provide further insight with regard to these concerns and regular interim analysis have been requested in order to monitor the use of xarelto in daily practice. This study is considered important to further monitor the benefit risk in daily practice and is added as a condition to the marketing authorisation. The RMP has been appropriately updated and will be further updated when the study protocol of the post-marketing study is reviewed and adopted.

It has been seen in recent trials in ACS patients that bleeding may adversely affect the CV event rate and mortality in the long term perspective and not only in relation to the acute bleeding event. Similar findings are made in the pivotal trial in this application. The MAH partially explains the lack of clear benefit for CV mortality in the 5 mg dose group with the higher bleeding incidence in this group as compared with the 2.5 mg bid dose group. It is accepted that this may have contributed to the differences in CV mortality between the two dose-groups,

Balance

Importance of favourable and unfavourable effects

A reduction of the mortality rate when rivaroxaban is added to ASA or ASA in combination with clopidogrel of approximately 1% as demonstrated in the 2.5 mg bid dose group is an important beneficial effect of obvious clinical relevance.

The MAH has calculated NNT/NNH rates based on the study results and estimated that 125 non-bleeding CV death, MI and ischemic strokes are prevented, while treatment causes 10 fatal bleedings or ICH per 10.000 patient years. These calculations should be interpreted with caution. The estimation that 68% of the primary efficacy events prevented would be CV deaths relies solely on the results for the different components in the 2.5 mg arm with little support from the 5 mg treatment arm. However, this is the best estimation that can be made based on current knowledge and it clearly indicates effects of important clinical relevance.

The results from the pivotal study need to be put into perspective and can be compared with the results of recent trials in this patient population. The comparability of patients included in the Atlas study with the recent trials was also discussed and reassurance was provided during the oral explanation, providing further external support and validity of the study in the ACS population. In the pivotal trial supporting the approval of ticagrelor a reduction of a similar primary composite endpoint of approximately 2% per treatment year as compared to clopidogrel was shown, both in combination with ASA. Thus, the reduction seen in this application appears less impressive. Significant reductions in CV mortality, total mortality and MI were seen in this study (PLATO). This was achieved with only a slight numerical non-significant increase in TIMI major bleedings (HR 1.04) vs the comparative treatment. Comparisons between studies must be done with great caution and there are major uncertainties associated with such comparisons. It is agreed with the MAH that ASA and clopidogrel will most probably remain as a viable treatment alternative for ACS patients in the future.

Benefit-risk balance

In summary, the majority of the CHMP considered that a statistically significant and clinically relevant reduction of the primary composite endpoint was demonstrated in the 2.5 mg b.i.d. dose group driven by a reduction in mortality. Additional sensivity analyses support the robustness of the primary efficacy results. The increased bleeding tendency is considered to be acceptable with no observed differences between the 2.5 mg dose group and placebo for fatal bleedings or intracranial bleedings. The overwhelming majority of bleedings observed were clinically manageable.

Taking into account the CV-SAG recommendation, and the discussion at the oral explanation, the CHMP finally agreed with the narrow indication than initally proposed.

Xarelto, co-administered with acetylsalicylic acid (ASA) alone or with ASA plus clopidogrel or ticlopidine, is indicated for the prevention of atherothrombotic events in adult patients after an acute coronary syndrome (ACS) with elevated cardiac biomarkers (see sections 4.3, 4.4 and 5.1).

A justification for this restriction has been provided by the MAH in response to the CHMP questions and the restriction as such is acceptable in the CHMP opinion.

Nevertheless, the post approval study (XA1301) planned to enroll 11000 patients in a short time frame will provide further insight on the use of xarelto in the post approval setting. Regular interim analysis on a yearly basis will enable appropriate monitoring of benefit risk of xarelto in the post authorisation setting under routine daily practice.

However, there were divergent opinions expressed by some members who considered that the benefit/risk balance was negative based on the safety profile considered insufficiently demonstrated especially with regard of major bleedings.

Conclusions

The CHMP agreed with the extension of the indication for Xarelto specifically for this new strength (2.5 mg) and considered that a positive benefit risk balance has been demonstrated in the targeted restricted indication.

The approved indication is as follows :

Xarelto co-administrated with acetylsalicylic acid (ASA) alone or with ASA plus clopidogrel or ticlopidine, is indicated for the prevention of atherothrombotic events in adult patients after an acute coronary syndrome (ACS) with elevated cardiac biomarkers (see sections 4.3, 4.4 and 5.1).

User consultation

No full user consultation with target patient groups on the package leaflet has been performed on the basis of a bridging report making reference to Xarelto and a focused user test. For future reference, the bridging report is not considered acceptable since the justification lacks vital information and a critical discussion. However, the focus test presents that the vital sections of the package leaflet are considered readable, and the focus test is therefore acceptable. However, the CHMP suggested some additional changes to the Package Leaflet due to the result of the user test. These changes will improve readability even further and have been implemented in the adopted Product information.

Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered by majority that the risk-benefit balance of Xarelto co-administrated with acetylsalicylic acid (ASA) alone or with ASA plus clopidogrel or ticlopidine, for the prevention of atherothrombotic events in adult patients after an acute coronary syndrome (ACS) with elevated cardiac biomarkers, is favourable and therefore recommends the granting of an extension of the marketing authorisation for Xarelto subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription

- **Periodic Safety Update Reports**

The marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list)) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

- **Additional risk minimisation measures**

The MAH shall provide an educational pack prior to launch, targeting all physicians who are expected to prescribe/use Xarelto. The educational pack is aimed at increasing awareness about the potential risk of bleeding during treatment with Xarelto and providing guidance on how to manage that risk. The physician educational pack should contain:

- The Summary of Product Characteristics
- Prescriber Guide
- Patient Alert Cards [Text included in Annex III]

The MAH must agree the content and format of the Prescriber Guide together with a communication plan, with the national competent authority in each Member State prior to distribution of the educational pack in their territory. The Prescriber Guide should contain the following key safety messages:

- Details of populations potentially at higher risk of bleeding
- Recommendations for dose reduction in at risk populations
- Guidance regarding switching from or to rivaroxaban treatment
- The need for intake of the 15 mg and 20 mg tablets with food
- Management of overdose situations
- The use of coagulation tests and their interpretation
- That all patients should be counselled about:
    - Signs or symptoms of bleeding and when to seek attention from a health care provider.
    - Importance of treatment compliance
    - The need for intake of the 15 mg and 20 mg tablets with food

- Necessity to carry the Patient Alert Card that is included in each pack, with them at all times
- The need to inform Health Care Professionals that they are taking Xarelto if they need to have any surgery or invasive procedure.

The MAH shall also provide a Patient Alert Card in each medication pack, the text of which is included in Annex III.

- **Obligation to complete post-authorisation measures**

The MAH shall complete, within the stated timeframe, the below measures:

Description	Due dates
Prospective cohort study, enrolling 11,000 patients, with the aim of analysing the safety of rivaroxaban in the secondary prevention of Acute Coronary Syndrome outside the clinical trial setting, especially with regard to frequency, severity, management and outcome of bleeding events.	• Protocol submitted by June 2013 for review • Interim analysis reports provided every year until completion of the cohort study • Interim analysis report of 5000 patients followed for at least 3 months by Q4 2015 • Final Study Report submitted by Q4 2018

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States.

Not applicable.

Divergent views were expressed and are in annex to this assessment report.