Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

Australian Public Assessment Report for Rivaroxaban

Proprietary Product Name: Xarelto

Sponsor: Bayer Australia Ltd

September 2012

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

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

About AusPARs

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

Contents

I. Introduction to product submission

Submission details

Type of Submission	Extension of indications: New strength
Decision:	Approved
Date of Decision:	3 April 2012
Active ingredient(s):	Rivaroxaban
Product Name(s):	Xarelto
Sponsor's Name and Address:	Bayer Australia Ltd PO Box 903 Pymble NSW 2073
Dose form(s):	Tablet (film coated)
Strength(s):	15 mg, 20 mg
Container(s):	PP/Al and PVC/PVDC/Al blister packs
Pack size(s):	7, 14, 28, 42, 84, 98 and 100 x 15 mg tablets (red) 7, 28, 84, 98 and 100 x 20 mg tablets (brown)
Approved Therapeutic uses:	(1) Prevention of stroke and systemic embolism in patients with non valvular atrial fibrillation and at least one additional factor for stroke. (2) Treatment of deep vein thrombosis (DVT) and for the prevention of recurrent DVT and pulmonary embolism (PE).
Route(s) of administration:	Oral
Dosage:	The recommended dose for the initial treatment of acute DVT is 15 mg twice daily for the first 3 weeks followed by 20 mg once daily for the continued treatment and the prevention of recurrent DVT and PE.
ARTG Number (s)	181185 (15 mg tablets) 181186 (20 mg tablets)

Product background

This AusPAR describes an application by the sponsor, Bayer Australia Ltd, to register Xarelto tablets containing rivaroxaban (BAY 59-7939) 15 mg or 20 mg. Tablets containing 10 mg of rivaroxaban were approved in Australia in November 2008 for the indication:

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

In this new submission, the maximum recommended daily dose of rivaroxaban is increased using new strength tablets of 15 mg and 20 mg, and new indications are added. The proposed new list of indications for rivaroxaban is:

- Prevention of venous thromboembolism (VTE) in adult patients who have undergone major orthopaedic surgery of the lower limbs (elective total hip replacement, treatment for up to 5 weeks; elective total knee replacement, treatment for up to 2 weeks);
- Prevention of stroke and systemic embolism in patients with non valvular atrial fibrillation; and
- Treatment of deep vein thrombosis (DVT) and for the prevention of recurrent DVT and pulmonary embolism (PE).

Regulatory status

Similar applications have been submitted in the European Union (EU; 27 countries), Iceland, USA, Switzerland, Colombia, Singapore, Malaysia, Brazil, Mexico, Chile, Canada, New Zealand, Liechtenstein and Norway.

A similar application has not been rejected, repeatedly deferred, or withdrawn in US or Canada.

The Australian application is identical to the Marketing Authorisation Applications submitted in the EU and New Zealand. At the time of submission, the indication of treatment of DVT and for the prevention recurrent DVT and PE had not been included in the application submitted in the US. The sponsor intended a separate submission to include this indication for March 2011 in Canada.

Product Information

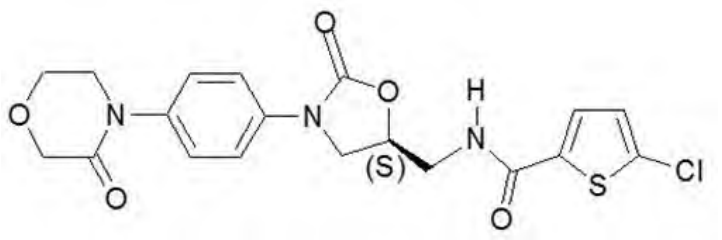
The approved product information (PI) current at the time this AusPAR was prepared can be found as Attachment 1.

II. Quality findings

Drug substance (active ingredient)

The drug substance has the chemical structure shown in Figure 1.

Figure 1: Chemical structure of rivaroxaban.



Molecular formula: 5-Chloro-N-({(5S)-2-oxo-3-[4-(3-oxo-4-morpholinyl)phenyl]-1,3-oxazolidin-5-yl}methyl)-2-thiophene-carboxamide

Formula: $C_{19}H_{18}ClN_3O_5S$

Molecular Weight: 435.89

The sponsor has stated that all aspects relating to the drug substance for the proposed products are identical to those relating to the registered 10 mg tablets.

For information, rivaroxaban is a selective serine protease coagulation Factor Xa (activated factor X) inhibitor. It is almost 100% orally bioavailable with a C_{max} (maximum plasma drug concentration) of 2-4 h. Three polymorphic crystalline forms, plus amorphous and hydrate forms, are known. These can be differentiated by Raman

spectroscopy; crystalline Form I is the form used in products. It is practicably insoluble in water (0.007 mg/ml), similarly insoluble in dilute acid, and the material is micronised prior to formulation in the tablets.

These specifications include a de facto limit of NMT (not more than) 0.5% for the *R*-enantiomer of rivaroxaban (EE [enantiomeric excess] NLT [not less than] 99.0%). Given that the maximum daily dose has increased from 10 mg to 30 mg, this limit may no longer be qualified.

All other impurities are controlled to the ICH (International Conference on Harmonisation) qualification and identification thresholds and as such the limits will not be affected by the increase in the maximum daily dose.

The specifications also tightly control particle size distribution with limits of $D_{10} \geq 0.5$ μm, D_{50} = 1-8 μm and $D_{90} \leq 15$ μm.

Drug product

The tablets are to be manufactured by Bayer Schering Pharma AG, Germany (as per the registered strength). The manufacturing process consists of wet granulation, followed by drying, blending, compression, film coating and polishing (as per the registered strength).

The different strengths are not direct scales but rather the same mass with proportionately less microcrystalline cellulose/lactose compensating for the increased amount of rivaroxaban in the tablet core. The different strengths are distinguished by the amounts of colourants (titanium dioxide and iron oxide red) used in the film coating and tablet markings.

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

Stability data were provided to support a shelf life of 3 years when stored below 30°C in the proposed packaging with the additional condition 'Store in the original pack until required' on the carton labels.

Biopharmaceutics

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

Administration of the 20 mg tablet after food resulted in significantly higher C_{max} values (approximately 75% increase) and a delay in T_{max} (time to reach maximum plasma concentration following drug administration). AUC (area under the plasma concentration-time curve) increased by 40% in the fed state. No study was provided on the effect of food on the 15 mg tablet; however, given that absorption is linear in the fasted state to 10 mg but linear in the fed state to 30 mg, a less pronounced food effect is expected for the 15 mg tablet.

Quality summary and conclusions

There are no objections to the registration of Xarelto 15 mg and 20 mg rivaroxaban tablets with regard to chemistry, manufacturing and controls.

III. Nonclinical findings

Introduction

The data submitted were of high quality and were performed by reputable laboratories. The pivotal carcinogenicity studies were performed according to GLP (Good Laboratory Practice) standards.

Some of the data submitted represent extensions of studies previously presented in the new chemical entity application and evaluated in a report of 12 August 2008. Other studies (notably, carcinogenicity) were ongoing at the time of the previous application.

Pharmacology

Primary pharmacodynamics (PD)

Data on the effect of rivaroxaban on PT (prothrombin time) and APTT (activated partial thromboplastin time) in human, rat, and rabbit PPP (platelet poor plasma) were presented in the new chemical entity application. In this application, the sponsor has presented data showing that the rivaroxaban concentrations needed to double the clotting time in the PT assay were 0.23 ± 0.03 μM and 0.15 ± 0.02 μM and in the APTT assay were 1.19 ± 0.17 μM and 0.57 ± 0.10 μM for dog and mouse plasma, respectively.

The antithrombotic activity of rivaroxaban was compared with other anticoagulants in two models. In one of these, the time to thrombotic occlusion following electrolytic injury of a carotid artery was measured in rats infused with drug. An IV (intravenous) infusion of rivaroxaban at 1 or 3 mg/kg (median time >30 mins as compared with control value of ~10-13 mins) was more effective than enoxaparin (LMWH [low molecular weight heparin]; ~22 mins). It was concluded that rivaroxaban has utility in treating arterial thrombotic disorders. The second model employed *in vitro* catheter induced clotting in human plasma. It was shown that drugs that inhibit thrombin as well as factor Xa (that is, heparin and enoxaparin) are superior to those that only inhibit factor Xa (that is, tick anti coagulant protein, fondaparinux, and rivaroxaban), and that inhibition of both free factor Xa and factor Xa incorporated into the prothrombinase complex (that is, rivaroxaban) is not superior to inhibition of only free factor Xa (that is, fondaparinux).

Secondary pharmacodynamics

Rivaroxaban contains an oxazolidone moiety. Because this moiety is also present in oxazolidinone antibiotics, such as linezolid, and is associated with mitochondrial toxicity via inhibition of mitochondrial protein synthesis, the sponsor tested whether rivaroxaban was capable of producing similar effects. Rivaroxaban showed no effective growth inhibitory activity towards three Gram positive bacteria species and was neither antagonistic nor agonistic towards the *in vitro* antibacterial activity of linezolid. The three major metabolites of rivaroxaban retain the oxazolidone moiety. Like the parent compound, they were also shown to lack effective bacteriostatic activity. Rivaroxaban was shown to have no effect on *in vitro* protein synthesis by rat liver mitochondria. Possible *in vivo* effects on mitochondrial protein synthesis were examined using mitochondria isolated from the heart and liver of rats given a daily oral dose of 60 mg/kg of rivaroxaban for four weeks. Unlike linezolid, repeat dosing with rivaroxaban had no effect on protein levels of mitochondrially encoded cytochrome c oxidase 1 or on the enzymic activity of mitochondrially encoded Complex IV, using mitochondria from either tissue. It was concluded that rivaroxaban is not an inhibitor of mitochondrial protein synthesis and would not be expected to produce the effects associated with long term linezolid use.

Patients treated with heparin can develop HIT (heparin induced thrombocytopenia). *In vitro* tests using sera from HIT patients showed that rivaroxaban did not activate platelets and, rather than mobilising platelet factor 4, was instead able to reduce platelet factor 4 release. It was concluded that rivaroxaban is a potential option for the prevention and treatment of thrombosis in patients with HIT.

Potential for PD interactions

The rat tail transection bleeding time model was used to assess possible interaction between rivaroxaban and the anti inflammatory drugs acetylsalicylic acid, diclofenac, and naproxen. There were no clear additive effects on bleeding time when rivaroxaban was combined with acetylsalicylic acid or diclofenac. However, there was an additive effect on bleeding time when a low dose of rivaroxaban (producing a statistically insignificant increase in bleeding time) was combined with naproxen.

Two studies examined possible antidotes to the anticoagulant action of rivaroxaban. A rat mesenteric artery bleeding time model was used to demonstrate that treatment with Beriplex (human prothrombin complex concentrate) subsequent to rivaroxaban could return the bleeding time to near baseline values. Similarly, administration of factor VIIa (human recombinant; NovoSeven) or activated prothrombin complex concentrate (FEIBA VH), subsequent to infusion of baboons with rivaroxaban, produced a significant reduction in PT.

Potential for pharmacokinetic (PK) interactions

Previous studies by the sponsor had suggested roles for the xenobiotic transporters Bcrp (breast cancer resistance protein) and Pgp (permeability glycoprotein) in the renal clearance of rivaroxaban. New studies in this submission defined these roles and examined the ability of other drugs to interfere with rivaroxaban clearance by these transporters. The studies monitored *in vitro* rivaroxaban transport across monolayers of cells expressing high levels of mouse or human Bcrp or human Pgp.

Incubation of known Bcrp substrates (topotecan, albendazole sulphoxide and prazosin) with high concentrations of rivaroxaban showed little effect on their transport by cells expressing mouse Bcrp. It was suggested that rivaroxaban is a low affinity/high velocity substrate for Bcrp. Conversely, a variety of CYP3A4 inhibitors (atazanavir, clarithromycin, clotrimazole, cyclosporine A, erythromycin, indinavir, itraconazole, miconazole, saquinavir and verapamil) had no significant effect on rivaroxaban transport by mouse Bcrp. Studies with cells expressing human BCRP suggested that only strong BCRP inhibitors (such as ketoconazole and ritonavir), when given at high doses, might result in relevant clinical interactions with rivaroxaban.

Similar conclusions were derived from studies of rivaroxaban transport by Pgp. Tests against a panel of drugs showed that only relatively high (supra therapeutic) doses of strong Pgp inhibitors, such as itraconazole, ivermectin and cyclosporin A, are likely to produce modest decreases in the renal clearance of rivaroxaban.

Relative exposure: corrections for new maximum dose

At the newly proposed long term daily dose of 20 mg per day the human $AUC_{0\text{-}24h}$ (area under the plasma concentration-time curve within time span 0 to 24 h) for rivaroxaban is 3.31 mg.h/L (compared with a value of 1.17 mg.h/L was used for a 10 mg daily dose). Table 1 shows the corrected relative exposure values for the pivotal toxicity studies evaluated in the previous application.

Table 1: Corrected relative exposure values for pivotal toxicity studies.

Species	Report No.	Study Duration	Doses (mg/kg/day)	Unbound fraction (%)	AUC (Total) (mg.h/L)	Exposure (AUC) at the NOEL/NOAEL	
						Total	Free
Mouse	PH-33902	13 weeks	♂: 50, **100**, 200 ♀: 50, 100, **200**	6.45	♂: 9.36, **20.4**, 22.3 ♀: 11.4, 30.3, **28.1**	♂: 6.2 ♀: 8.5	♂: 7.8 ♀: 10.8
Rat	PH-33611	6 months	♂: **12.5**, 50, 200 ♀: 12.5, 50, **200**	1.27	♂: **18.0**, 75.6, 137 ♀: 32.4, 114, **280**	♂: 5.4 ♀: 85	♂: 1.4 ♀: 21.2
Dog	PH-34235	1 year	5, 15, 50	10.4	**5.99**, 10.2, 22.4	1.8	3.7
Pregnant rat	PH-33582	GD 6-20	10, **35**, 120	1.27	18.9, **77.7**, 188	23.5	5.9
Pregnant rabbit	PH-33380	GD 6-20	**2.5**, 10, 40, 160	23.4	**0.736**, 2.78, 13.1, 23.9	0.2	1.0
Human	Nonclinical Overview	Steady state	**0.4**#	5.07	**3.31**	1.0	1.0

assuming 50kg body weight; NOEL/NOAEL shown in bold

Systemic exposure achieved in most species and studies was higher than in humans at the maximum recommended therapeutic dose, despite the technical limitations in high dose selection in the repeat dose toxicity studies in rodents

Toxicology

Carcinogenicity

An overview of carcinogenicity studies is shown in Table 2.

Table 2: Overview of carcinogenicity studies.

Species	Dosing duration	Dose (mg/kg/day; oral [gavage]))	$AUC_{0\text{-}24\,h}$ (mg•h/L)[a]		Exposure ratio[b]
Mouse (CD-1)	2 years	10	♂	0.98 (0.063)	0.3 (0.4)
			♀	1.71 (0.110)	0.5 (0.7)
		20	♂	1.54 (0.099)	0.5 (0.6)
			♀	3.29 (0.212)	1.0 (1.3)
		60[c]	♂	2.52 (0.163)	**0.8 (1.0)**[c]
			♀	4.24 (0.273)	**1.3 (1.6)**
Rat (Wistar)	2 years	10	♂	13.4 (0.170)	4.1 (1.0)
			♀	34.7 (0.441)	10.5 (2.6)
		20	♂	15.4 (0.196)	4.7 (1.2)
			♀	47.5 (0.603)	14.4 (3.6)
		60	♂	20.3 (0.258)	**6.1 (1.5)**
			♀	48.2 (0.612)	**14.6 (3.6)**

[a] Mean AUC value at ~Week 52 of dosing. Values in brackets are unbound drug exposures assuming that the unbound fraction of drug in plasma is 6.45% (mouse) and 1.27% (rat) of the total; [b] Ratio of rodent $AUC_{0\text{-}24h}$ value to human $AUC_{0\text{-}24h}$ value for subjects dosed at 20 mg/day (3.31 mg•h/L, value provided in sponsor's nonclinical overview). Value in brackets is unbound drug exposure ratio (assumes the unbound fraction of drug in human plasma is 5.07%); [c] Bolded figures are the highest non carcinogenic dose tested and the corresponding exposure ratios.

The sponsor provided results from long term (2 year) carcinogenicity studies using mice (CD-1) and rats (Wistar) of both sexes. These studies compared the incidence of neoplastic lesions in a control group with three drug dosed groups. Both premature decedents and animals sacrificed at the conclusion of scheduled dosing were subjected to gross and histopathological examination. The range of drug doses, the length of exposure, and the numbers of animals per group were appropriate for rigorously testing the potential carcinogenicity of rivaroxaban.

The rat carcinogenicity study showed no effects (compared with control groups) of rivaroxaban dosing that were considered to be of toxicological relevance. Several organs (for example, pancreas, adrenal glands) from HD (hypertensive diabetic) rats showed increased pigment deposition that was considered to derive from micro haemorrhages, a likely consequence of the pharmacological action of rivaroxaban. Rivaroxaban dosing produced no significant increase in the incidences of premature decedents or of neoplastic lesions. It was concluded that daily oral dosing with rivaroxaban at up to 60 mg/kg is non carcinogenic in both male and female rats. Daily oral dosing with rivaroxaban at 60 mg/kg produced exposure ratios (relative to humans receiving the recommended dose of 20 mg/day) of 6.1 (or 1.5, if calculation is based on unbound fraction of drug in plasma) in male rats and 14.6 (unbound = 3.6) in female rats.

Non neoplastic findings in the mouse carcinogenicity study were largely unremarkable. Similar to the rat study, there was evidence in mice receiving rivaroxaban for increases in micro haemorrhages (elevated pigment deposition in ovary) and in haemopoiesis (elevated extramedullary haemopoiesis in the red pulp of the spleen). The incidence of various types of primary tumours in the mouse carcinogenicity study showed no statistically significant effect of rivaroxaban dosing. However, there was one potential exception to the lack of effect of rivaroxaban in the carcinogenicity assay: the incidence of hepatic carcinoma in the control, 10, 20 and 60 mg/kg/day groups of male mice was 2/58 (3.4%), 4/60 (6.7%), 7/58 (12.1%) and 7/60 (11.7%), respectively. When the incidence of hepatic adenoma (0/58, 3/60, 4/58 and 4/60, respectively) was included (based on the assumptions that both neoplasms derive from the same cell type and are interrelated), the combined figures for hepatic adenoma and carcinoma in male mice were 2/58 (3.4%), 7/60 (11.7%), 11/58 (19.0%) and 11/60 (18.3%), respectively. Analysis of the latter figures using a trend test (Exact Peto) gave a highly significant *p* value of 0.0089.

Hepatic tumours are commonly associated with ageing in some mouse strains such as the CD-1 strain.[1] It has long been recognised that tumours that occur at high background frequency are particularly susceptible to producing false positive results in carcinogenicity studies.[2] For example, an unusually low tumour incidence in the control group combined with average or above average incidences in test groups could falsely suggest a positive carcinogenicity result. Accordingly, it has been suggested that less stringent *p* values, such as 0.01[2] or 0.005,[3] be adopted when assessing results for common tumour types. Based on published guidelines,[3] the above data on hepatic adenoma and carcinoma incidence in

[1] King-Herbert A, Thayer K. (2006) NTP workshop: Animal models for the NTP rodent cancer bioassay: stocks and strains- should we switch?, *Toxicologic Pathology* 34: 802-805.

[2] Haseman JK. (1983) A reexamination of false positive rates for carcinogenesis studies, *Fundamental and Applied* Toxicology 3: 334-339.

[3] Food and Drug Administration, "Guidance for Industry: Statistical aspects of the design, analysis, and interpretation of chronic rodent carcinogenicity studies of pharmaceuticals", May 2001, Web, accessed 24 July 2012 <www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatory Information/Guidances/ucm079272.pdf>.

rivaroxaban dosed male mice would not be considered indicative of a positive carcinogenicity result.

Another approach to resolving this issue is the use of historical control data. Although it is recognised that multiple factors can influence the "background" incidence of tumours in rodents and that results from concurrent control animals are therefore the most appropriate comparison for test groups, the use of control values from other studies can be valuable in assessing problematic data.[4] Results from several sources suggest that the sponsor's control value for the incidence of hepatic tumours in male CD-1 mice is unusually low:

1. Two proprietary databases gave average incidences for hepatic tumours in male CD-1 mice of 10.8 and 10.1% (adenomas) and 10 and 6.7% (carcinomas).
2. Charles River Laboratories (source of the animals used in the sponsor's study) report average incidences for hepatic adenomas and carcinomas, in control groups from 52 studies of 18 months to 2 years duration using CD-1 male mice, of 10.47 and 5.75%, respectively.[5]
3. Covance Laboratories, from an analysis of 10 carcinogenicity studies of ~2 years duration and using male CD-1 mice, reported average incidences for hepatic adenomas and carcinomas of ~20 and 3%, respectively.[6]
4. A concurrent study by the sponsor (Bayer Healthcare AG, report no. AT05038 (2008)) reported a control incidence of hepatic tumours in male CD-1 mice of 12/50 (24%).

It is clear that the hepatic tumour incidences found in the sponsor's rivaroxaban treated groups are comparable with the historical control data for male CD-1 mice reported in other studies. Therefore, it can be concluded that the results for CD-1 mice are not indicative of carcinogenic potential at daily rivaroxaban doses up to 60 mg/kg producing exposure ratios (total or unbound drug) of ~1. Furthermore, previous studies by the sponsor have shown no evidence for genotoxicity by rivaroxaban in both mutagenicity and clastogenicity assays.

Comments on the Safety Specification of the Risk Management Plan

Results and conclusions drawn from the nonclinical program for rivaroxaban detailed in the sponsor's draft Risk Management Plan (RMP) are in general concordance with those of the Nonclinical Evaluator.

Nonclinical summary and conclusions

Summary

- Bayer Australia Ltd has applied to register two new indications for the direct acting factor Xa inhibitor rivaroxaban: (1) the treatment of DVT and the prevention of recurrent DVT and PE, and (2) the prevention of stroke in patients with non valvular atrial fibrillation.

[4] Keenan C, et al. (2009) Best practices for use of historical control data of proliferative rodent lesions, *Toxicological Pathology* 37: 679-693.

[5] Giknis ML, Clifford CB, "Spontaneous neoplastic lesions in the Crl:CD-1(ICR) mouse in control groups from 18 month to 2 year studies", March 2005, Web, accessed 24 July 2012 <www.criver.com/sitecollectiondocuments/rm_rm_r_lesions_crlcd_1_icr_mouse.pdf>.

[6] Baldrick P, Reeve L. (2007) Carcinogenicity evaluation: Comparison of tumor data from dual control groups in the CD-1 mouse, *Toxicologic Pathology* 35: 562-569.

- Rivaroxaban is currently approved in Australia for the prevention of venous thrombosis in patients having elective knee or hip replacement at a maximum clinical oral dose of 10 mg once daily for up to 5 weeks. In this new submission the maximum recommended daily dose is increased using new strength tablets of 15 mg and 20 mg: for the initial treatment of acute DVT it is 15 mg rivaroxaban twice daily for the first 3 weeks, followed by 20 mg rivaroxaban once daily for continued treatment and the prevention of recurrent DVT and PE. Therapy is to be continued as long as the risk of thromboembolism persists.
- The studies submitted by the sponsor are a mixture of extensions of work presented in the new chemical entity application and of new areas of investigation (possible carcinogenicity and mitochondrial toxicity of rivaroxaban).
- The data submitted were of high quality and the pivotal carcinogenicity studies were performed according to GLP standards.
- *In vitro,* rivaroxaban reduced platelet factor 4 release in sera from HIT patients suggesting that it is a potential option for the prevention and treatment of thrombosis in patients with HIT. Moreover, IV rivaroxaban was more effective than enoxaparin in a rat arterial thrombosis model, indicating its potential utility in treating arterial thrombotic disorders. However, rivaroxaban and other drugs that only inhibit factor Xa (tick anti coagulant protein, fondaparinux) were shown to be less effective at inhibiting *in vitro* catheter induced clotting than drugs that inhibit thrombin as well as factor Xa (heparin and enoxaparin).
- Rivaroxaban is chemically related to the antibiotic linezolid and contains an oxazolidone moiety, which has been associated with mitochondrial toxicity via inhibition of mitochondrial protein synthesis. Both *in vitro* and *in vivo* testing failed to provide evidence that rivaroxaban has effective bacteriostatic action or is an inhibitor of mitochondrial protein synthesis. It was concluded that rivaroxaban would not be expected to produce the effects associated with long term linezolid use.
- Combination of rivaroxaban with the anti inflammatory drugs acetylsalicylic acid or diclofenac did not produce additive effects on bleeding time in the rat tail transection model. However, there was an additive effect on bleeding time when a low dose of rivaroxaban (producing a statistically insignificant increase in bleeding time) was combined with naproxen.
- Activated prothrombin complex and factor VIIa were identified as antidotes to the anticoagulant action of rivaroxaban in animal models.
- *In vitro* studies with cell lines expressing high levels of Bcrp or Pgp proteins indicated that only high doses of strong Bcrp or Pgp inhibitors are likely to produce modest decreases in the renal clearance of rivaroxaban. Potential drug interactions are extensively covered in the PI document.
- Two year carcinogenicity studies were performed using mice and rats of both sexes. The studies compared the incidence of neoplastic lesions in a control group with three groups receiving a daily oral dose of rivaroxaban up to 60 mg/kg. Unbound plasma rivaroxaban exposure levels in the HD groups were similar to humans (in mice) or up to 3.6 fold higher (in rats) than in humans. Rivaroxaban showed no carcinogenic potential in either species.

Conclusions

No issues of clinical concern were noted in the studies presented. There are no objections on nonclinical grounds to the registration of rivaroxaban (Xarelto) for the proposed

indications. The RMP presents an appropriate overview of the toxicological findings. The PI should be amended as proposed.

IV. Clinical findings

Introduction

Of all the extensive number of clinical studies submitted, only Study R-8564 was not conducted in complete adherence to ICH guidelines as some of the documentation was not available, for example, audit certificates. This is not a serious deficiency and the data from the study were not rejected for evaluation.

All the other studies appear to have been conducted in accordance with GCP (Good Clinical Practice) and the Declaration of Helsinki.

Pharmacokinetics

The following studies were submitted in support of PK:

- There were six studies examining aspects of bioavailability and bioequivalence: Study 011938, Study 011585, Study 013371, Study 012362, Study 014022 and Study 014588.
- There was one report of an *in vitro* study using human biomaterials: Study PH-36090.
- There were two studies of intrinsic factor effects on PK: Study 012980 and Study 12024.
- There were five studies of extrinsic factor effects on PK: Study 012680, Study 012612, Study R-8564, Study 010849 and Study 012606.
- There were eight population PK studies: Study PPK03-002, Study PPK03-000130, Study 012623, Study PPK03-010, Study PPK04-009, Study 012143, Study AFL3001 and Study PH-36318.

Data submitted in support of PK

Bioavailability data

Study 011938 was a single centre, randomised, open label, non placebo controlled, two way crossover study of the effect of food on rivaroxaban 20 mg tablet bioavailability. The study included 24 healthy male subjects, 22 of whom were included in the PK analysis. Food increased the bioavailability of rivaroxaban: AUC was increased by 39% and C_{max} by 76% (Table 3).

Table 3: Single centre, randomised, open label, non placebo controlled, two way crossover Study 011938 of the effect of food on rivaroxaban bioavailability.

Pharmacokinetics

Parameter	Unit	n	Rivaroxaban fasted (n = 22)	n	Rivaroxaban with food (n = 22)
AUC	µg*h/L	22	1477/23.28 (1051 – 2754)	22	2048/22.75 (1422 – 4078)
AUC_{norm}	kg*h/L	22	5.893/21.60 (3.940 – 8.942)	22	8.169/19.19 (6.330 – 12.64)
AUC(0-tn)	µg*h/L	22	1457/23.34 (1043 – 2739)	22	2031/22.84 (1419 – 4070)
%AUC(tn-∞)	%	22	1.179/60.30 (0.5205 – 3.693)	22	0.6602/74.32 (0.1918 – 2.545)
C_{max}	µg/L	22	159.9/33.79 (76.30 – 257.2)	22	281.4/27.49 (145.8 – 551.3)
$C_{max,norm}$	kg/L	22	0.6381/34.65 (0.3471 – 1.132)	22	1.123/26.72 (0.5467 – 2.012)
$t_{½}$	h	22	7.996/30.90 (4.922 – 16.22)	22	7.483/45.98 (3.866 – 21.71)
MRT	h	22	12.27/26.10 (6.710 – 19.09)	22	9.773/23.81 (6.650 – 14.65)
t_{max} [a]	h	22	2.500 (0.75 – 6.00)	22	4.000 (2.50 – 6.00)

Bioavailability

Test	Reference	Parameter	Estimated ratio (90%CI)
Rivaroxaban with food	Rivaroxaban fasted	AUC	1.386 (1.293 – 1.486)
Rivaroxaban with food	Rivaroxaban fasted	C_{max}	1.760 (1.549 – 1.999)

Pharmacodynamics

Analyte	Parameter	Test	Reference	Ratio (90% CI)
Factor Xa inhibition	AUC(0-tn)	With food	Fasted	1.40 (1.26 – 1.57)
	E_{max}	With food	Fasted	1.38 (1.28 – 1.49)
PT prolongation	AUC(0-tn)	With food	Fasted	1.28 (1.15 – 1.42)
	E_{max}	With food	Fasted	1.18 (1.13 – 1.23)
	AUC_{abs}(0-tn)	With food	Fasted	1.71 (1.52 – 1.93)
	$E_{max,abs}$	With food	Fasted	1.64 (1.45 – 1.85)

Study 011585 was a single centre, randomised, non blinded, non controlled, three way crossover study conducted during the development of an extended release formulation.

Study 013371 demonstrated bioequivalence between rivaroxaban 15 mg tablet formulations 365 and 367 in healthy male Japanese subjects under fasted conditions (Table 4).

Table 4: Randomised, non blinded, two way crossover bioequivalence Study 013371 comparing two 15 mg tablet formulations of rivaroxaban.

Pharmacokinetics

Parameters	Unit	Formulation 365	Formulation 367
AUC_{0-tn}	[µg*h/L]	1810.60 / 23.44 (1101.89, 2517.59)	1797.35 / 20.85 (1268.70, 2804.35)
C_{max}	[µg/L]	256.36 / 22.51 (159.93, 390.21)	235.03 / 24.81 (154.21, 400.05)
t_{max} [a]	[h]	2.50 (0.50, 4.00)	1.50 (0.50, 6.00)
$t_{1/2}$	[h]	8.21 / 30.42 (5.67, 16.85)	8.94 / 39.04 (4.30, 17.72)

a Median (range)

Parameters	Point estimates [a]	90% confidence interval
AUC_{0-tn}	1.007	(0.920, 1.104)
C_{max}	1.091	(0.985, 1.208)

a Ratio (Formulation 365/Formulation 367)

Study 012362 was a single centre, randomised, open, non controlled, three way crossover study of dose proportionality of rivaroxaban 10 mg, 15 mg and 20 mg tablets, taken orally with food. The study demonstrated dose proportionality for AUC and C_{max} from 10 mg to 20 mg (Table 5).

Table 5: Single centre, randomised, open, non controlled, three way crossover Study 012362 of dose proportionality of rivaroxaban taken orally with food.

Pharmacokinetics

Parameter	Unit	10 mg (n=24)	15 mg (n=24)	20 mg (n=24)
AUC	µg*h/L	1201/21.3 (621.5-1798)	1801/22.2 (952.1-2870)	2294/19.0 (1464-3227)
AUC/D	h/L	0.1201/21.3 (0.06215-0.1798)	0.1201/22.2 (0.06348-0.1913)	0.1147/19.0 (0.07322-0.1614)
C_{max}	µg/L	161.7/17.2 (127.3-235.4)	234.2/17.4 (170.8-347.1)	294.4/15.0 (225.4-360.6)
C_{max}/D	1/L	0.01617/17.2 (0.01273-0.02354)	0.01561/17.4 (0.01138-0.02314)	0.01472/15.0 (0.01127-0.01803)
$t_{1/2}$	h	10.98/44.7 (4.718-21.75)	11.10/62.1 (5.112-33.76)	12.08/60.8 (4.787-36.43)
MRT	h	10.12/16.8 (7.924-14.30)	10.15/22.4 (6.817-14.82)	10.92/29.0 (7.714-24.45)
t_{max} [a]	h	3.000 (0.5000-6.000)	3.500 (1.000-6.000)	3.000 (0.5000-6.000)

a median(range)

Ratio	Parameter	Unit	n	CV	Estimated Ratio (%)	95% confidence interval (%)
15 mg / 10 mg	AUC/D	h/L	24	9.14	99.97	[94.80 ; 105.42]
	C_{max}/D	1/L	24	10.72	96.52	[90.70 ; 102.72]
20 mg / 10 mg	AUC/D	h/L	24	9.14	95.50	[90.57 ; 100.71]
	C_{max}/D	1/L	24	10.72	90.99	[85.51 ; 96.83]
20 mg / 15 mg	AUC/D	h/L	24	9.14	95.53	[90.59 ; 100.74]
	C_{max}/D	1/L	24	10.72	94.27	[88.58 ; 100.32]

Study 014022 was a single dose, open label, randomised, four way crossover study to compare 10 mg and 20 mg of an oral suspension of rivaroxaban under fasted conditions with 20 mg under fed conditions and a 10 mg immediate release tablet under fasted conditions. The study included 17 healthy male volunteers. The 10 mg tablet and suspension doses were bioequivalent.

Study 014588 demonstrated bioequivalence for two rivaroxaban 5 mg tablets in comparison with one 10 mg tablet, as a single dose under fasted conditions (Table 6).

Table 6: Single dose, open label, randomised, two way crossover bioequivalence Study 014588.

Pharmacokinetics

Parameter	Unit	1x10 mg (n=26)		2x5 mg (n=26)	
AUC	µg*h/L	1268/30.7	(544.5-2330)	1374/29.3	(833.2-2204)
AUC(0-tn)	µg*h/L	1252/31.6	(524.8-2293)	1354/29.8	(806.0-2188)
C_{max}	µg/L	161.1/38.7	(60.61-297.2)	179.8/31.1	(110.1-332.4)
$t_{1/2}$	h	8.721/55.7	(4.376-29.17)	8.932/48.6	(5.021-27.69)
t_{max} [a]	h	2.500	(0.7500-4.000)	2.500	(0.7500-3.000)

a median (range)

Test	Reference	Parameter	Ratio test/reference [geometric LS mean (90% confidence interval)]
2x5 mg	1x10 mg	AUC	1.0835 (1.0159 - 1.1557)
		AUC(0-tn)	1.0819 (1.0131 - 1.1554)
		C_{max}	1.1164 (1.0114 - 1.2323)

In vitro studies using human biomaterials

Study PH-36090 was a report of *in vitro* studies in MDCKII-BCRP cells to evaluate the substrate characteristics of rivaroxaban for human BCRP. Rivaroxaban was found to be a substrate of human BCRP, but with lesser affinity than topotecan. Ritonavir was found to be an inhibitor of BCRP, and this was advanced as an explanation for the inhibition of rivaroxaban clearance by ritonavir.

Studies of intrinsic factor effects on PK

Study 012980 was a multicentre, randomised, study of PK, PD and safety in subjects with acute (open label, active control) or chronic (double blind, placebo controlled) CHF

(congestive heart failure). The study treatments were either: rivaroxaban 10 mg once daily oral tablet for six days, enoxaparin 40 mg subcutaneously daily or placebo. In the acute CHF group (Cohort 1) there were eight subjects: six received rivaroxaban and two received placebo; and in the chronic CHF group (Cohort 2) there were 18 subjects: 12 received rivaroxaban and six received placebo. There were 19 (73%) males, seven (27%) females; the age range was 25 to 87 years; and six (23%) subjects had calculated CrCl (creatinine clearance) 30 to <50 mL/min. All subjects completed the study. Mean AUC and C_{max} were approximately 20% higher in subjects with CHF compared with healthy subjects (Table 7).

Table 7: Study 012980 of PK, PD and safety in subjects with acute (open label, active control) or chronic (double blind, placebo controlled) CHF.

Pharmacokinetics

PK Parameter	Cohort 1			Cohort 2		
	n	Mean ± SD	Median	n	Mean ± SD	Median
Day 1						
t_{max}, h	5		3.22 (1.08-4.00)*	11		1.05 (1.00-5.98)*
C_{max}, ng/mL	5	238 ±88.5	229	11	197 ± 73.9	175
AUC_{24h}, ng.h/mL	5	2184 ± 779	1699	10	1770 ± 372	1740
AUC_{∞}, ng.h/mL	5	2547 ± 1125	1933	11	2127 ± 462	2288
$t_{1/2}$, h	6	6.93 ± 2.53	6.26	12	8.64 ± 2.86	8.24
Day 6						
t_{max}, h	3		2.92 (1.12-3.00)*	12		1.92 (0.98-4.00)*
C_{min}, ng/mL	3	27.3 ± 11.2	23.4	12	28.6 ± 17.1	23.8
C_{max}, ng/mL	3	251 ± 55.6	259	12	216 ± 82.8	190
AUC_{24h}, ng.h/mL	3	2609 ± 668	2603	12	2369 ± 741	2366
$t_{1/2}$, h	6	7.04 ± 2.56	5.95	12	7.95 ± 1.88	7.43
Acc. Index	2	0.785-1.22*		10	1.23 ± 0.210	1.30
$C_{avg, ss}$, ng/mL	3	110 ± 25.9	108	12	98.1 ± 29.4	98.4
FI, %	3	205 ± 12.7	204	12	194 ± 59.9	177
CL/F, L/h	3	4.01 ± 1.06	3.84	12	4.55 ± 1.22	4.24

*: range.

Study 12024 was an exploratory PK/PD study conducted in 100 Japanese subjects with AF (atrial fibrillation) aged 46 to 83 years. The study examined rivaroxaban at doses between 2.5 mg and 10 mg twice daily. There was no apparent difference in PK parameters between Day 14 and Day 28. The study did not examine efficacy endpoints.

Studies of extrinsic factor effects on PK

Study 012680 was a single centre non randomised, non blinded study of the interaction of rifampicin with rivaroxaban. Rivaroxaban was administered as a 20 mg tablet as a single dose, with and without concurrent rifampicin (150 to 450 mg Days 1-3 and 600 mg Days 4 to 7). The AUC of rivaroxaban showed a 49% decrease and C_{max} a 22% decrease after the co administration of rifampicin. The $t_{1/2}$ of rivaroxaban was halved and clearance doubled when rifampicin was co administered.

Study 012612 was a single centre, randomised, two way crossover study of the interaction of clarithromycin with rivaroxaban. The study subjects were administered rivaroxaban orally as a 10 mg tablet, single dose as monotherapy and at the end of 5 days of clarithromycin 500 mg twice daily. The study included 16 healthy White male subjects aged 24 to 50 years, and 15 were included in the PK and PD analyses. Clarithromycin increased exposure to rivaroxaban. The ratio (90% confidence interval [CI]), rivaroxaban rivaroxaban + clarithromycin/rivaroxaban for AUC was 1.54 (1.44-1.64) and for C_{max} was 1.40 (1.30-1.52). Clearance of rivoxaraban was decreased in combination with clarithromycin (Table 8).

Table 8: Crossover Study 012612 of the interaction of clarithromycin with rivaroxaban.

Pharmacokinetics

Parameter	Unit	n	rivaroxaban	n	rivaroxaban + clarithromycin
AUC	µg*h/L	15	963.8/22.10 (652.2 – 1517)	15	1469/24.53 (904.7 – 2161)
AUC_{norm}	kg*h/L	15	7.723/21.64 (5.165 – 10.31)	15	11.77/21.94 (8.526 – 18.37)
$AUC(0\text{-}t_n)$	µg*h/L	15	951.6/22.26 (647.2 – 1512)	15	1461/24.82 (888.8 – 2153)
C_{max}	µg/L	15	139.4/16.32 (103.5 – 198.6)	15	194.4/21.75 (122.5 – 283.9)
$C_{max,norm}$	kg/L	15	1.117/18.35 (0.7648 – 1.405)	15	1.558/23.39 (1.105 – 2.413)
$t_{½}$	h	15	6.703/38.93 (4.915 – 21.68)	15	5.666/16.80 (3.849 – 7.249)
MRT	h	15	8.357/22.60 (6.661 – 15.93)	15	8.461/13.58 (6.659 – 9.956)
V_z/f	L	15	100.3/36.46 (55.47 – 249.6)	15	55.64/21.65 (39.02 – 76.08)
CL/f	L/h	15	10.38/22.10 (6.594 – 15.33)	15	6.807/24.53 (4.628 – 11.05)
f_u	%	15	10.59/16.46 (8.26 – 14.40)	15	10.54/13.35 (7.45 – 12.30)
CL_R	L/h	15	3.773/30.92 (1.983 – 5.952)	15	3.365/27.51 (1.866 – 4.645)
CL_{RF}	L/h	14	0.6228/21.29 (0.3852 – 0.8607)	15	0.5671/19.59 (0.4417 – 0.7956)
CL_{RS}	L/h	14	3.057/38.93 (1.329 – 5.114)	15	2.778/31.86 (1.422 – 4.020)
Ae_{ur} [a]	mg	15	3.745/0.8625 (1.492 – 5.133)	15	4.995/0.7060 (3.754 – 6.212)
Ae_{ur} [a]	%	15	37.45/23.03 (14.92 – 51.33)	15	49.95/14.13 (37.54 – 62.12)
t_{max} [b]	h	15	4.00 (1.0 – 6.0)	15	4.00 (0.5 – 6.0)

a arithmetic mean / standard deviation (range); b Median (range)

Study R-8564 was a single centre, open label two way crossover study of the interaction of omeprazole with rivaroxaban. A total of 22 healthy White volunteers were administered rivaroxaban 20 mg tablet, as a single dose in the fed state; and omeprazole 40 mg once daily for 5 days in the fasted state followed by rivaroxaban 20 mg tablet in the fed state. There was no apparent effect for omeprazole on PK parameters.

Study 010849 was a randomised, placebo controlled parallel group study of switching from warfarin to rivaroxaban. The study treatments were:

1. Rivaroxaban 20 mg tablet, orally for 4 days
2. 5 mg Coumadin; dose titrated to INR (international normalised ratio) 2.0 to 3.0 for 6 days; oral administration; followed by rivaroxaban 20 mg daily for 4 days
3. 5 mg Coumadin; dose titrated to INR 2.0 to 3.0 for 6 days; oral administration; followed by placebo daily for 4 days

Subjects were administered oral 10 mg Konakion prior to discharge. The study included 96 healthy male subjects; with an age range of 18 to 45 years. Subjects were homozygous for the wild type allele 2C9*1 and carriers of the C-allele at positions 6484 and 7566 of the VKORC1 gene, respectively. There were 29 subjects in the warfarin rivaroxaban group, 31 in the warfarin placebo, and 29 in the rivaroxaban alone group. There were 83 subjects that completed the study but data from 84 were included in the analysis. Co administration of warfarin did not have any significant effect upon the PK parameters of rivaroxaban. There was no significant effect of rivaroxaban on the half life of either *s*-warfarin or *r*-warfarin.

Study 012606 was a single centre, open label, randomised, two way crossover study of the interaction of fluconazole 400 mg daily with rivaroxaban 20 mg as a single dose. Fluconazole increased exposure to rivaroxaban: AUC was increased by 42% and C_{max} by 28%. Fluconazole decreased the clearance of rivaroxaban by 30%, by decreasing both renal and non renal clearance. This was interpreted as an effect of fluconazole on CYP3A4 hepatic metabolism and also Pgp/BCRP mediated active renal secretion.

Although listed by the sponsor as extrinsic factor studies, Study A45974/A45974a did not report PK results and will be discussed below.

Population PK studies

The sponsor conducted a series of population PK/PD studies.

Study PPK03-002 (PH-33730) was an exploratory population PK/PD study of the oral multiple dose Study 10847 using data from 43 healthy male volunteers. The study was intended to explore the structural PK/PD model in an ascending dose study. Rivaroxaban was administered in the dose range 5 mg once daily through to 30 mg twice daily. The final structural model was an oral two compartment model with inter occasion variability (IOV) on absorption lag time and rate constant. This reflected a high degree of variability in absorption. PK was linear up to 30 mg twice daily. The concentration effect relationships for the biomarkers tested (factor Xa activity, PTT and Heptest) could be described with a conventional direct effect model (E_{max} [maximum effect]) model. The concentration effect relationship for PT was described by a linear intercept model.

Study PPK03-000130, PPK000131 (PH-34655) was an exploratory population PK/PD study of data from Studies 11002 (in subjects with renal failure) and 11003 (in subjects with hepatic failure). The analysis included 32 subjects with varying degrees of renal failure and 32 subjects with varying degrees of hepatic failure. Renal and hepatic failure both resulted in decreased clearance of rivaroxaban. Moderately hepatically impaired subjects had a 54% decrease in clearance.

Study 012623 (PH-34928) was an exploratory population PK/PD study of data from Studies 11273, 11865, 10992, 11936 and 11935 in order to explore the effect of Pgp and CYP3A4 inhibition (by erythromycin, ketoconazole and ritonavir) on rivaroxaban hepatic and renal clearance and bioavailability. Renal clearance was modelled as the sum of renal filtration and renal secretion (active transport) using the formula:

$$CL_R = CL_{Rf} (= GFR * f_u) + CL_{Rs} \qquad CL_R = renal\ clearance$$

Where:

CL_{Rf} = glomerular filtration part of CL_R

CL_{Rs} = active secretion part of CL_R

GF_R = glomerular filtration capacity of renal function assessed via CrCl determination

f_u = fraction unbound of total plasma drug concentration

CL_{Rs} represents the fraction of renal clearance that can be decreased by inhibition of renal drug transporters. Non renal clearance was decreased by 26% by co medication with erythromycin (data from Study 10865). Ritonavir decreased non renal clearance by 50.3% to 60.7% and clearance by renal secretion by 67.7% to 73.5% (data from Study 11935). Ketoconazole decreased non renal clearance by 41.5% and 90.6% and clearance by renal secretion by 26.8% to 34.3% (data from Studies 11936 and 10992). The study concluded that CYP3A4 and Pgp inhibition decrease both renal and non renal clearance of rivaroxaban (Table 9).

Table 9: The effect of P-glycoprotein and CYP3A4 inhibition on rivaroxaban hepatic and renal clearance and bioavailability.

Pharmacokinetics

		inhibition on								
		CL_{RS}			CL_R			CL_{NR}		
study	inhibition by co-medication	max. [%]	IC_{50} [mg/L]	max. in this study [%]	max. [%]	IC_{50} [mg/L]	max. in this study [%]	max. [%]	IC_{50} [mg/L]	max. in this study [%]
10865	via flag	-	-	-	-	-	-	-	-	**26.5**
11935	via flag	-	-	**67.7**	-	-	-	-	-	**50.3**
11935	via concentration (max. 26 mg/L ritonavir in this study)	73.6	0.022	**73.5**	-	-	-	61.2	0.202	**60.7**
11936	via flag	-	-	**30.2**	-	-	-	-	-	**65.6**
11936	via concentration (max. 15 mg/L ketoconazole in this study)	34.3	0.000	**34.3**	-	-	-	88.9	0.430	**86.4**
10992	via flag	-	-	**26.8**	-	-	-	-	-	**41.5**
10992	via concentration (max. 6 mg/L ketocoanzole in this study)	-	-	-	37.6	0.423	**35.1**	100	0.625	**90.6**

IC50 = concentration of co-medication leading to 50% of maximum inhibition
CL_R = renal clearance
CL_{RS}= active secretion part of renal clearance
CL_{NR}= non-renal (hepatic) clearance
Study 11865: erythromycin; Study 11935: ritonavir; Studies 11936 and 10992: ketoconazole

Study PPK03-010 (PH-33957) was an exploratory population PK/PD analysis using data from a Phase 2 dose ranging study on the prevention of VTE in subjects undergoing elective total hip replacement (Study 10944). The study medication was rivaroxaban 1.25 mg, 5 mg, 10 mg, 20 mg or 30 mg twice daily over 8 days; in either the fed or fasted state. The analysis included 517 subjects undergoing total hip replacement. There was a decrease in clearance with increasing age compared to a median age of 65, translating to a 38% higher drug exposure for a 90 year old subject (Table 10). There was a decrease in clearance with increasing serum creatinine (21% decrease in clearance per unit change in creatinine from a median of 0.78 mg/dL). Volume of distribution was related to lean body mass.

Table 10: Population estimates for the final pharmacokinetic (one compartment) model (Study PPK03-010 (PH-33957)).

Parameter	mean estimate	RSE [%][a]	Interindividual variability CV[%][b]	RSE [%][a]	Description
ka day 3 pop 1 [h–1]	0.092	15.0	n.a.	n.a.	first-order absorption rate constant on study day <=3 for mixed population 1
ka day 3 pop 2 [h–1]	1.81	8.3	n.a.	n.a.	first-order absorption rate constant on study day <=3 for mixed population 2; and for total population on study day > 3
mixtured ka [%]	44.8	8.2	n.a.	n.a.	percentage of study population with ka DAY 3 pop 1 on study day <= 3
F1 5+10 mg	0.740	4.5	n.a.	n.a.	relative bioavailability factor for 5 mg and 10 mg treatment in relation to 2.5 mg treatment with F1 = 1 per definition
F1 20+30 mg	0.533	5.0	n.a.	n.a.	relative bioavailability factor for 20 mg and 30 mg treatment in relation to 2.5 mg treatment with F1 = 1 per definition
CL day 3 [L/h]	6.38	5.5	70.1	18.0	clearance on study days <= 3
CL day 6/7 [L/h]	7.3	4.0	38.6	8.3	clearance on study days > 3
Age on CL [%]	– 1.5	12.7	n.a.	n.a.	percent de-/increase in CL per year difference to the median age (of 65 y)
Serum Creatinine (SCR) on CL day 6/7 [%]	– 21.0	21.6	n.a.	n.a.	percent de-/increase in CL day 6/7 per unit SCR1 (= serum creatinine [mg/dL] as measured over the course of the study) difference to the median SCR1
V [L]	49.1	4.3	n.a.	n.a.	volume of distribution
Lean body mass (LBM) on V [%]	1.8	13.5	n.a.	n.a.	percent in-/decrease in V per unit LBM ([kg] assessed at baseline on study day 1) difference to the median LBM (of 51 kg)
SIGMA [%]	37.1	4.0	n.a.	n.a.	proportional residual error

a relative standard error, expressed as percentage of the estimate
b coefficient of variation, calculated as the square root of the variance (which is approximately equivalent to CV%)

Study PPK04-009 (9PH-34169) was an exploratory population PK/PD study of data from a Phase 2 dose ranging study of the prevention of VTE in subjects undergoing elective total knee replacement (Study 10945). The treatments were rivaroxaban 1.25 mg, 5 mg, 10 mg, 20 mg or 30 mg twice daily over 8 days; in either the fed or fasted state. The analysis included 492 subjects who had undergone total knee replacement surgery. Rivaroxaban clearance was related to CrCl. Subjects with lower postoperative haematocrit had greater exposure to rivaroxaban. Female subjects had 15% lower clearance of rivaroxaban. Lower body surface area was associated with greater exposure to rivaroxaban.

Study 012143 (PH-34581 V3) was an exploratory PK/PD study using data from two Phase 2 dose ranging studies in subjects with acute symptomatic DVT (Studies 11223 and 11528). Rivaroxaban was administered in daily doses of 20 mg to 60 mg. Data from 870 subjects were included in the analysis. Clearance decreased with age and with increasing plasma creatinine concentration. Volume of distribution increased with increasing lean body mass.

Study AFL3001 (R-8587) was an exploratory population PK/PD study conducted using data from a Phase 3 study conducted in Japanese subjects (Study JNJ39039039AFL3001). Subjects were administered rivaroxaban 20 mg once daily (15 mg in subjects with renal impairment). Data were analysed for 161 subjects. Clearance decreased with age and with increasing plasma creatinine concentration. Volume of distribution increased with increasing lean body mass.

Study PH-36318 was a pooled analysis of PK and PD of rivaroxaban in subjects included in Phase 1 clinical trials. The analysis included data from 1030 subjects from 59 studies. The PD variables were: baseline adjusted $AUC_{0\text{-}24}$/D of effect on PT, baseline adjusted E_{max}/D (maximum effect/dose normalised) of effect on PT, slope of PT linearly regressed on rivaroxaban plasma concentration. The PK variables were: AUC/D, C_{max}/D, AUC_{norm}, $C_{max,norm}$, t_{max}, and $t_{1/2}$. The analysis was performed using SAS (Statistical Analysis System). The data were not analysed using a model or using population PK/PD approaches. Hence the analysis did not contribute any information with regard to covariate effects.

Product Information with respect to PK

The proposed changes to the PK information in the PI document are supported by the data presented in the submission. There is appropriate information with regard the effects of age, renal failure, hepatic impairment and interactions at the level of CYP3A4 and Pgp/BCRP.

Evaluator's overall conclusions on PK

Food was demonstrated to increase the bioavailability and T_{max} for rivaroxaban. Study 011938 demonstrated that rivaroxaban AUC was increased by 39% and C_{max} by 76%. Study 011585 confirmed food increased bioavailability.

Study 012362 demonstrated dose proportionality between rivaroxaban 10 mg, 15 mg and 20 mg.

Rivaroxaban was found to be a substrate of human BCRP *in vitro* (Study PH-36090). This was proposed as a mechanism for the interaction between ritonavir and rivaroxaban.

Exposure to rivaroxaban was increased in subjects with CHF. Mean AUC and C_{max} were approximately 20% higher in subjects with CHF compared with healthy subjects (Study 012980).

Rifampicin decreased exposure to rivaroxaban and increased its clearance (Study 012680). The AUC of rivaroxaban showed a 49% decrease and C_{max} a 22% decrease after the co-administration of rifampicin. The $t_{1/2}$ of rivaroxaban was halved and clearance doubled when rifampicin was co administered. Clarithromycin increased exposure to rivaroxaban and decreased its clearance (Study 012612). The ratio (90% CI), rivaroxaban rivaroxaban + clarithromycin/rivaroxaban for AUC was 1.54 (1.44-1.64) and for C_{max} was 1.40 (1.30-1.52). Omeprazole had no apparent effect on the PK of rivaroxaban (Study R-8564). Rivaroxaban had no apparent effect on the PK of warfarin (Study 010849). Fluconazole appears to decrease rivaroxaban clearance through inhibition of CYP3A4 hepatic metabolism and also Pgp/BCRP mediated active renal secretion (Study 012606). AUC was increased by 42% and C_{max} by 28%; and clearance decreased by 30%.

The population PK studies found:

- A high degree of variability in absorption (Study PPK03-002);
- Renal and hepatic failure both resulted in decreased clearance of rivaroxaban with moderately hepatically impaired subjects having a 54% decrease in clearance (Study PPK03-000130);
- CYP3A4 and Pgp inhibition decreases both renal and non renal clearance of rivaroxaban (Study 012623);
- There was a decrease in clearance with increasing age compared to a median age of 65, translating to a 38% higher drug exposure for a 90 year old subject (Study PPK03-010);
- Female subjects had 15% lower clearance of rivaroxaban (Study PPK04-009); and
- Clearance decreased with age and with increasing plasma creatinine concentration; and volume of distribution increased with increasing lean body mass (Study 012143, Study AFL3001).

Pharmacodynamics

Introduction

The following studies submitted in support of PK also provided data in support of PD: Study 011938, Study 014022, Study 012980, Study 012680, Study 012612, Study R-8564, Study 010849, Study PPK03-010, Study PPK04-009 and Study AFL3001.

Further data evaluable for PD were provided by Study A45974, Study A45974a, *in vitro* Study 011940 and the post hoc analysis Study AFL3001/R-8593. Two pooled analyses also provided data evaluable for PD: Study PH-35408 and Study PH-34764.

Data submitted in support of PD

In Study 011938, food increased the effect of oral rivaroxaban 20 mg. For Factor Xa inhibition AUC was increased by 40% and E_{max} by 38%. For PT prolongation, AUC was increased by 28% and E_{max} by 18%.

In Study 014022, there was similar effect upon PT and aPPT following rivaroxaban 10 mg suspension fasted, 20 mg suspension fasted, 20 mg suspension fed and 10 mg tablet fasted.

In Study 012980, in both acute and chronic CHF, the effect of rivaroxaban on PT was from one hour post dose through to 12 hours post dose, but had worn off by 24 h post dose. PT was increased by up to 50%.

In Study 012680, AUC and E_{max} for the inhibition of Factor Xa activity were decreased by 47% and 11%, respectively, after rivaroxaban was co administered with rifampicin. AUC_{abs} (area under the curve above the baseline) and $E_{max,abs}$ for PT prolongation showed a decrease of 28% and 21%, respectively.

In Study 012612, when rivaroxaban was co administered with clarithromycin, there was a slight increase in effect on factor Xa: maximum median inhibition occurred at 4 h post dose and was 44.3% in combination and 35% with rivaroxaban 10 mg alone. There was also a greater effect on PT in combination: 1.46 time baseline at 4 h, compared with 1.35 times for rivaroxaban alone.

In Study R-8564, there was no apparent interactive effect of omeprazole on PT in combination with rivaroxaban.

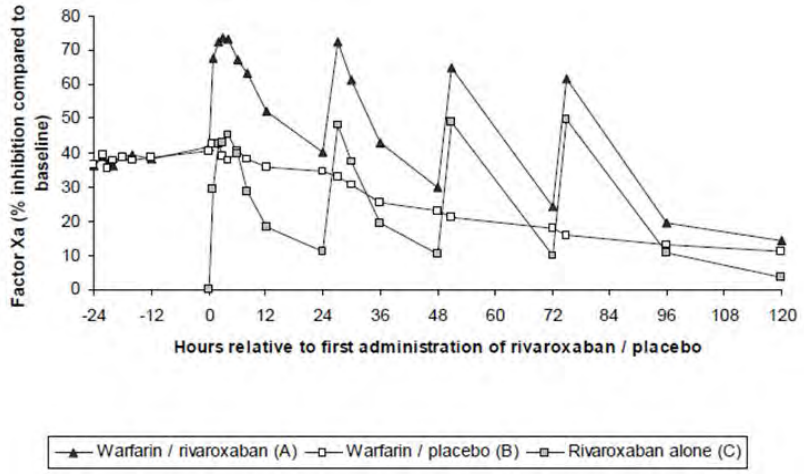
In Study 010849, the PD outcome measures were:

- Factor Xa inhibition;
- anti Factor Xa activity;
- PT(s), PT(INR);
- aPTT;
- HepTest;[7]
- PiCT (prothrombinase induced clotting time);
- ETP (endogenous thrombin potential; lag time, peak, AUC);
- Factor VIIa activity; and
- Factor IIa content.

[7] Bara L, et al. (1990) In vitro effect on Heptest of low molecular weight heparin fractions and preparations with various anti-IIa and anti-Xa activities, *Thromb Res.* 57: 585-592.

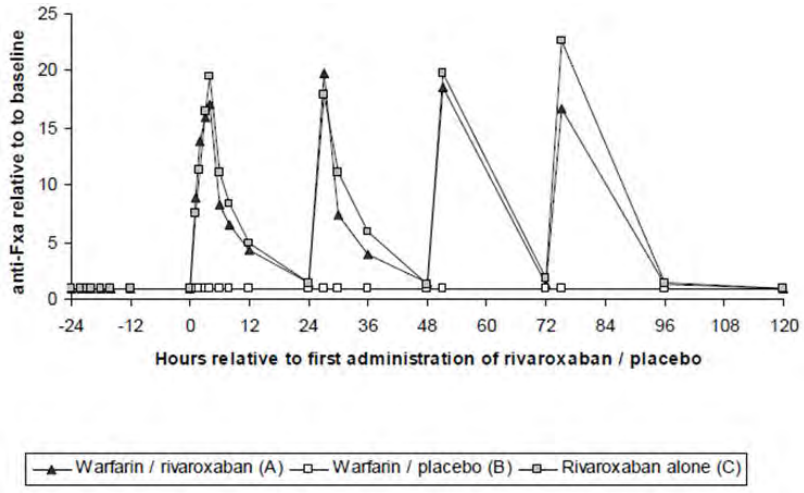
Factor Xa level did not permit discrimination between warfarin effect and rivaroxaban effect. Median Factor Xa inhibition with warfarin was increased 41 to 42% compared to baseline (Figure 1). With placebo following warfarin, the warfarin induced effect declined over the 4 days of the treatment phase. Rivaroxaban as a 20 mg dose inhibited Factor Xa activity by 50% (E_{max} of the effect versus time curve), an effect that lasted for about 24 hours after dosing. Rivaroxaban following warfarin led to a maximum inhibition of 76% (E_{max}).

Figure 1: Inhibition of Factor Xa activity: Median inhibition (%) compared to baseline following warfarin/rivaroxaban treatment (A), warfarin/placebo (B) and rivaroxaban alone (C) on last day of warfarin (Day 1) and 4 days of 20 mg rivaroxaban or placebo once daily (Day 0d to 3d), PD set, n=84 (Study 010849).



However, the increase in anti factor Xa activity appeared to be specific to rivaroxaban (Figure 2). Following rivaroxaban anti Factor Xa activity increased to a maximum of 15.8 times baseline (E_{max} of the time versus effect curve). The increase was transient with a peak 3 to 4 h after dosing and wearing off by 24 h post dose.

Figure 2: Anti Factor Xa activity: Relative change expressed as median of ratio to baseline following warfarin/rivaroxaban treatment (A), warfarin/placebo (B) and rivaroxaban alone (C) on last day of warfarin (Day 1) and 4 days of 20 mg rivaroxaban or placebo once daily (Day 0d to 3d), PD set, n=84 (Study 010849).



PT prolongation was more marked with the combination of rivaroxaban and warfarin with a maximum PT prolongation of 45 s, 4.4 times baseline (geometric mean E_{max} of the effect versus time curve) on Day 0 (Figure 3). Individual PT values close to 90 s were observed 1 h after dosing on Day 0. However, as the warfarin effect declined, baseline conditions were

reached in the morning of Day 4d prior to rivaroxaban dosing. The findings were similar when PT was measured using INR Neoplastin (Figures 4 and 5).

Figure 3: PT prolongation: Relative prolongation expressed as median of ratio to baseline following warfarin/rivaroxaban treatment (A), warfarin/placebo (B) and rivaroxaban alone (C) on last day of warfarin (Day 1) and 4 days of 20 mg rivaroxaban or placebo once daily (Day 0d to 3d), PD set, n=84 (Study 010849).

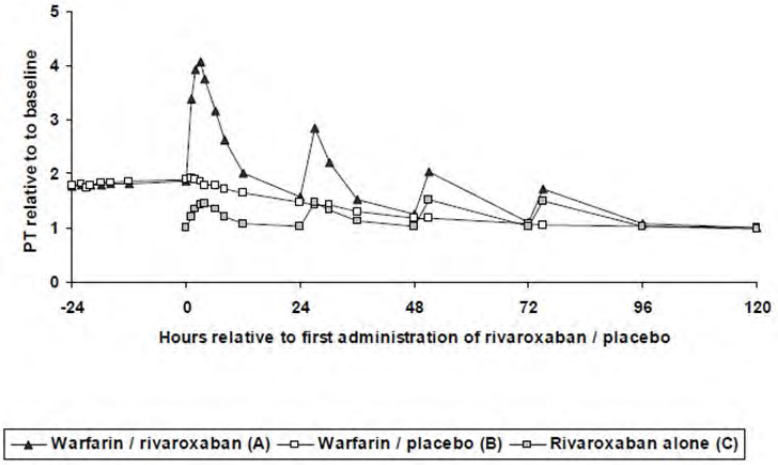


Figure 4: PT (INR Neoplastin): Median absolute values following warfarin/rivaroxaban treatment (A), warfarin/placebo (B) and rivaroxaban alone (C) on last day of warfarin (Day 1) and 4 days of 20 mg rivaroxaban or placebo once daily (Day 0d to 3d), PD set, n=84 (Study 010849).

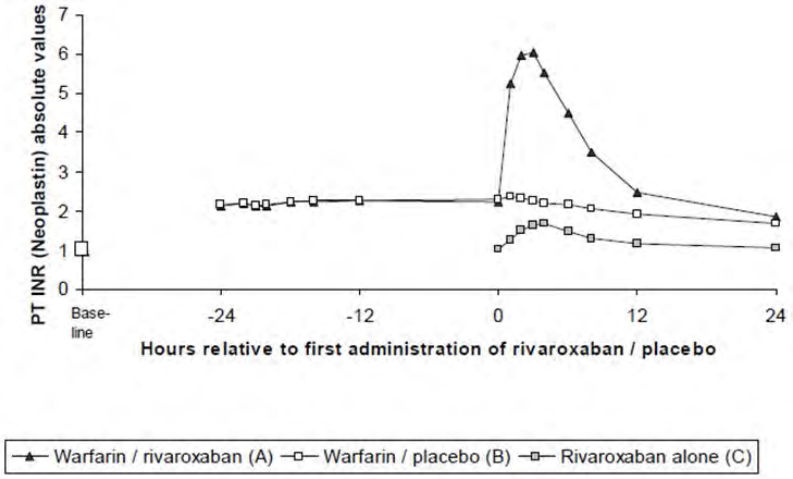
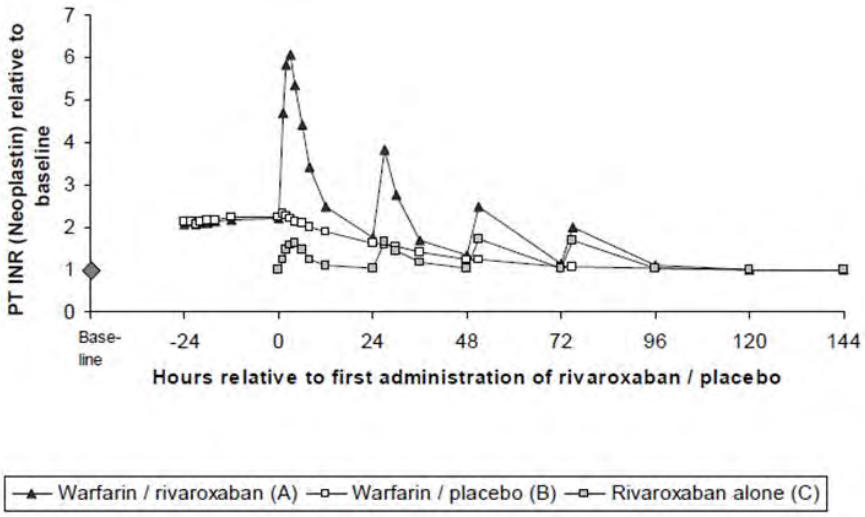
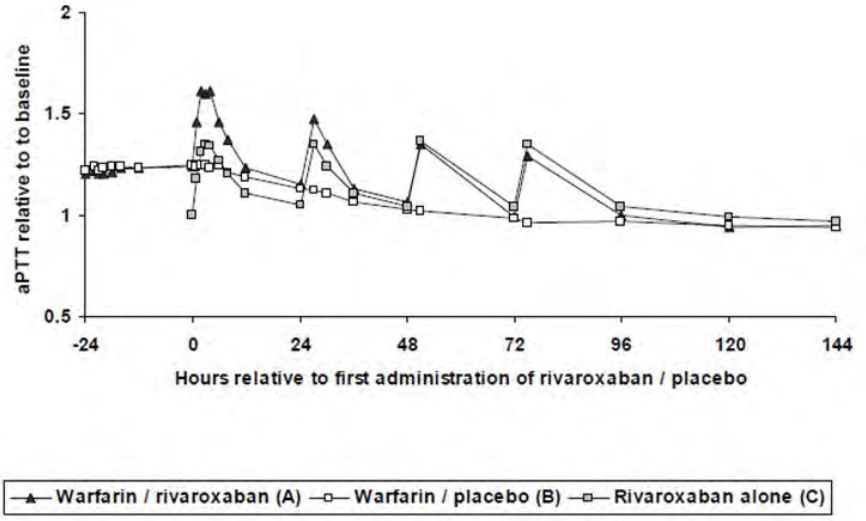


Figure 5: PT (INR Neoplastin): Relative change expressed as median of ratio to baseline following warfarin/rivaroxaban treatment (A), warfarin/placebo (B) and rivaroxaban alone (C) on last day of warfarin (Day 1) and 4 days of 20 mg rivaroxaban or placebo once daily (Day 0d to 3d), PD set, n=84 (Study 010849).



Rivaroxaban and warfarin both prolonged aPTT and their effects were additive (Figure 6). Warfarin alone prolonged aPTT by a median factor of 1.25; rivaroxaban alone prolonged aPTT by a factor of 1.41 times baseline; and in combination around 1.6 times baseline (E_{max} of the time versus effect curve).

Figure 6: aPTT prolongation: Relative prolongation expressed as median of ratio to baseline following warfarin/rivaroxaban treatment (A), warfarin/placebo (B) and rivaroxaban alone (C) on last day of warfarin (Day 1) and 4 days of 20 mg rivaroxaban or placebo once daily (Day 0d to 3d), PD set, n=84 (Study 010849).



HepTest and PiCT were also specific for rivaroxaban effect (Figures 7 and 8). Warfarin treatment and placebo following warfarin did not affect either HepTest or PiCT. Maximum effects after rivaroxaban alone were HepTest prolongations 2.01 times baseline; and following warfarin 2.15 times baseline (E_{max} of the time versus effect curve). Peak prolongations were seen 3 to 4 h after dosing and returned to pretreatment baseline 24 h. Rivaroxaban alone prolonged PiCT to a maximum of 2.7 times baseline; and following warfarin to 3.2 times baseline (E_{max} of the time versus effect curve). The peak effect was observed 3 h after dosing. After 24 h and prior to the next rivaroxaban dose, PiCT had

almost returned to baseline. As a result, HepTest and PiCT do not pick up warfarin effect and are therefore capable of monitoring rivaroxaban without warfarin interference.

Figure 7: HepTest: Relative change expressed as median of ratio to baseline following warfarin/rivaroxaban treatment (A), warfarin/placebo (B) and rivaroxaban alone (C) on last day of warfarin (Day 1) and 4 days of 20 mg rivaroxaban or placebo once daily (Day 0d to 3d), PD set, n=84 (Study 010849).

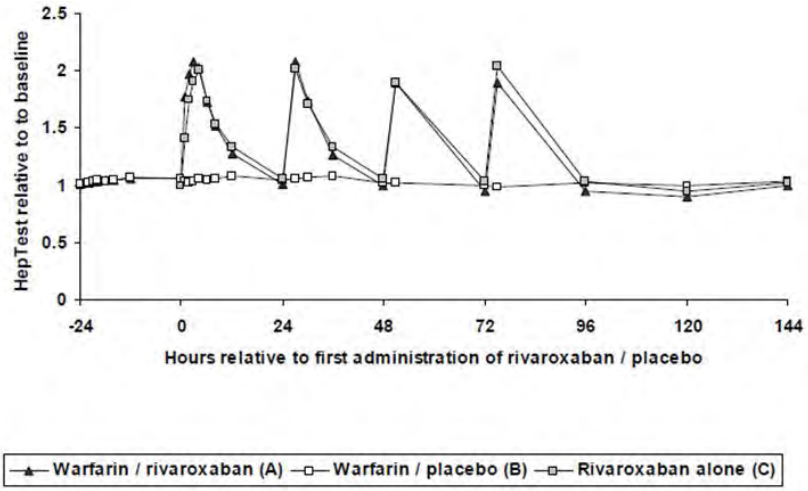
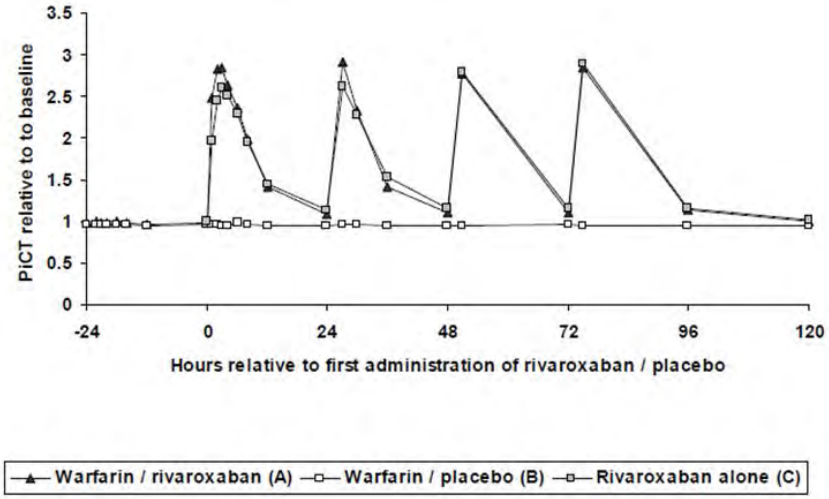


Figure 8: PiCT: Relative change expressed as median of ratio to baseline following warfarin/rivaroxaban treatment (A), warfarin/placebo (B) and rivaroxaban alone (C) on last day of warfarin (Day 1) and 4 days of 20 mg rivaroxaban or placebo once daily (Day 0d to 3d), PD set, n=84 (Study 010849).



Rivaroxaban and warfarin both increased ETP AUC over time but in combination this effect was decreased (Figure 9). For ETP lag time and ETP peak, warfarin alone had little effect, and the effects of warfarin on rivaroxaban were additive (Figures 10 and 11). Warfarin did not alter ETP time to peak, but in combination decreased the effect of rivaroxaban (Figure 12).

Figure 9: ETP AUC: Relative change expressed as median of ratio to baseline during following warfarin/rivaroxaban treatment (A), warfarin/placebo (B) and rivaroxaban alone (C) on last day of warfarin (Day 1) and 4 days of 20 mg rivaroxaban or placebo once daily (Day 0d to 3d), PD set, n=84 (Study 010849).

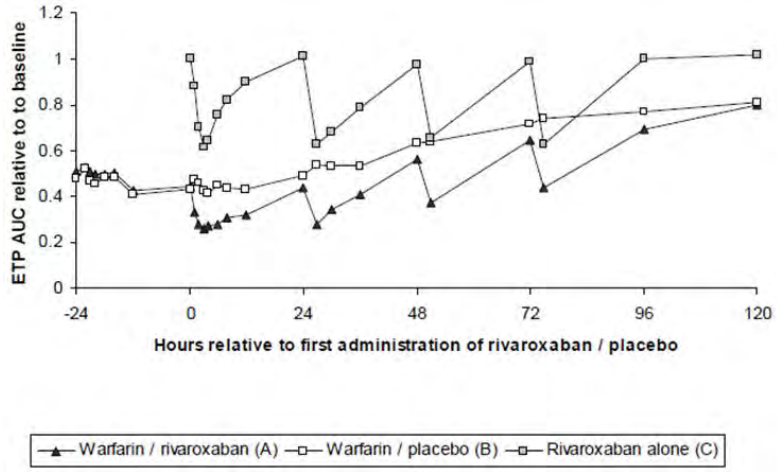


Figure 10: ETP lag time: Relative change expressed as median of ratio to baseline following warfarin/rivaroxaban treatment (A), warfarin/placebo (B) and rivaroxaban alone (C) on last day of warfarin (Day 1) and 4 days of 20 mg rivaroxaban or placebo once daily (Day 0d to 3d), PD set, n=84 (Study 010849).

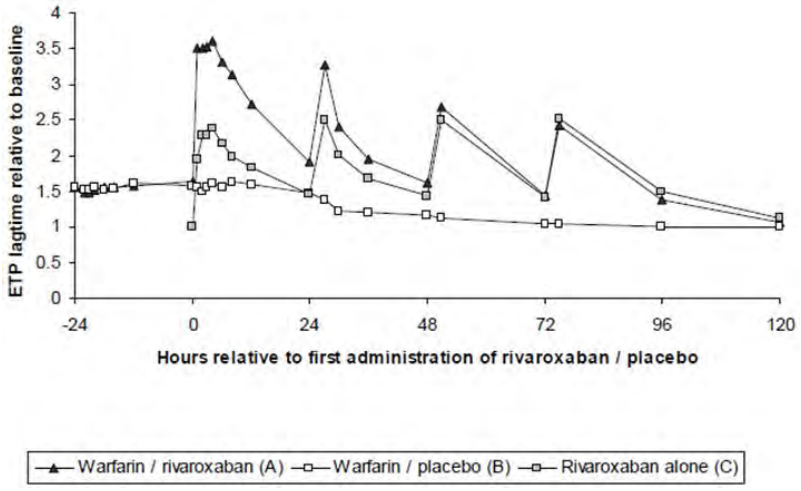


Figure 11: ETP peak: Relative change expressed as median of ratio to baseline following warfarin/rivaroxaban treatment (A), warfarin/placebo (B) and rivaroxaban alone (C) on last day of warfarin (Day 1) and 4 days of 20 mg rivaroxaban or placebo once daily (Day 0d to 3d), PD set, n=84 (Study 010849).

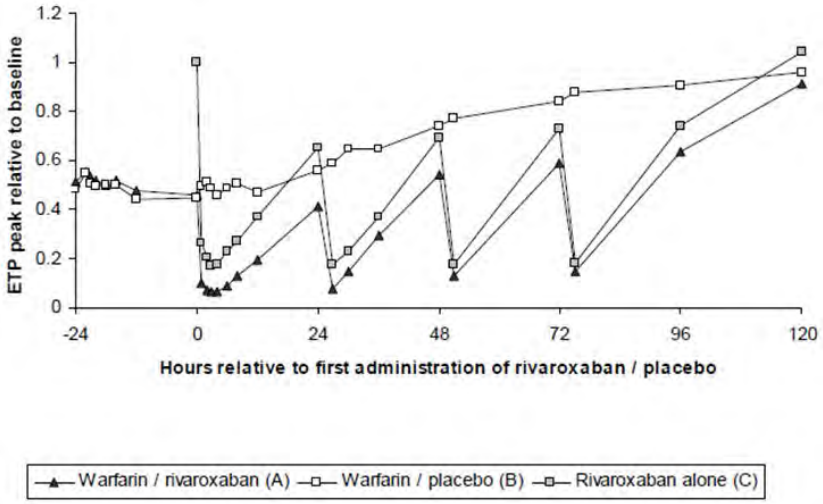
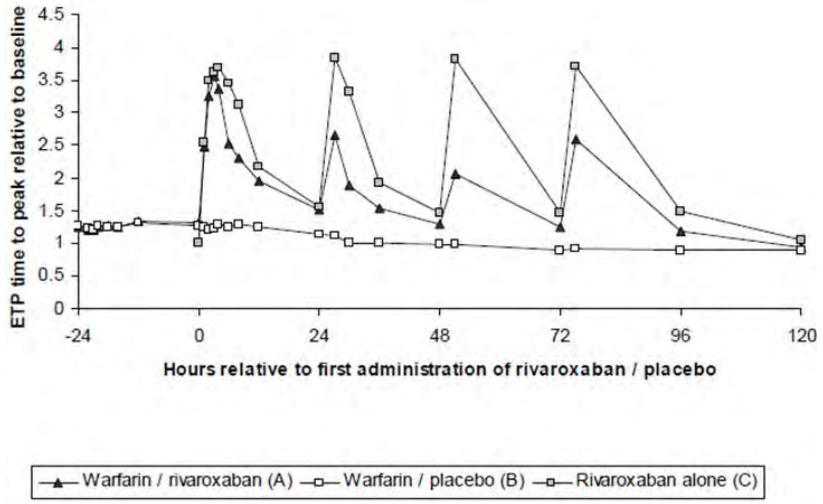
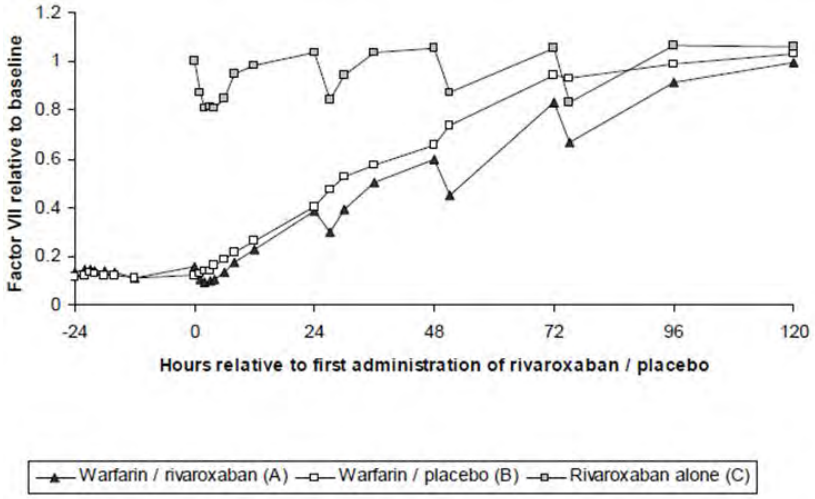


Figure 12: ETP time to peak: Relative change expressed as median of ratio to baseline following warfarin/rivaroxaban treatment (A), warfarin / placebo (B) and rivaroxaban alone (C) on last day of warfarin (Day 1) and 4 days of 20 mg rivaroxaban or placebo once daily (Day 0d to 3d), PD set, n=84 (Study 010849).



Warfarin over 6 days reduced Factor VIIa to 0.15 of its baseline values (Figure 13). Rivaroxaban alone decreased Factor VIIa to 0.74 of baseline for a period up to 8 h after dosing. Warfarin reduced Factor IIa content to 0.36 of baseline. Rivaroxaban did not significantly affect Factor IIa.

Figure 13: Factor VIIa activity: Relative change expressed as median of ratio to baseline following warfarin/rivaroxaban treatment (A), warfarin/placebo (B) and rivaroxaban alone (C) on last day of warfarin (Day 1) and 4 days of 20 mg rivaroxaban or placebo once daily (Day 0d to 3d), PD set, n=84 (Study 010849).



Studies A45974 and A45974a indicated that although CYP2C19 polymorphisms influenced the effect of clopidogrel on platelet function, there was no interactive effect of rivaroxaban.

In Study PPK03-010 (PH-33957), there was a linear relationship between PT and rivaroxaban plasma concentrations. An inhibitory E_{max} model described the plasma concentration effect relationship for factor Xa activity, HepTest and PTT.

In Study PPK04-009 (PH-34169), the plasma concentration response relationship for PT was described by a linear model with intercept (amended with a declining exponent on plasma concentration); and for factor Xa activity, HepTest and PT was described by inhibitory E_{max} models.

In Study 012143 (PH-34581 V3), the plasma concentration response relationship for PT was described by a linear model with intercept (amended with a declining exponent on plasma concentration).

In Study AFL3001 (R-8587), the plasma concentration response relationship for PT was again described by a linear model with intercept (amended with a declining exponent on plasma concentration).

Study 011940 was a perfusion chamber study examining the effect of different doses of rivaroxaban on thrombus formation with and without aspirin, and in comparison with clopidogrel and aspirin. The study compared rivaroxaban 5 mg, 10 mg, and 20 mg tablets; as single doses, with and without comedication with aspirin 100 mg (for 3 days) and 300 mg (for 1 day) as tablets; and in comparison with clopidogrel 75 mg tablet: 300 mg for 1 day, 75 mg for 3 days, in combination with aspirin. The study included 51 healthy male volunteers aged 18 to 54 years. ASA (acetylic salicylic acid) alone, or in combination with clopidogrel did not affect HepTest, aPPT, or ETP. ASA did not modify the effects of rivaroxaban on these parameters. Thrombus formation in the perfusion chamber as assessed by determination of D-dimers was reduced dose dependently by rivaroxaban both at low and high shear rates.

Study AFL3001/R-8593 was an exploratory analysis of sparse PD coagulation measurements utilising data from Study 39039039AFL3001. The report only presented the methodology for the study and states the results will be reported elsewhere.

Study PH-35408 was an integrated analysis of coagulation parameters measured in subjects actively treated with rivaroxaban based on pooled analysis of data from Studies

11354, 11355, 11356 and 11357 in order to explore the relationship between PT and adjudicated bleeding events. These studies were conducted in subjects undergoing either elective hip replacement or elective knee replacement. No hypothesis tests were performed on the data and there was no apparent association between PT and adjudicated bleeding events.

Study PH-34764 was an integrated analysis of rivaroxaban based on data from the Studies 11223 and 11528 with regard to exposure response in adjudicated efficacy events and bleeding events in subjects treated for VTE. The study explored the relationship between exposure to rivaroxaban, expressed as estimated steady state $AUC_{0\text{-}24h}$, C_{max} and C_{trough} (drug concentration in plasma at expected time of minimum [trough] concentration) and adjudicated bleeding events. There was a trend for association of increasing C_{max} with bleeding events ($p<0.05$).

Evaluator's overall conclusions on PD

The effect upon PD in the PK studies with respect to the effects of food, dose proportionality, CHF, rifampicin, clarithromycin, and omeprazole were as would be expected from the effects on PK.

Factor Xa activity, HepTest and PiCT enabled discrimination between rivaroxaban and warfarin effect (Study 010849). Rivaroxaban influenced all three of these indices whereas warfarin did not. Warfarin decreased factor IIa whereas rivaroxaban did not have a significant effect on this index.

The plasma concentration response relationship for PT was described by a linear model with intercept; and an inhibitory E_{max} model described the plasma concentration effect relationship for factor Xa activity, HepTest and PTT (Study PPK03-010, Study PPK04-009, Study AFL3001).

ASA alone, or in combination with clopidogrel did not affect HepTest, aPPT or ETP (Study 011940).

There was a trend for association of increasing C_{max} with bleeding events (Study PH-34764).

Efficacy

There was one pivotal study, Study 11702 (EINSTEIN DVT), of efficacy for the indication of "Treatment of deep vein thrombosis (DVT) and for the prevention of recurrent DVT and pulmonary embolism (PE)". This study was supported by a follow on study: Study 11899 (EINSTEIN DVT Extension); and two Phase 2 studies: Study 11223 and Study 11528.

There was one pivotal study, Study 11630 (ROCKET AF), of efficacy for the indication of "Prevention of stroke and systemic embolism in patients with non valvular atrial fibrillation". This study was supported by an efficacy study, using a different dose of rivaroxaban, in Japanese subjects: Study 12620.

Efficacy data for prevention of recurrent DVT/PE

Study 11702 (EINSTEIN DVT)

Methods for Study 11702 (EINSTEIN DVT)

Study 11702 (EINSTEIN DVT) was a multicentre, randomised, open label, parallel group, active controlled, event driven, non inferiority (NI) study; for prevention of symptomatic recurrent VTE (recurrent DVT or non fatal or fatal PE). There was a central independent

adjudication committee for suspected clinical outcomes that was blinded to treatment allocation. The study was conducted at 253 centres in 32 countries.

The inclusion criteria were: confirmed acute symptomatic proximal DVT without symptomatic PE. Diagnosis of DVT was based on either: a non compressible proximal vein on compression ultrasonography; or an intraluminal filling defect in the proximal veins on venography.

The exclusion criteria included:

- Thrombectomy, insertion of a caval filter, or use of a fibrinolytic agent to treat the current episode of DVT
- Indication for VKA (vitamin K antagonist) other than DVT
- Treatment with therapeutic dosages of LMWH/fondaparinux for more than 48 h pre randomisation, or more than a single dose of VKA prior to randomisation
- Creatinine clearance < 30 mL/min
- Significant liver disease (for example, acute hepatitis, chronic active hepatitis, cirrhosis) or ALT (alanine aminotransferase) >3x ULN
- Bacterial endocarditis
- Life expectancy <3 months
- Active bleeding or high risk for bleeding contraindicating treatment with enoxaparin or VKA
- Systolic blood pressure >180 mmHg or diastolic blood pressure >110 mmHg
- Childbearing potential without proper contraceptive measures, pregnancy or breast feeding
- Any other contraindication listed in the local labeling of warfarin, acenocoumarol, or enoxaparin
- Concomitant use of strong CYP3A4 inhibitors (for example, HIV protease inhibitors, systemic ketoconazole) or strong CYP3A4 inducers like rifampicin

The study treatments were:

1. Rivaroxaban 15 mg twice daily for 3 weeks, followed by 20 mg once daily; and
2. Enoxaparin 1 mg/kg twice daily, VKA (acenocoumarol or warfarin) to achieve target INR of 2.5 (range 2.0 to 3.0). Enoxaparin was continued until INR ≥2.0 for two consecutive measurements at least 24 h apart.

Treatment duration was for 3, 6 or 12 months as determined by the investigator prior to randomisation.

The primary efficacy outcome was symptomatic recurrent VTE; which was the composite of recurrent DVT or non fatal or fatal PE. Secondary efficacy outcome variables were:

- Secondary outcome: Recurrent DVT, non fatal PE and all cause mortality
- Net clinical benefit 1: Recurrent DVT or non fatal or fatal PE (the primary efficacy outcome) and major bleeding events
- Net clinical benefit 2: Recurrent DVT or non fatal or fatal PE (the primary efficacy outcome), major bleeding events, CV (cardiovascular) deaths, MI (myocardial infarction), strokes, and non CNS (central nervous system) systemic embolisms

The definitions for the outcome variables were:

1. Suspected (recurrent) DVT with one of the following findings:
    a. abnormal CUS where compression had been normal or, if non compressible during screening, a substantial increase (4 mm or more) in diameter of the thrombus during full compression
    b. an extension of an intraluminal filling defect, or a new intraluminal filling defect or an extension of non visualisation of veins in the presence of a sudden cut off on venography.
2. Suspected PE with one of the following findings:
    a. a (new) intraluminal filling defect in segmental or more proximal branches on spiral CT (computed tomography) scan
    b. a (new) intraluminal filling defect or an extension of an existing defect or a new sudden cutoff of vessels more than 2.5 mm in diameter on the pulmonary angiogram
    c. a (new) perfusion defect of at least 75% of a segment with a local normal ventilation result (high probability) on ventilation/perfusion lung scan (VPLS)
    d. inconclusive spiral CT, pulmonary angiography or lung scintigraphy with demonstration of DVT in the lower extremities by compression ultrasound or venography.
3. Fatal PE was:
    a. PE based on objective diagnostic testing, autopsy *or*
    b. death which cannot be attributed to a documented cause and for which DVT/PE cannot be ruled out (unexplained death).

The safety outcome variables were AEs (adverse events) and laboratory tests.

Statistical issues for Study 11702 (EINSTEIN DVT)

Hypothesis tests were performed using Kaplan Meier estimates and Cox proportional hazards models. The study was designed as a NI study, with the criterion for NI being that the upper bound of the 95% CI for the hazard ratio (HR) must be <2.0. The sample size calculation estimated that 88 events would be required to give a power of 90% to demonstrate NI for rivaroxaban with a two sided α of 0.05. It is not clear why a margin of NI of 2.0 was chosen.[8]

Results for Study 11702 (EINSTEIN DVT)

A total of 3459 subjects were enrolled, and 3449 were randomised. Included in the ITT (intention to treat) analysis were 3449 subjects (1731 rivaroxaban and 1718 enoxaparin/VKA). The safety analysis included 3429 subjects (1718 rivaroxaban and 1711 enoxaparin/VKA). The PP (per protocol) analysis included 3096 subjects (1525 rivaroxaban and 1571 enoxaparin/VKA). There were 1960 (56.8%) males, 1489 (43.2%) females and the age range was 18 to 97 years. The treatment groups were similar in demographic characteristics. The treatments groups were similar in risk factors for thromboembolism, although the pattern of thrombophilic conditions differed. The treatment groups were similar in prior medical conditions, prior antithrombotic medications, and concomitant antithrombotic medication.

Overall there were fewer events in the rivaroxaban group compared to the enoxaparin/VKA (Table 11). NI was demonstrated for rivaroxaban in comparison with enoxaparin/VKA for the primary efficacy outcome variable: HR (95% CI) 0.680 (0.443 to

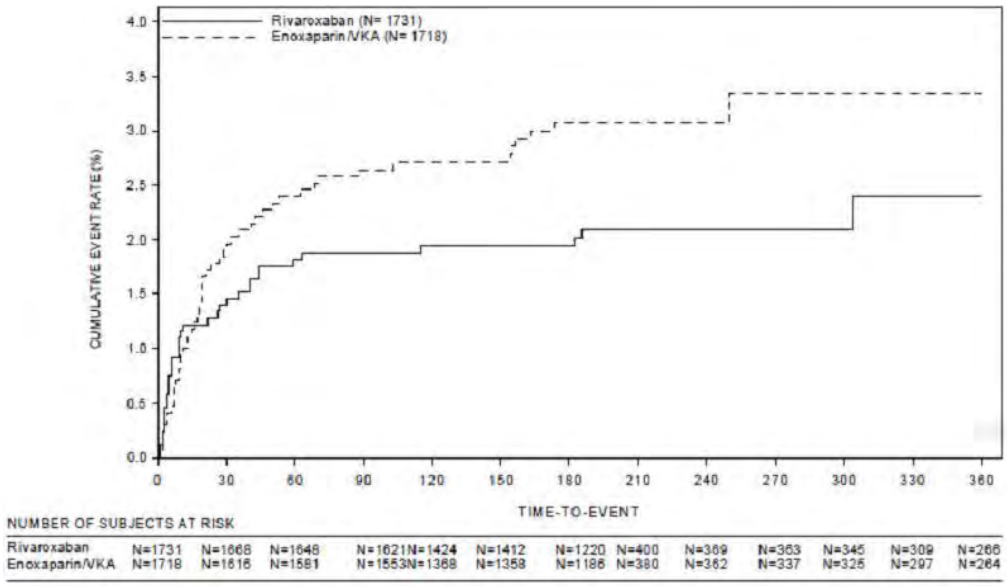
[8] Sponsor comment: "A detailed description of the choice of the NI margin was provided in the protocol."

1.042) for the ITT population and 0.698 (0.444 to 1.097) for the PP population, p<0.0001. Any apparent benefit for rivaroxaban was after the first two weeks of treatment and persisted for 12 months (Figure 14). However, in the 30 days following cessation of treatment there was a higher rate of the primary efficacy outcome variable in the rivaroxaban group (twelve (0.8%) subjects compared with seven (0.5%) in the comparator); this was attributed by the sponsor to the longer duration of action of VKA. The secondary outcome variables supported the conclusion of NI. The stratified analysis indicated increased risk of recurrence in subjects with malignancy at baseline. The incidence of all cause mortality was 38 (2.2%) subjects in the rivaroxaban group and 49 (2.9%) in the enoxaparin/VKA.

Table 11: Incidence rates of the primary and secondary efficacy outcomes (ITT population) (Study 11702 (EINSTEIN DVT)).

Outcome/ components	Rivaroxaban N=1731 (100%)	Enox/VKA N=1718 (100%)
Primary efficacy outcome (pre-specified)	36 (2.1%)	51 (3.0%)
Death (PE)	1 (<0.1%)	0
Death (PE cannot be excluded)	3 (0.2%)	6 (0.3%)
Symptomatic PE and DVT	1 (<0.1%)	0
Symptomatic recurrent PE only	20 (1.2%)	18 (1.0%)
Symptomatic recurrent DVT only	14 (0.8%)	28 (1.6%)
Secondary efficacy outcome (pre-specified)	69 (4.0%)	87 (5.1%)
Death (PE)	1 (<0.1%)	0
Death (PE cannot be excluded)	3 (0.2%)	6 (0.3%)
Death (bleeding)	1 (<0.1%)	5 (0.3%)
Death (cardiovascular)	2 (0.1%)	4 (0.2%)
Death (other)	31 (1.8%)	34 (2.0%)
Symptomatic PE and DVT	1 (<0.1%)	0
Symptomatic recurrent PE only	20 (1.2%)	18 (1.0%)
Symptomatic recurrent DVT only	14 (0.8%)	28 (1.6%)
Net clinical benefit 1 (pre-specified)	51 (2.9%)	73 (4.2%)
Death (PE)	1 (<0.1%)	0
Death (PE cannot be excluded)	3 (0.2%)	6 (0.3%)
Symptomatic PE and DVT	1 (<0.1%)	0
Symptomatic recurrent PE only	20 (1.2%)	18 (1.0%)
Symptomatic recurrent DVT only	14 (0.8%)	28 (1.6%)
Major bleeding	15 (0.9%)	23 (1.3%)
Net clinical benefit 2 (post-hoc)	62 (3.6%)	81 (4.7%)
Death (PE)	1 (<0.1%)	0
Death (PE cannot be excluded)	3 (0.2%)	6 (0.3%)
Death (cardiovascular)	2 (0.1%)	4 (0.2%)
Symptomatic PE and DVT	1 (<0.1%)	0
Symptomatic recurrent PE only	20 (1.2%)	18 (1.0%)
Symptomatic recurrent DVT only	14 (0.8%)	28 (1.6%)
Major bleeding	15 (0.9%)	23 (1.3%)
STEMI	1 (<0.1%)	0
NSTEMI	5 (0.3%)	1 (<0.1%)
Ischemic Stroke	3 (0.2%)	5 (0.3%)
Non CNS systemic embolism	2 (0.1%)	2 (0.1%)

Figure 14: Kaplan-Meier analysis: cumulative rate of primary efficacy outcome (Study 11702 (EINSTEIN DVT)).



Study 11899 (MRR-00273)

Methods for Study 11899 (MRR-00273)

Study 11899 (MRR-00273) was a multicentre, randomised, placebo controlled, double blind, parallel group, event driven superiority study for efficacy (extension of EINSTEIN study). The study was conducted at 173 centres in 28 countries. The study included subjects who had completed six months treatment with either rivaroxaban or VKA in Study 11702 (EINSTEIN DVT).[9]

The study treatments were:

1. Rivaroxaban 20 mg once daily, oral
2. Placebo once daily oral tablet

Treatment duration was for 6 or 12 months, and was determined for each subject prior to randomisation. The study was terminated once a total of at least 30 confirmed recurrent thromboembolic events had been reached.

The primary efficacy outcome measure was: composite of recurrent DVT or non fatal or fatal PE. The secondary efficacy outcome measures were:

- Secondary efficacy outcome 1:
  - a composite outcome comprising recurrent DVT, non fatal PE and all cause mortality
- Secondary efficacy outcome 2:
  - a composite outcome comprising recurrent DVT, non fatal PE, all cause mortality, strokes and myocardial infarctions
- Secondary efficacy outcome 3:
  - net clinical benefit as composite of recurrent DVT or non fatal or fatal PE (the primary efficacy outcome) and major bleeding events.

[9] Sponsor comment: "As according to protocol, patients were included if they had previously received 6 to 14 months of VKA or rivaroxaban treatment for an acute DVT or PE."

Recurrent DVT, PE and fatal PE were defined in the same manner as for Study 11702 (EINSTEIN DVT). The safety outcome measures were major bleeding events, clinically relevant non major bleeding events, all deaths, and other vascular events.

Statistical issues for Study 11899 (MRR-00273)

Hypothesis tests were performed using Cox proportional hazards models. The sample size was estimated assuming a 70% risk reduction in the rivaroxaban group as compared to the placebo group, and a total of 30 events was calculated to give a power of 90% to demonstrate that rivaroxaban was superior to placebo (two sided, α=0.05). Assuming a mean frequency for the primary efficacy outcome of 3% to 4% for the placebo group, approximately 650 subjects per group were required in each treatment group.

Results for Study 11899 (MRR-00273)

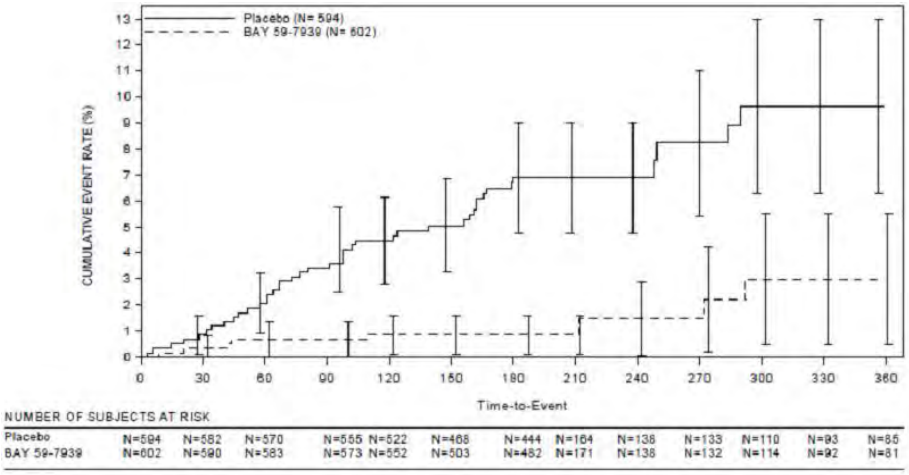
A total of 1200 subjects were enrolled, and 1197 subjects were randomised: 602 to rivaroxaban and 595 to placebo. Thirty nine (6.5%) subjects in the rivaroxaban group and 18 (3.1%) in the placebo discontinued because of an AE. There were 693 (57.9%) males, 503 (42.1%) females, and the age range was 18 to 96 years. The treatment groups were similar in demographic characteristics and risk factors for thromboembolism. There were 152 (25.2%) subjects in the rivaroxaban group and 170 (28.6%) in the placebo who received concomitant antithrombotic agents.

Superiority was demonstrated for the primary efficacy outcome measure and for all three secondary efficacy outcome measures (Table 12). For the primary efficacy outcome measure the HR (95% CI) was 0.185 (0.087 to 0.393); for secondary outcome 1: 0.180 (0.085 to 0.383); for secondary outcome 2: 0.198 (0.096 to 0.405) and for secondary outcome 3: 0.278 (0.146 to 0.528), $p<0.0001$ for all outcome measures. The treatment effect was apparent from the start of treatment through to the end of the study, 12 months in total (Figure 15). Efficacy was not influenced by demographic or baseline characteristics.

Table 12: Incidence rates of the primary and secondary efficacy outcomes and the associated results of the primary analysis (ITT population) (Study 11899 (MRR-00273)).

Variable/ components	Rivaroxaban 20 mg o.d. N=602 (100%)	Placebo N=594 (100%)	Cox's model hazard ratio rivaroxaban vs. placebo	Confidence interval (CI)
Primary efficacy outcome	8 (1.3%)	42 (7.1%)	**0.185** (p<0.0001)	0.087-0.393
Death (PE)	0	1 (0.2%)	-	-
Death (PE cannot be excluded)	1 (0.2%)	0	-	-
Symptomatic recurrent PE	2 (0.3%)	13 (2.2%)	-	-
Symptomatic recurrent DVT	5 (0.8%)	31 (5.2%)	-	-
Secondary efficacy outcome 1	8 (1.3%)	43 (7.2%)	**0.180** (p<0.0001)	0.085-0.383
Death (PE)	0	1 (0.2%)	-	-
Death (PE cannot be excluded)	1 (0.2%)	0	-	-
Death (other)	0	1 (0.2%)	-	-
Symptomatic recurrent PE	2 (0.3%)	13 (2.2%)	-	-
Symptomatic recurrent DVT	5 (0.8%)	31 (5.2%)	-	-
Secondary efficacy outcome 2	9 (1.5%)	44 (7.4%)	**0.198** (p<0.0001)	0.096-0.405
Death (PE)	0	1 (0.2%)	-	-
Death (PE cannot be excluded)	1 (0.2%)	0	-	-
Death (other)	0	1 (0.2%)	-	-
Symptomatic recurrent PE	2 (0.3%)	13 (2.2%)	-	-
Symptomatic recurrent DVT	5 (0.8%)	31 (5.2%)	-	-
STEMI	1 (0.2%)	0	-	-
Ischemic Stroke	0	1 (0.2%)	-	-
Secondary efficacy outcome 3	12 (2.0%)	42 (7.1%)	**0.278** (p<0.0001)	0.146-0.528
Death (PE)	0	1 (0.2%)	-	-
Death (PE cannot be excluded)	1 (0.2%)	0	-	-
Symptomatic recurrent PE	2 (0.3%)	13 (2.2%)	-	-
Symptomatic recurrent DVT	5 (0.8%)	31 (5.2%)	-	-
Major bleeding	4 (0.7%)	0	-	-

Figure 15: Kaplan-Meier analysis: cumulative rate of primary efficacy outcome (Study 11899 (MRR-00273)).



Study 11223

Study 11223 (MRR-00150) was a multicentre, randomised, open label, parallel group, comparator controlled, dose finding study. The study was conducted in 107 centres in 19 countries. The study included men and women ≥18 years of age with acute symptomatic proximal DVT (objectively confirmed by CCUS [complete compression ultrasound]).

The study treatments were:

1. Rivaroxaban 10 mg twice daily
2. Rivaroxaban 20 mg twice daily

3. Rivaroxaban 40 mg once daily
4. Rivaroxaban 30 mg twice daily
5. Enoxaparin 1 mg/kg bd (twice daily) subcutaneously for 5-7 days, discontinued once INR was in the range 2 to 3 for 2 consecutive days/ VKA

The primary efficacy outcome measure was the response to treatment as determined by CCUS after 3 weeks of treatment. A positive response was defined as an improvement in the CCUS score by 4 score points compared to baseline; in the absence of any confirmed symptomatic recurrence or extension of DVT, symptomatic PE or any VTE related death up to Day 21. The secondary efficacy outcome measures were:

- Improvement in the CCUS and/or PLS without any deterioration in either at Day 21.
- Response to treatment at Day 84 as assessed by CCUS.
- Residual vein diameter as assessed by CCUS on Day 84 (not evaluated in the report).
- Incidence of symptomatic and confirmed recurrence or extension of DVT during the 3 month treatment period.
- Incidence of symptomatic and confirmed PE during the 3 month treatment period.
- Composite endpoint of symptomatic and confirmed recurrence and extension of DVT and symptomatic PE (nonfatal DVT and/or nonfatal PE) and deaths during the 3 months treatment period.
- Composite endpoint of symptomatic and confirmed recurrence and extension of DVT and symptomatic PE (nonfatal DVT and/or nonfatal PE) and deaths related to VTE during the 3 months treatment period.
- Incidence of symptomatic and confirmed recurrence and extension of DVT and symptomatic PE within 30 days after ceasing treatment with study drug.

The safety outcome measures were bleeding events, AEs, and transfusion requirements.

Hypothesis tests were performed using incidence rates and exact 95% CIs. The sample size was calculated for the primary efficacy outcome measure assuming a response rate 32% in the lowest dose group and 54% in the highest dose group, for a two sided trend test with an α=0.05, a power of 85%, and a dropout rate of 25%, resulting in a requirement of 120 subjects in each treatment group.

The study included 613 subjects who were randomised to treatment: 120 to rivaroxaban 10 mg bd, 120 to 20 mg bd, 123 to 40 mg od (once daily), 124 to 30 mg bd and 126 to enoxaparin/VKA. There were 368 (61%) males, 236 (39%) females, and the age range was 10 to 91 years. The treatment groups were similar in demographic characteristics. The results for CCUS score and CCUS score plus VTE events suggested a plateau of effect at the 20 mg twice daily dose (Table 13). There were few DVT events, VTE events or deaths and this data did not contribute greatly to the analysis. There was no difference between the treatment groups in the CI analysis.

Table 13: Response to treatment based on CCUS thrombus score at visit Day 21 (ITT population) (Study 11223 (MRR-00150)).

Cut Off Score		BAY 59-7939 10 mg bid (N=106)	BAY 59-7939 mg bid (N=100)	BAY 59-7939 40 mg od (N=114)	BAY 59-7939 30 mg bid (N=111)	VKA / enoxaparin (N=112)
1 point	Missing	1 (0.9%)	1 (1.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)
	Unchanged	13 (12.3%)	9 (9.0%)	16 (14.0%)	13 (11.7%)	19 (17.0%)
	Improved	90 (84.9%)	90 (90.0%)	94 (82.5%)	95 (85.6%)	91 (81.3%)
	Deteriorated	2 (1.9%)	0 (0.0%)	4 (3.5%)	2 (1.8%)	2 (1.8%)
2 points	Missing	1 (0.9%)	1 (1.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)
	Unchanged	22 (20.8%)	22 (22.0%)	28 (24.6%)	23 (20.7%)	31 (27.7%)
	Improved	82 (77.4%)	77 (77.0%)	83 (72.8%)	87 (78.4%)	81 (72.3%)
	Deteriorated	1 (0.9%)	0 (0.0%)	3 (2.6%)	0 (0.0%)	0 (0.0%)
3 points	Missing	1 (0.9%)	1 (1.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)
	Unchanged	36 (34.0%)	31 (31.0%)	53 (46.5%)	37 (33.3%)	54 (48.2%)
	Improved	69 (65.1%)	68 (68.0%)	60 (52.6%)	73 (65.8%)	58 (51.8%)
	Deteriorated	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)
4 points	Missing	1 (0.9%)	1 (1.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)
	Unchanged	48 (45.3%)	40 (40.0%)	65 (57.0%)	47 (42.3%)	60 (53.6%)
	Improved	57 (53.8%)	59 (59.0%)	49 (43.0%)	63 (56.8%)	52 (46.4%)
	Deteriorated	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
30% change	Missing	1 (0.9%)	1 (1.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)
	Unchanged	48 (45.3%)	51 (51.0%)	69 (60.5%)	52 (46.8%)	67 (59.8%)
	Improved	56 (52.8%)	48 (48.0%)	43 (37.7%)	58 (52.3%)	45 (40.2%)
	Deteriorated	1 (0.9%)	0 (0.0%)	2 (1.8%)	0 (0.0%)	0 (0.0%)

BAY 59-7939 = rivaroxaban

Study 11528

Study 11528 (MRR-00223) was a multicentre, randomised, open label, parallel group, comparator controlled, dose finding study. The study included subjects with confirmed acute symptomatic DVT, that is, proximal or extensive calf vein thrombosis involving at least the upper third part of the calf veins, without concomitant symptomatic PE. The exclusion criteria included:

- Thrombectomy, insertion of a caval filter, or use of a fibrinolytic agent to treat the current episode of DVT
- Other indication for VKA than PE/DVT
- More than 36 h pre randomisation treatment with therapeutic dosages of LMWH or more than a single dose of VKA prior to randomisation
- CrCl <30 mL/min, impaired liver function (transaminases >2 x ULN), or bacterial endocarditis
- Life expectancy <3 months
- Active bleeding or high risk for bleeding contraindicating treatment with LMWH
- Uncontrolled hypertension: systolic blood pressure >200 mmHg and diastolic blood pressure >110 mmHg
- Pregnancy or childbearing potential without proper contraceptive measures
- Any other contraindication listed in the labeling of warfarin, acenocoumarol, phenprocoumon, fluidione, UFH, enoxaparin, or tinzaparin
- Systemic treatment with azole compounds or other strong CYP3A4 inhibitors (for example, ketoconazole, fluconazole, itraconazole, HIV protease inhibitors) within 4 days prior to randomisation and during the study

The study treatments were:

1. Rivaroxaban 20 mg orally, once daily

2. Rivaroxaban 30 mg orally, once daily
3. Rivaroxaban 40 mg orally, once daily
4. Heparin followed by VKA. The heparins could be:
    a. Unfractionated heparin 5,000 IU bolus and 1,250 IU/h IV infusion, aPTT adjusted (range 1.5-2.5)
    b. Tinzaparin 175 IU/kg once daily, subcutaneous injection
    c. Enoxaparin 1.5 mg/kg, once daily, subcutaneous injection
    d. Enoxaparin 1.0 mg/kg, twice daily, subcutaneous injection
    e. The VKA could be: warfarin, acenocoumarol, phenprocoumon or fluidione.

Treatment duration was for 12 weeks.

The primary efficacy outcome measure was the composite of symptomatic recurrent DVT or symptomatic fatal and non fatal PE at 12 weeks and deterioration in thrombotic burden, as assessed by CUS and PLS, at baseline and at 12 weeks. The secondary efficacy outcome measures were:

- All separate components of the primary efficacy outcome.
- The proportion of subjects in each study arm with improvement, no change, and deterioration on the CUS and PLS assessment.

The safety outcome measures were bleeding events and AEs.

Hypothesis tests were performed using logistic regression, Fisher's exact test and OR (95% CI). The sample size calculation used a difference in event rates of 20%, a power of 80% an alpha of 0.05 and resulted in a sample size estimation of 120 subjects in each group. This was increased to 130 per group to allow for missing data.

The study included 543 subjects, of which 136 were randomised to rivaroxaban 20 mg, 134 to 30 mg, 136 to 40 mg and 137 to LMWH/VKA. A total of 480 (89%) subjects completed. There were 277 (51.1%) males, 265 (48.9%) females, and the age range was 18 to 94 years. The treatment groups were similar in demographic characteristics. The event rates were slightly lower in the rivaroxaban groups: four (3.3%) subjects for rivaroxaban 20 mg; seven (5.9%) for 30 mg and two (1.6%) for 40 mg; compared with eight (6.7%) for heparin/VKA (Table 14). In the 30 days after ceasing treatment, there two (1.7%) VTE related deaths in the 30 mg group. The results for compression ultrasonography were similar for the four groups. The highest proportion of subjects with improvement in the PLS was in the rivaroxaban 30 mg once daily group: 40 (33%) for rivaroxaban 20 mg, 57 (48%) for 30 mg, 34 (27%) for 40 mg and 35 (29%) for heparin/VKA (Table 15). Overall, response rate to treatment was highest in the rivaroxaban 30 mg group: 95 (77%) subjects for rivaroxaban 20 mg, 98 (82%) for 30 mg, 93 (74%) for 40 mg and 82 (69%) for heparin VKA (Table 16), but there was no significant difference between the groups on CI analysis.

Table 14: Incidence of confirmed symptomatic VTE events and deaths up to Day 98 following randomisation or during follow up (ITT population) (Study 11528 (MRR-00223)).

Endpoint	BAY 59-7939 20 mg od (N=123)	BAY 59-7939 30 mg od (N=119)	BAY 59-7939 40 mg od (N=126)	(LMW) heparin/VKA (N=119)
Any event	4 (3.3%)	7 (5.9%)	2 (1.6%)	8 (6.7%)
Recurrent DVT or PE or death of any cause	3 (2.4%)	5 (4.2%)	2 (1.6%)	8 (6.7%)
Death (any cause)	1 (0.8%)	3 (2.5%)	1 (0.8%)	1 (0.8%)
PE, non fatal	1 (0.8%)	2 (1.7%)	0 (0.0%)	1 (0.8%)
DVT	2 (1.6%)	1 (0.8%)	1 (0.8%)	8 (6.7%)
Recurrent DVT or PE or VTE-related death [d]	3 (2.4%)	5 (4.2%)	2 (1.6%)	8 (6.7%)
Death (VTE related)	0 (0.0%)	2 (1.7%)	1 (0.8%)	0 (0.0%)
PE, non fatal	1 (0.8%)	2 (1.7%)	0 (0.0%)	1 (0.8%)
DVT	2 (1.6%)	1 (0.8%)	1 (0.8%)	8 (6.7%)
Recurrent VTE (DVT or PE)	3 (2.4%)	3 (2.5%)	1 (0.8%)	8 (6.7%)
PE	1 (0.8%)	2 (1.7%)	0 (0.0%)	1 (0.8%)
DVT	2 (1.6%)	1 (0.8%)	1 (0.8%)	8 (6.7%)
Recurrent DVT	2 (1.6%)	1 (0.8%)	1 (0.8%)	8 (6.7%)
DVT, proximal	2 (1.6%)	1 (0.8%)	1 (0.8%)	7 (5.9%)
DVT, distal	1 (0.8%)	0 (0.0%)	0 (0.0%)	4 (3.4%)
Recurrent PE	1 (0.8%)	2 (1.7%)	0 (0.0%)	1 (0.8%)
PE, non fatal	1 (0.8%)	2 (1.7%)	0 (0.0%)	1 (0.8%)
Recurrent DVT or PE or VTE-related death during 30-day follow-up	1 (0.8%)	4 (3.4%)	0 (0.0%)	0 (0.0%)
Death (VTE related)	0 (0.0%)	2 (1.7%)	0 (0.0%)	0 (0.0%)
PE, non fatal	1 (0.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
DVT	0 (0.0%)	2 (1.7%)	0 (0.0%)	0 (0.0%)
Recurrent DVT or PE during 30-day follow-up	1 (0.8%)	2 (1.7%)	0 (0.0%)	0 (0.0%)
PE	1 (0.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
DVT	0 (0.0%)	2 (1.7%)	0 (0.0%)	0 (0.0%)

a Incidence rate = # of subjects reporting the event after start of treatment / # of subjects in reference population.
b Except for the follow-up analysis, only events starting up to 98 days after start of treatment were included.
c Events during follow-up: Events starting between 1 day and 30 days after the end of treatment were included.
d Used for primary efficacy analysis.

BAY 59-7939 = rivaroxaban

Table 15: Perfusion lung scan evaluation (ITT population) (Study 11528 (MRR-00223)).

Evaluation result	BAY 59-7939 20 mg od (N=123)	BAY 59-7939 30 mg od (N=119)	BAY 59-7939 40 mg od (N=126)	(LMW) heparin/ VKA (N=119)
Not evaluable	0 (0%)	0 (0%)	0 (0%)	1 (1%)
Outside time window [a]	2 (2%)	3 (3%)	2 (2%)	2 (2%)
Normal (baseline and post-baseline)	40 (33%)	24 (20%)	33 (26%)	38 (32%)
Improved	40 (33%)	57 (48%)	34 (27%)	35 (29%)
Unchanged	38 (31%)	33 (28%)	53 (42%)	40 (34%)
Deteriorated	3 (2%)	2 (2%)	4 (3%)	3 (3%)

a No measurement was performed between Day 70 and Day 98 after randomization.

BAY 59-7939 = rivaroxaban

Table 16: Overall response to treatment based on CUS, PLS and confirmed symptomatic VTE events on Day 84 (ITT population) (Study 11528 (MRR-00223)).

Overall response	BAY 59-7939 20 mg od (N=123)	BAY 59-7939 30 mg od (N=119)	BAY 59-7939 40 mg od (N=126)	(LMW) heparin/ VKA (N=119)
Improved	95 (77%)	98 (82%)	93 (74%)	82 (69%)
Unchanged	19 (15%)	14 (12%)	25 (20%)	26 (22%)
Deteriorated	9 (7%)	7 (6%)	8 (6%)	11 (9%)

a Time window was Day 70 to Day 98 for CUS and PLS and up to Day 98 for VTE events.
b Response was defined as follows:
(1) Improvement – improvement in thrombus burden score (CUS) or in PLS without deterioration in either CUS and PLS and without any VTE event. If either CUS or PLS measurements were missing or outside the time window, the response was set to "missing".
(2) Unchanged – no change in thrombus burden score (CUS) or in PLS without deterioration in either CUS and PLS and without any VTE event. If either CUS or PLS measurements were missing or outside the time window, the response was set to "missing".
(3) Deterioration – deterioration in thrombus burden score (CUS) or in PLS or any VTE event.

BAY 59-7939 = rivaroxaban

Efficacy data for prevention of stroke in AF

Study 11630 (R-8570) ROCKET AF

Methods for Study 11630 (R-8570) ROCKET AF

Study 11630 (R-8570) ROCKET AF was a multicentre, randomised, double blind, double dummy, parallel group, active comparator, event driven, NI study. The study was conducted at over 1170 sites in 45 countries.

The inclusion criteria included:

- Men or women aged ≥18 years with non valvular AF (that is, AF in the absence of rheumatic mitral valve disease, a prosthetic heart valve or mitral valve repair)
- AF was documented by ECG (electrocardiogram) evidence (for example, 12 lead ECG, rhythm strip, Holter, pacemaker interrogation) within 30 days before randomisation. In addition, subjects had to have medical evidence of AF within one year before and at least one day before the qualifying ECG evidence;
- Subjects with newly diagnosed AF provided that:
  - AF was non valvular;
  - Cardioversion was not planned;
  - ECG evidence on two occasions 24 h apart demonstrating AF;
- History of prior ischemic stroke, TIA (transient ischemic attack) or non CNS systemic embolism believed to be cardioembolic in origin or with two or more of the following risk factors:
  - Heart failure and/or left ventricular ejection fraction ≤35%;
  - Hypertension (defined as use of antihypertensive medications within 6 months before the screening visit or persistent systolic blood pressure above 140 mmHg or diastolic blood pressure above 90 mmHg);
  - Age ≥75 years;
  - Diabetes mellitus (defined as a history of type 1 or type 2 diabetes mellitus or use of anti diabetic medications within 6 months before screening visit);
- Female subjects were postmenopausal (for at least 2 years), surgically sterile, abstinent, or, if sexually active, practicing an effective method of birth control and, for those of childbearing potential, had a negative β-hCG (human chorionic gonadotropin) pregnancy test at screening.

The exclusion criteria included:

- Cardiac Related Conditions: hemodynamically significant mitral valve stenosis; prosthetic heart valve; planned cardioversion; transient AF caused by a reversible disorder (for example, thyrotoxicosis, PE, recent surgery, MI); known presence of atrial myxoma or left ventricular thrombus; and active endocarditis
- Hemorrhage Risk Related Criteria:
  - Active internal bleeding
  - History of or condition associated with increased bleeding risk including, but not limited to:
    - Major surgical procedure or trauma within 30 days
    - Clinically significant gastrointestinal bleeding within 6 months

  - History of intracranial, intraocular, spinal, or atraumatic intra-articular bleeding
  - Chronic haemorrhagic disorder
  - Known intracranial neoplasm, arteriovenous malformation, or aneurysm
  - Planned invasive procedure with potential for uncontrolled bleeding, including major surgery
  - Platelet count <90,000/μL at the screening visit
  - Sustained uncontrolled hypertension: systolic blood pressure ≥180 mmHg or diastolic blood pressure ≥100 mmHg

- Concomitant Conditions and Therapies
  - Severe, disabling stroke (modified Rankin score of 4 to 5, inclusive) within 3 months or any stroke within 14 days
  - TIA within 3 days before the randomisation visit
  - Indication for anticoagulant therapy for a condition other than AF (for example, VTE)
  - Treatment with:
    - ASA >100 mg daily
    - ASA in combination with thienopyridines within 5 days before randomisation
    - IV antiplatelets within 5 days before randomisation;
    - Fibrinolytics within 10 days before randomisation
    - Anticipated need for chronic treatment with a NSAID (non steroidal anti inflammatory drug)
    - Systemic treatment with a strong inhibitor of CYP3A4, such as ketoconazole or protease inhibitors, within 4 days before randomisation, or planned treatment during the time period of the study
    - Treatment with a strong inducer of cytochrome CYP3A4, such as rifampin/rifampicin, within 4 days before randomisation, or planned treatment during the time period of the study
  - Anaemia (haemoglobin <10 g/dL) at the screening visit
  - Any other contraindication to warfarin
  - Known human immunodeficiency virus (HIV) infection at time of screening
  - Calculated CrCl <30 mL/min at the screening visit
  - Known significant liver disease (for example, acute clinical hepatitis, chronic active hepatitis, cirrhosis), or ALT >3x ULN)
- Serious concomitant illness associated with a life expectancy of less than 2 years
- Drug addiction or alcohol abuse within 3 years before the randomisation visit
- Known allergy or hypersensitivity to any component of rivaroxaban, warfarin or placebo excipients

The study treatments were:

1. Oral Rivaroxaban 20 mg once daily plus oral warfarin placebo once daily titrated to a target sham INR of 2.5 (range 2.0 to 3.0, inclusive). Subjects with moderate renal

impairment at screening (defined as calculated CrCl between 30 and 49 mL/min, inclusive) had a dose adaptation to oral rivaroxaban, 15 mg once daily; and

2. Oral warfarin once daily titrated to a target INR of 2.5 (range 2.0 to 3.0, inclusive) plus oral rivaroxaban placebo once daily.

Subjects were randomised to rivaroxaban or placebo in a 1:1 ratio using a computer generated randomisation schedule.

All subjects were required to have periodic INR testing regardless of treatment allocation. To maintain the study blind, a point of care device – the Hemosense INRatio PT/INR monitor – was used to obtain INRs. The INRatio monitor was slightly modified by the manufacturer (Hemosense) with a software program so that it did not report an INR value. The readout on the screen was a seven digit code that corresponded to the actual or shammed INR value (there were multiple seven digit codes assigned to each INR value to prevent inadvertent unblinding by the investigative site). To obtain an INR value for that individual test, the investigator called the IVRS (interactive voice response system) or accessed the IWRS (interactive web response system) and entered the subject's identifying information. After entering the identifying information as well as the last three doses of warfarin or warfarin placebo, the investigator entered the seven digit code obtained from the INRatio monitor. If the subject was randomized to warfarin, the INR value reported by the IVRS/IWRS was the actual value. If the subject was randomised to rivaroxaban (with warfarin placebo) the INR value given by the IVRS/IWRS was a sham value that mimicked values obtained as if the subject were taking warfarin.

The primary efficacy outcome measure was the composite of stroke and non CNS systemic embolism. Adjudicated results (by the independent blinded CEC [Clinical Endpoint Committee]) were used for the analysis. Stroke was defined as a new, sudden, focal neurological deficit resulting from a presumed cerebrovascular cause that was not reversible within 24 h and not due to another readily identifiable cause such as a tumour, seizure, or trauma. A non CNS embolism was defined as an abrupt vascular insufficiency associated with clinical or radiological evidence of arterial occlusion in the absence of other likely mechanisms. The major secondary efficacy outcome measures were:

- Major Secondary Endpoint 1: composite of stroke, non CNS systemic embolism, and vascular death
- Major Secondary Endpoint 2: composite of stroke, non CNS systemic embolism, MI, and vascular death

Other secondary efficacy outcome measures were:

- Individual components of the composite primary and major secondary efficacy endpoints
- Disabling stroke
- All cause mortality

The subject's global function was measured using the modified Rankin Scale where:

- 0 = No symptoms at all
- 1 = No significant disability despite symptoms: able to carry out all usual duties and activities
- 2 = Slight disability: unable to carry out all previous activities but able to look after own affairs without assistance
- 3 = Moderate disability: requiring some help, but able to walk without assistance

- 4 = Moderately severe disability: unable to walk without assistance and unable to attend to own bodily needs without assistance
- 5 = Severe disability: bedridden, incontinent and requiring constant nursing care and attention
- 6 = Subject death

The safety outcome measures were: AEs, bleeding events, laboratory tests, ECGs and vital signs.

Statistical Issues for Study 11630 (R-8570) ROCKET AF

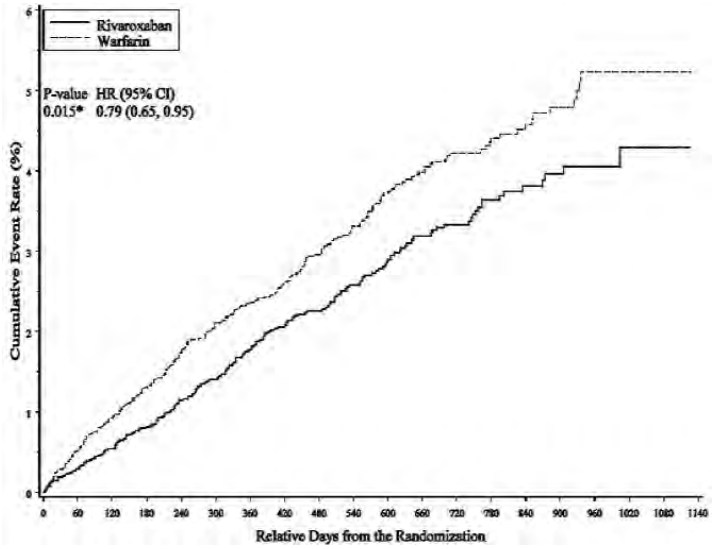
Hypothesis tests were performed using Cox proportional hazards models to determine HR (95% CI). The criterion for NI was that the upper 95% CI for the HR for rivaroxaban/warfarin must be <1.46. It is not clear in the report why this margin for NI was selected.[8] There was a predefined procedure for multiple hypothesis testing. The sample size calculation was performed on the basis of the number of events required at a two sided significance level of 0.05, for a power of >95% when the true risk ratio is 1; this was estimated to be 363 events. This value was increased by ~10% to 405 events in order to provide a more robust number of events to assess consistency across important subgroups. Assuming a total duration of enrollment of approximately 1.5 years, a warfarin treatment group event rate of 2.3% per patient year and a yearly dropout rate of 14%, the total number of randomised subjects was estimated to be approximately 14000.

Results for Study 11630 (R-8570) ROCKET AF

There were 14269 subjects randomised to treatment: 7133 to rivaroxaban and 7136 to warfarin. The ITT population included 7131 subjects in the rivaroxaban group and 7133 in the warfarin. There were 5637 subjects treated with rivaroxaban 20 mg once daily, 1474 treated with rivaroxaban 15 mg once daily and 7125 treated with warfarin. In the ITT population, there were 8604 (60.32%) males, 5660 (39.68%) females, and the age range was 25 to 97 years. The treatment groups were similar in baseline and demographic variables, risk factors and concomitant medication. The treatment groups were also similar in antithrombotic treatments received after ceasing study treatment. For the warfarin treatment group, only 55.16% of INR measurements taken during the study were in the target range of 2 to 3.

For the primary efficacy outcome measure NI was demonstrated by the PP analysis and superiority by the ITT analysis. The HR (95%) CI was 0.79 (0.66 to 0.96), p<0.001 for the PP analysis and 0.79 (0.65 to 0.95), p=0.015, for the ITT analysis. For the ITT analysis, the event rate for rivaroxaban was 1.70/100 patient years and for warfarin was 2.15/100 patient years. The effect was apparent from the beginning to the end of the study (Figure 16). Effect was not apparent for subjects with prior stroke/TIA/non CNS systemic embolism at baseline: HR 0.91 (0.72 to 1.14) compared to those without: HR 0.59 (0.42 to 0.83) (p = 0.039 for covariate effect). Other than this, the primary efficacy outcome measure was not influenced by baseline characteristics. Efficacy was also demonstrated for major Secondary Endpoint 1 (composite of stroke, non CNS systemic embolism, and vascular death), HR (95% CI) 0.86 (0.74 to 0.99) and also major Secondary Endpoint 2 (composite of stroke, non CNS systemic embolism, MI, and vascular death), 0.85 (0.85 (0.74 to 0.96); but not for all cause mortality. Efficacy was also demonstrated for the secondary efficacy outcomes of primary haemorrhagic stroke, HR (95% CI) 0.59 (0.37 to 0.93) and non CNS systemic embolism, 0.23 (0.09 to 0.61) but not for any other secondary efficacy outcome measure.

Figure 16: Kaplan-Meier plots of time from randomisation to the first occurrences of primary efficacy endpoint (adjudicated by CEC) while on treatment (up to last dose plus 2 days) (Study 39039039AFL3001: Safety (Excluding Site 042012) Analysis Set) (Study 11630 (R-8570) ROCKET AF).



When stratified by time in the TTR (therapeutic range), NI was still demonstrated for rivaroxaban in comparison with those centres where subjects treated with warfarin were in the TTR 65.54% to 100% of the time: HR (95% CI) 0.74 (0.49 to 1.12). However, the effect size was in favour of rivaroxaban to a greater extent in those centres where there was poor INR control.

Study 12620 (A49701)

Methods for Study 12620 (A49701)

Study 12620 (A49701) was a randomised, double blind, double dummy, parallel group study in Japanese subjects.

The inclusion criteria included:

- Age 20 years or older
- Japanese male or female subjects
- AF that was non valvular and documented by ECG within 30 days before randomisation. In addition, subjects with medical evidence of AF within 1 year before and at least 1 day before the qualifying ECG. Subjects with newly diagnosed AF were eligible provided that there was evidence that the AF was non valvular, and that there was ECG evidence on two occasions 24 h apart demonstrating AF.
- Subjects with a history of prior ischemic stroke, TIA or non CNS systemic embolism, or those with at least two of the following risk factors:
  - Heart failure and/or left ventricular ejection fraction of less than or equal to 35%
  - Hypertension (defined as use of antihypertensive medications within 6 months before the screening visit or persistent systolic blood pressure above 140 mmHg or diastolic blood pressure above 90 mmHg)
  - 75 years or older
  - Diabetes (defined as a history of type 1 or type 2 diabetes mellitus or use of anti diabetic medications within 6 months before screening visit)

The exclusion criteria included:

Cardiac related conditions:

- Hemodynamically significant mitral valve stenosis
- Prosthetic heart valve
- Planned cardioversion (electrical or pharmacological)
- Transient AF caused by reversible disease (for example, thyrotoxicosis, PE, recent surgery, or myocardial infarction)
- Known presence of atrial myxoma or left ventricular thrombus
- Active endocarditis

Hemorrhagic risk related criteria:

- Active internal bleeding
- History of or condition associated with increased bleeding including, but not limited to:
  - History of major surgery or trauma within 30 days before randomisation
  - History of significant gastrointestinal bleeding within 6 months before randomisation
  - History of intra cranial bleeding, intra ocular bleeding, spinal bleeding, or atraumatic intra articular bleeding
  - Chronic haemorrhagic disorder
  - Known intra cranial neoplasm, arteriovenous malformation, or aneurysm
  - Scheduled invasive procedure including major surgery for which haemorrhage may not be controlled
  - Thrombocytopenia at screening visit (platelet count <90,000/μL)
  - Persistent, poorly controlled hypertension: systolic blood pressure ≥180 mmHg or diastolic blood pressure ≥100 mmHg

Concomitant conditions and therapy:

- Stroke with severe residual disability within 3 months before randomisation (4 to 5 points, inclusive, according to modified Rankin scale) or any stroke within 14 days before randomisation (irrespective of severity)
- TIA within 3 days before randomisation
- Diseases other than AF for which anticoagulation therapy was indicated (for example, VTE)
- Subjects treated with anti platelet therapy by the oral or transvenous route within 5 days before randomisation, or who concomitantly required it during the trial (except for 100 mg/day or lower of aspirin; thienopyridines or cilostazol was allowed for subjects who received coronary stent insertion) or subjects treated with fibrinolytic therapy within 10 days before randomisation or who concomitantly required it during the trial
- Subjects expected to chronically use a NSAID except for external preparations
- Subjects treated with a strong cytochrome CYP3A4 inhibitor such as ketoconazole, clarithromycin or protease inhibitors, and a strong cytochrome CYP3A4 inducer such as rifampicin within 4 days before randomisation, or those scheduled to receive such a drug during the trial

- Anaemia (haemoglobin <10 g/dL)
- Pregnant or lactating women
- Subjects for whom warfarin was contraindicated
- Known HIV infection
- Calculated CrCl of less than 30 mL/min using the Cockroft Gault formula
- ALT level greater than 3 x ULN or significant liver disease (such as acute hepatitis, chronic active hepatitis, or liver cirrhosis)

Study participation and follow up criteria:

- Serious concomitant illness associated with a life expectancy of less than 2 years
- Drug addiction or alcohol abuse within 3 years before randomisation
- Known allergy or hypersensitivity to any component of rivaroxaban, warfarin, or their placebo excipients

The study treatments were:

1. Rivaroxaban 15 mg once daily, dose decreased to rivaroxaban 10 mg once daily in subjects with CrCl 30 to 49 mL/min
2. Warfarin: adjusted on the basis of INR values (1.6 to 2.6 for subjects ≥70 years old, 2.0 to 3.0 for subject <70 years old

Assignment to treatment group was by interactive voice response system. A lower dose was selected for these Japanese subjects because steady state exposure in Japanese AF patients treated with rivaroxaban 20 mg once daily was ~20 to 30% higher in Japanese patients versus Caucasian patients based on the results of population PK models. In addition, VKA therapy in Japan is different to that in other regions because the local treatment guidelines in Japan recommend lower INR levels compared to the ACCP (American College of Chest Physicians) guidelines.

The primary efficacy outcome measure was the composite of adjudicated stroke and non CNS systemic embolism. The secondary efficacy outcome measures were:

- Major secondary efficacy endpoint 1: the composite of adjudicated stroke, non CNS systemic embolism, and vascular death
- Major secondary efficacy endpoint 2: The composite of adjudicated stroke, non CNS systemic embolism, myocardial infarction, and vascular death
- Each component of the above composite events
- Stroke with serious residual disability (3 to 5 points, inclusive, according to the modified Rankin scale)
- All cause death

Safety outcome measures included bleeding events, AEs and laboratory tests.

Statistical Issues for Study 12620 (A49701)

Hypothesis tests were performed using Cox proportional hazards models. The study was designed as a NI study, based on the primary efficacy outcome measure, with a margin of 2 for the upper 95% CI of the HR. The choice of NI margin appears to be based on clinical judgement of an acceptable margin of risk but it is not clear how the sponsor determined this.[8] A total of 65% of the subjects in the warfarin group maintained target INR range throughout the study.

Results for Study 12620 (A49701)

A total of 1439 subjects were screened, of whom 1280 were randomised to treatment and included in the ITT population: 640 in each treatment group. A total of 480 (75.1%) subjects in the rivaroxaban group and 468 (73.2%) in the warfarin completed the double blind treatment period. There were 1030 (80.6%) males, 248 (19.4%) females, and the age range was 34 to 90 years. The treatment groups were similar in demographic characteristics, prior morbidity and thromboembolism risk factors. However, more subjects in the rivaroxaban group were receiving concomitant ASA: 245 (38.3%) compared with 225 (35.2%) in the warfarin group. In the warfarin group, during the treatment phase, 28.0% of INR results were below TTR, 65.0% were in the TTR and 6.9% were above the TTR.

For the primary efficacy outcome measure NI was demonstrated by the PP analysis. There were 11 events in the rivaroxaban group and 22 in the warfarin, HR (95% CI) 0.49 (0.24 to 1.00). The ITT analysis supported NI but did not demonstrate superiority for rivaroxaban. There were 22 events in the rivaroxaban group and 26 in the warfarin, HR (95% CI) 0.82 (0.46 to 1.45). The PP analysis was not influenced by baseline demographic characteristics or risk factors. The secondary endpoints were analysed for the PP population rather than the ITT population. The results that were supportive of the primary efficacy outcome measure were: major secondary efficacy endpoint 1: HR (95% CI) 0.65 (0.34 to 1.22); major secondary efficacy endpoint 2: 0.74 (0.41 to 1.34); stroke 0.46 (0.22 to 0.98); primary haemorrhagic stroke 0.73 (0.16 to 3.25); primary ischemic stroke: 0.40 (0.17 to 0.96); and stroke with serious residual disability: 0.48 (0.16 to 1.39). The results that did not support the primary efficacy outcome measure were: myocardial infarction: HR (95% CI) 2.92 (0.30 to 28.12); vascular death: 2.96 (0.60 to 14.69) and all cause death 1.37 (0.43 to 4.31). The result for non CNS systemic embolism was equivocal: HR (95% CI) 0.99 (0.06 to 15.83).

Evaluator's overall conclusions on clinical efficacy

Conclusions regarding DVT treatment and prevention of recurrent VTE

Study 11702 (EINSTEIN DVT) demonstrated NI for rivaroxaban in comparison with enoxaparin/VKA for the indication of "treatment of DVT and for the prevention of recurrent DVT and PE". The use of survival analysis was appropriate. The outcome measures were clinically relevant and related directly to the proposed indication. The NI margin of 2 was generous and it is not clear how it was determined, but the actual upper 95% CI was less than 1.5, and the HR was less than 1. The secondary analyses and secondary efficacy outcome measures were supportive of the primary analysis. The benefit was maintained throughout the duration of the study. However, in the 30 days following cessation of treatment there was a higher rate of the primary efficacy outcome variable in the rivaroxaban group (12 subjects; 0.8%) compared with the comparator (7 subjects; 0.5%). Although this was attributed by the sponsor to the longer duration of action of VKA, it raised the question as to whether longer duration of treatment with rivaroxaban should be advised. Rivaroxaban did not result in a statistically significant improvement in mortality compared to warfarin but the incidence of all cause mortality was 38 (2.2%) subjects in the rivaroxaban group and 49 (2.9%) in the enoxaparin/VKA.

The dose of enoxaparin used in Study 11702 (EINSTEIN DVT) was consistent with the enoxaparin PI. The target INR range of 2 to 3 was consistent with accepted guidelines. The open label design of Study 11702 (EINSTEIN DVT) could have introduced bias, but the use of a "central independent adjudication committee for suspected clinical outcomes that was blinded to treatment allocation" should have minimised such bias. In addition, the outcome measures were objective measures, as opposed to subjective measures such as questionnaires, and less prone to measurement bias.

A separate statistical analysis was not presented for the outcome of PE. However, PE was included in the composite primary outcome measure, which is also similar in wording to the proposed indication. The rates of PE were similar in the two treatment groups and there does not appear to be a divergence in effect for DVT and PE. Hence, it is reasonable to include PE in the indication.

Study 11899 (EINSTEIN DVT Extension) demonstrated superiority for rivaroxaban in comparison with placebo for extension of treatment for VTE prophylaxis. Efficacy was convincingly demonstrated for all the outcome measures. For the primary efficacy outcome measure, the HR (95% CI) was 0.185 (0.087 to 0.393); for secondary outcome 1: 0.180 (0.085 to 0.383); for secondary outcome 2: 0.198 (0.096 to 0.405); and for secondary outcome 3: 0.278 (0.146 to 0.528); p<0.0001 for all outcome measures. The treatment effect was maintained for 12 months. Hence, although the extended duration of treatment was not standard practice the study has demonstrated benefit for extended treatment.

The dose finding studies did not give a clear indication as to the choice of rivaroxaban dose for in the Phase 3 studies. There appeared to be a plateau of effect at the rivaroxaban 20 mg twice daily dose in Study 11223. In Study 11528, the overall response rate to treatment was highest in the rivaroxaban 30 mg once daily group: 95 (77%) subjects for rivaroxaban 20 mg, 98 (82%) for 30 mg, 93 (74%) for 40 mg, and 82 (69%) for heparin VKA. It is not clear why the sponsor decided to proceed with the 20 mg once daily dose in the development program instead of the 30 mg once daily dose. The sponsor may have used additional data, from other studies using rivaroxaban, in determining the final dose used in the Phase 2 studies, but this is not transparent.[10]

Conclusions regarding stroke prevention in AF

Study 11630 (ROCKET AF) demonstrated superiority for rivaroxaban in comparison with VKA for the indication *"prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation"*. This was demonstrated using the predefined procedure for multiple hypothesis testing where firstly for the primary efficacy outcome measure NI was demonstrated by the PP analysis and then superiority by the ITT analysis. The HR (95%) CI was 0.79 (0.66 to 0.96), p<0.001 for the PP analysis; and 0.79 (0.65 to 0.95), p=0.015 for the ITT analysis. The reduction in event rate was clinically significant: ITT analysis event rate for rivaroxaban was 1.70/100 patient years and for warfarin was 2.15/100 patient years. The outcome measures were clinically relevant and related directly to the proposed indication. Although the NI margin of 1.46 for the HR for rivaroxaban/warfarin was generous, the ITT analysis subsequently proved superiority. The effect was apparent from the beginning to the end of the study. The effect was not apparent for subjects with prior stroke/TIA/non CNS systemic embolism at baseline but other than this, the primary efficacy outcome measure was not influenced by baseline characteristics. The conclusion of efficacy was supported by Major Secondary Endpoint 1 (composite of stroke, non CNS systemic embolism, and vascular death), HR (95% CI) 0.86 (0.74 to 0.99); Major Secondary Endpoint 2 (composite of stroke, non CNS systemic embolism, MI, and vascular death), 0.85 (0.85 (0.74 to 0.96); primary haemorrhagic stroke, HR (95% CI) 0.59 (0.37 to 0.93); and non CNS systemic embolism, 0.23 (0.09 to 0.61). However, there was no significant improvement in all cause mortality or for any other secondary efficacy outcome measure. For the warfarin treatment group, only 55.16% of INR measurements were in the target range of 2 to 3. This may have influenced the results in favour of rivaroxaban, but is also fairly typical of warfarin treatment control in clinical practice. However, NI was also demonstrated in those centres with good INR control.

[10] Sponsor comment: "All data generated were submitted in the dossier and a detailed description of dose selection was provided."

Non CNS systemic embolism is also included in the proposed indication and the HR (95% CI) of 0.23 (0.09 to 0.61) support its inclusion. The results for stroke (except for non disabling stroke) were also in favour of rivaroxaban. Hence, the separate components of the indication are supported by the data.

Study 12620 was conducted in Japanese subjects using a lower dose than that used in Study 11630 (ROCKET AF). For the primary efficacy outcome measure, NI was demonstrated by the PP analysis. There were 11 events in the rivaroxaban group and 22 in the warfarin group, HR (95% CI) 0.49 (0.24 to 1.00). This was supported by the ITT analysis. The margin for NI of 2 was generous, but the primary analysis had an upper 95% CI of 1; this was well within the NI margin.

Safety

Safety data were primarily from the efficacy studies reviewed above. In the efficacy studies there were 3212 subjects exposed to rivaroxaban for the indication of "treatment of DVT and for the prevention of recurrent DVT and PE". There were 7751 subjects exposed to rivaroxaban for the indication of "prevention of stroke and systemic embolism in patients with non valvular AF".

Pooled analyses of safety data from Phase 1 studies were also provided, in addition to some pooled safety analyses from the efficacy studies.

Patient exposure

In Study 11702 (EINSTEIN DVT), 1731 subjects were exposed to rivaroxaban, with 859 exposed for 6 months or more and 49 for 12 months or more.

In Study 11899 (MRR-00273), 598 subjects were exposed to rivaroxaban, with 372 exposed for ≥6 months, and 12 exposed for ≥12 months.

In Study 11223 (MRR-00150), 119 subjects were treated with rivaroxaban 10 mg twice daily for up to 97 days, 117 with 20 mg twice daily for up to 107 days, 121 with 40 mg once daily for up to 104 days, and 121 with 30 mg twice daily for up to 106 days.

In Study 11528 (MRR-00223), 135 subjects were treated with rivaroxaban 20 mg once daily for up to 96 days, 134 subjects with 30 mg for up to 95 days, and 136 with 40 mg for up to 96 days.

In Study 11630 (R-8570) ROCKET-AF, a total of 7111 subjects were exposed to rivaroxaban, with 5558 subjects exposed for ≥12 months, 2512 subjects for ≥24 months and 141 for ≥36 months. It is not clear how many subjects were treated with rivaroxaban 20 mg and how many with rivaroxaban 15 mg.

In Study 12620 (A49701), a total of 640 subjects were exposed to rivaroxaban 15 mg or 10 mg, 608 were exposed for ≥12 months, and 196 for ≥24 months.

Adverse Events (AEs)

Treatment Emergent Adverse Events (TEAEs)

In Study 11702 (EINSTEIN DVT), TEAEs were reported in 1078 (62.7%) subjects in the rivaroxaban group and 1080 (63.1%) in the enoxaparin/VKA. The profile of TEAEs was similar for the two treatment groups (Table 17). Menorrhagia was more common in the rivaroxaban group: 49 (2.9%) subjects compared with 19 (1.1%). There were fewer hepatic AEs in the rivaroxaban group: 83 (4.8%) subjects compared with 161 (9.4%) in the enoxaparin/VKA.

Table 17: Incidence of TEAEs (at least 2% in any treatment group) by MedDRA preferred term (Study 11702 (EINSTEIN DVT)).

MedDRA system organ class Preferred term (Primary term)	Rivaroxaban N=1718 (100%)	Enox/VKA N=1711 (100%)
ANY EVENT	1078 (62.7%)	1080 (63.1%)
Gastrointestinal disorders		
Constipation	48 (2.8%)	43 (2.5%)
Diarrhoea	54 (3.1%)	40 (2.3%)
Gingival bleeding	36 (2.1%)	28 (1.6%)
Nausea	47 (2.7%)	38 (2.2%)
Rectal haemorrhage	36 (2.1%)	19 (1.1%)
General disorders and administration site conditions		
Chest pain	36 (2.1%)	31 (1.8%)
Oedema peripheral	41 (2.4%)	41 (2.4%)
Pyrexia	43 (2.5%)	38 (2.2%)
Infections and infestations		
Influenza	38 (2.2%)	38 (2.2%)
Nasopharyngitis	93 (5.4%)	84 (4.9%)
Urinary tract infection	37 (2.2%)	32 (1.9%)
Injury, poisoning and procedural complications		
Contusion	53 (3.1%)	68 (4.0%)
Investigations		
Alanine aminotransferase increased	20 (1.2%)	52 (3.0%)
International normalised ratio increased	1 (<0.1%)	38 (2.2%)
Musculoskeletal and connective tissue disorders		
Arthralgia	43 (2.5%)	38 (2.2%)
Back pain	50 (2.9%)	31 (1.8%)
Pain in extremity	76 (4.4%)	66 (3.9%)
Nervous system disorders		
Dizziness	38 (2.2%)	22 (1.3%)
Headache	91 (5.3%)	68 (4.0%)
Renal and urinary disorders		
Haematuria	39 (2.3%)	41 (2.4%)
Reproductive system and breast disorders		
Menorrhagia	49 (2.9%)	19 (1.1%)
Respiratory, thoracic and mediastinal disorders		
Cough	72 (4.2%)	51 (3.0%)
Dyspnoea	33 (1.9%)	37 (2.2%)
Epistaxis	89 (5.2%)	74 (4.3%)
Vascular disorders		
Haematoma	37 (2.2%)	59 (3.4%)
Hypertension	38 (2.2%)	40 (2.3%)

Notes: Incidences are based on the number of subjects, not the number of events. Although a subject may have had 2 or more clinical AEs, the subject is counted only once in a category. The same subject may appear in different categories. Percentages calculated with the number of subjects in each group as denominator. Sorted first by System Organ Class (alphabetical order). Treatment-emergent AE is defined as the AE occurred after randomization and up to 2 days after the last dose of study drug.

In Study 11899 (MRR-00273), TEAEs were reported in 335 (56.0%) subjects in the rivaroxaban group and 325 (55.1%) subjects in the placebo group with contusion, epistaxis and haematuria more commonly reported in the rivaroxaban group (Table 18).

Table 18: Incidence of TEAEs (at least 2% in any treatment group) by MedDRA preferred term (Study 11899 (MRR-00273).

MedDRA system organ class Preferred term (Primary term)	Rivaroxaban 20 mg o.d. (N=598) n (%)	Placebo (N=590) n (%)
ANY EVENT	335 (56.0%)	325 (55.1%)
General disorders and administration site conditions		
Chest pain	16 (2.7%)	15 (2.5%)
Oedema peripheral	13 (2.2%)	17 (2.9%)
Infections and infestations		
Bronchitis	11 (1.8%)	17 (2.9%)
Influenza	11 (1.8%)	12 (2.0%)
Nasopharyngitis	31 (5.2%)	30 (5.1%)
Injury, poisoning and procedural complications		
Contusion	19 (3.2%)	16 (2.7%)
Musculoskeletal and connective tissue disorders		
Arthralgia	20 (3.3%)	21 (3.6%)
Back pain	22 (3.7%)	7 (1.2%)
Pain in extremity	29 (4.8%)	35 (5.9%)
Nervous system disorders		
Headache	18 (3.0%)	15 (2.5%)
Renal and urinary disorders		
Haematuria	13 (2.2%)	2 (0.3%)
Respiratory, thoracic and mediastinal disorders		
Cough	16 (2.7%)	21 (3.6%)
Epistaxis	24 (4.0%)	11 (1.9%)

Note: Only treatment-emergent adverse events which occurred up to 2 days after the last dose of study medication are included.

In Study 11223 (MRR-00150), TEAEs were reported in 84 (70.6%) subjects in the 10 mg twice daily group, 81 (69.2%) in the 20 mg twice daily, 82 (67.8%) in the 40 mg once daily, 81 (66.9%) in the 30 mg twice daily and 80 (63.5%) in the enoxaparin/VKA. Although the overall rates of TEAEs were similar for the treatment groups, there were more gastrointestinal TEAEs in the rivaroxaban groups. This did not appear to be dose related (Table 19).

Table 19: Incidence rates (≥5% in any treatment group) of TEAEs by MedDRA system organ class and preferred terms (safety population) (Study 11223 (MRR-00150)).

System organ class *Preferred term (primary terms)*	BAY 59-7939 10 mg bid (N=119) n (%)	BAY 59-7939 20 mg bid (N=117) n (%)	BAY 59-7939 40 mg od (N=121) n (%)	BAY 59-7939 30 mg bid (N=121) n (%)	VKA / enoxapari n (N=126) n (%)
Any event	84 (71%)	81 (69%)	82 (68%)	81 (67%)	80 (63%)
Cardiac disorders	6 (5%)	5 (4%)	3 (2%)	2 (2%)	3 (2%)
Gastrointestinal disorders	22 (18%)	18 (15%)	24 (20%)	21 (17%)	11 (9%)
Constipation	6 (5%)	4 (3%)	4 (3%)	4 (3%)	0 (0%)
Diarrhea	3 (3%)	1 (<1%)	6 (5%)	1 (<1%)	6 (5%)
Nausea	1 (<1%)	5 (4%)	4 (3%)	6 (5%)	2 (2%)
General disorders and administration site conditions	6 (5%)	8 (7%)	20 (17%)	14 (12%)	13 (10%)
Infections and infestations	15 (13%)	21 (18%)	19 (16%)	12 (10%)	17 (13%)
Urinary tract infection	2 (2%)	3 (3%)	0 (0%)	2 (2%)	6 (5%)
Injury, poisoning and procedural complications	10 (8%)	7 (6%)	7 (6%)	10 (8%)	6 (5%)
Contusion	7 (6%)	2 (2%)	6 (5%)	10 (8%)	3 (2%)
Investigations	22 (18%)	20 (17%)	26 (21%)	18 (15%)	37 (29%)
ALT increased	6 (5%)	8 (7%)	10 (8%)	6 (5%)	16 (13%)
AST increased	4 (3%)	5 (4%)	9 (7%)	5 (4%)	14 (11%)
GGT increased	2 (2%)	5 (4%)	7 (6%)	2 (2%)	8 (6%)
Hepatic enzyme increased	1 (<1%)	0 (0%)	1 (<1%)	1 (<1%)	8 (6%)
Metabolism and nutrition dis.	5 (4%)	5 (4%)	9 (7%)	9 (7%)	5 (4%)
Musculoskeletal and connective tissue disorders	13 (11%)	8 (7%)	11 (9%)	14 (12%)	10 (8%)
Pain in extremity	6 (5%)	1 (<1%)	4 (3%)	6 (5%)	4 (3%)
Nervous system disorders	7 (6%)	12 (10%)	14 (12%)	6 (5%)	14 (11%)
Headache	2 (2%)	8 (7%)	9 (7%)	3 (2%)	6 (5%)
Psychiatric disorders	2 (2%)	3 (3%)	6 (5%)	8 (7%)	5 (4%)
Renal and urinary disorders	11 (9%)	9 (8%)	15 (12%)	13 (11%)	12 (10%)
Hematuria	5 (4%)	8 (7%)	12 (10%)	9 (7%)	9 (7%)
Reproductive system / breast dis.	3 (3%)	9 (8%)	7 (6%)	6 (5%)	5 (4%)
Respiratory, thoracic and mediastinal disorders	11 (9%)	12 (10%)	20 (17%)	16 (13%)	7 (6%)
Epistaxis	5 (4%)	9 (8%)	10 (8%)	8 (7%)	3 (2%)
Skin and subcutaneous tissue dis.	7 (6%)	8 (7%)	8 (7%)	8 (7%)	10 (8%)
Vascular disorders	13 (11%)	17 (15%)	8 (7%)	16 (13%)	10 (8%)
Deep vein thrombosis	4 (3%)	3 (3%)	3 (2%)	6 (5%)	2 (2%)
Hypertension	4 (3%)	6 (5%)	1 (<1%)	1 (<1%)	3 (2%)
Post-thrombotic syndrome	0 (0%)	4 (3%)	1 (<1%)	6 (5%)	2 (2%)

a Incidence rate = # of events / # at risk, where:
# of events = # of subjects reporting the event after start of treatment.
at risk = # of subjects in reference population.
b Only TEAEs which occurred up to 2 days after the last dose of study medication are included.
c Given are the TEAEs that occurred in at least 5% of subjects in any treatment group at SOC level (primary terms) or primary preferred term level (the latter written in Italics).

BAY 59-7939 = rivaroxaban

In Study 11528 (MRR-00223), TEAEs were reported in 89 (65.9%) subjects in the rivaroxaban 20 mg once daily group, 90 (67.2%) subjects in the 30 mg, 83 (61.0%) in the 40 mg, and 76 (55.5%) in the heparin/ VKA. The pattern of TEAEs was similar for the four treatment groups (Table 20).

Table 20: Incidence rates (≥5% in any treatment group) of TEAEs by MedDRA system organ class (safety population) (Study 11528 (MRR-00223)).

MedDRA system organ class Preferred term (primary term)	BAY 59-7939 20 mg od (N=135)	BAY 59-7939 30 mg od (N=134)	BAY 59-7939 40 mg od (N=136)	(LMW) heparin/ VKA (N=137)
Any event	89 (66%)	90 (67%)	83 (61%)	76 (55%)
Gastrointestinal disorders	20 (15%)	21 (16%)	22 (16%)	25 (18%)
Diarrhea	3 (2%)	7 (5%)	1 (<1%)	5 (4%)
Nausea	2 (1%)	5 (4%)	8 (6%)	3 (2%)
General disorders and administration site conditions	12 (9%)	19 (14%)	12 (9%)	16 (12%)
Edema peripheral	2 (1%)	7 (5%)	5 (4%)	1 (<1%)
Infections and infestations	17 (13%)	21 (16%)	24 (18%)	15 (11%)
Injury, poisoning and procedural complications	13 (10%)	10 (7%)	13 (10%)	11 (8%)
Investigations	13 (10%)	14 (10%)	11 (8%)	10 (7%)
Musculoskeletal and connective tissue disorders	15 (11%)	17 (13%)	11 (8%)	9 (7%)
Pain in extremity	8 (6%)	6 (4%)	5 (4%)	4 (3%)
Neoplasms benign, malignant, and unspecified (including cysts and polyps)	7 (5%)	6 (4%)	4 (3%)	8 (6%)
Nervous system disorders	18 (13%)	16 (12%)	14 (10%)	13 (9%)
Headache	9 (7%)	12 (9%)	4 (3%)	7 (5%)
Psychiatric disorders	3 (2%)	7 (5%)	4 (3%)	2 (1%)
Renal and urinary disorders	5 (4%)	2 (1%)	11 (8%)	6 (4%)
Reproductive system and breast disorders	8 (6%)	10 (7%)	7 (5%)	3 (2%)
Respiratory, thoracic and mediastinal disorders	13 (10%)	12 (9%)	18 (13%)	17 (12%)
Epistaxis	5 (4%)	7 (5%)	9 (7%)	5 (4%)
Skin and subcutaneous tissue disorders	12 (9%)	7 (5%)	10 (7%)	7 (5%)
Vascular disorders	12 (9%)	10 (7%)	11 (8%)	17 (12%)
Hematoma	7 (5%)	2 (1%)	3 (2%)	6 (4%)

a Only treatment-emergent adverse events which occurred up to 2 days after the last dose of study medication are included.

b Incidence rate = # of subjects reporting the event after start of treatment / # of subjects in reference population.

BAY 59-7939 = rivaroxaban

In Study 11630 (R-8570) ROCKET-AF, TEAEs were reported in 5791 (81.44%) subjects in the rivaroxaban group and 5810 (81.54%) in the warfarin. Overall, AEs were reported at similar rates for both treatment groups. The profile of TEAEs was similar for the two treatment groups. The most frequently reported AEs for rivaroxaban were epistaxis in 721 (10.14%) subjects, peripheral edema in 435 (6.12%) and dizziness in 433 (6.09%) subjects. And, for warfarin, were epistaxis in 609 (8.55%) subjects, nasopharyngitis in 455 (6.39%) and dizziness in 449 (6.30%) subjects. Treatment emergent acute renal failure was reported in 263 (3.70%) subjects in the rivaroxaban group and 282 (3.96%) in the warfarin. Treatment emergent pancreatitis was reported in 21 (0.30%) subjects in the rivaroaxaban group and 23 (0.32%) in the warfarin. MI was reported by 13 (0.18%) subjects in the rivaroxaban group and 18 (0.25%) in the warfarin.

In Study 12620 (A49701), TEAEs were reported in 595 (93.1%) subjects in the rivaroxaban group and 605 (94.7%) in the warfarin. More subjects in the rivaroxaban group reported epistaxis, 104 (16.3%) subjects compared with 60 (9.4%) in the warfarin; gingival bleeding, 54 (8.5%) compared with 31 (4.9%); and occult blood, 17 (2.7%) compared with five (0.8%) (Table 21). However, more subjects in the warfarin group had elevated ALT as a TEAE: 17 (2.7%) compared with 5 (0.8%) in the rivaroxaban group.

Table 21: Incidence (≥2.0% in either treatment group) of TEAEs by MedDRA preferred term (population: subjects valid for safety analyses) (Study 12620 (A49701)) (continued next page).

MedDRA system organ class Preferred term	Rivaroxaban (N=639) n (%)	Warfarin (N=639) n (%)
Any event	595 (93.1)	605 (94.7)
Infections and infestations		
Nasopharyngitis	206 (32.2)	232 (36.3)
Bronchitis	20 (3.1)	28 (4.4)
Pharyngitis	17 (2.7)	20 (3.1)
Pneumonia	20 (3.1)	14 (2.2)
Gastroenteritis	18 (2.8)	14 (2.2)
Cystitis	8 (1.3)	15 (2.3)
Gastrointestinal disorders		
Diarrhoea	57 (8.9)	40 (6.3)
Gingival bleeding	54 (8.5)	31 (4.9)
Constipation	38 (5.9)	32 (5.0)
Dental caries	28 (4.4)	34 (5.3)
Periodontitis	29 (4.5)	24 (3.8)
Colonic polyp	18 (2.8)	17 (2.7)
Gastritis	19 (3.0)	13 (2.0)
Haemorrhoids	15 (2.3)	13 (2.0)
Vomiting	8 (1.3)	19 (3.0)
Gingivitis	11 (1.7)	14 (2.2)
Haemorrhoidal haemorrhage	14 (2.2)	10 (1.6)
Stomatitis	11 (1.7)	13 (2.0)
Mouth haemorrhage	14 (2.2)	2 (0.3)
Skin and subcutaneous tissue disorders		
Haemorrhage subcutaneous	67 (10.5)	80 (12.5)
Eczema	37 (5.8)	43 (6.7)
Rash	13 (2.0)	24 (3.8)
Pruritus	17 (2.7)	14 (2.2)
Dermatitis contact	19 (3.0)	12 (1.9)
Urticaria	13 (2.0)	7 (1.1)
Respiratory, thoracic and mediastinal disorders		
Epistaxis	104 (16.3)	60 (9.4)
Upper respiratory tract inflammation	56 (8.8)	74 (11.6)
Haemoptysis	16 (2.5)	13 (2.0)
Cough	14 (2.2)	13 (2.0)
Asthma	15 (2.3)	7 (1.1)
Musculoskeletal and connective tissue disorders		
Back pain	50 (7.8)	56 (8.8)
Arthralgia	27 (4.2)	29 (4.5)
Pain in extremity	21 (3.3)	20 (3.1)
Osteoarthritis	16 (2.5)	15 (2.3)
Musculoskeletal pain	14 (2.2)	16 (2.5)
Myalgia	12 (1.9)	15 (2.3)
Spinal osteoarthritis	12 (1.9)	13 (2.0)
Periarthritis	15 (2.3)	8 (1.3)
Lumbar spinal stenosis	3 (0.5)	13 (2.0)

Table 21: continued.

MedDRA system organ class Preferred term	Rivaroxaban (N=639) n (%)	Warfarin (N=639) n (%)
Injury, poisoning and procedural complications		
Contusion	59 (9.2)	56 (8.8)
Wound haemorrhage	33 (5.2)	27 (4.2)
Limb injury	16 (2.5)	21 (3.3)
Excoriation	14 (2.2)	13 (2.0)
Investigations		
Blood urine present	22 (3.4)	19 (3.0)
Alanine aminotransferase increased	20 (3.1)	20 (3.1)
Aspartate aminotransferase increased	5 (0.8)	17 (2.7)
Occult blood positive	17 (2.7)	5 (0.8)
International normalised ratio increased	0 (0.0)	15 (2.3)
Nervous system disorders		
Headache	24 (3.8)	39 (6.1)
Dizziness	27 (4.2)	30 (4.7)
Ischaemic stroke [a]	9 (1.4)	22 (3.4)
Hypoaesthesia	14 (2.2)	11 (1.7)
Eye disorders		
Conjunctival haemorrhage	26 (4.1)	42 (6.6)
Cataract	31 (4.9)	24 (3.8)
Conjunctivitis	15 (2.3)	18 (2.8)
Metabolism and nutrition disorders		
Diabetes mellitus	44 (6.9)	31 (4.9)
Hyperuricaemia	19 (3.0)	17 (2.7)
Gout	8 (1.3)	14 (2.2)
Cardiac disorders		
Cardiac failure	42 (6.6)	35 (5.5)
General disorders and administration site conditions		
Oedema peripheral	23 (3.6)	26 (4.1)
Chest pain	15 (2.3)	16 (2.5)
Pyrexia	6 (0.9)	22 (3.4)
Renal and urinary disorders		
Haematuria	29 (4.5)	18 (2.8)
Renal impairment	15 (2.3)	4 (0.6)
Vascular disorders		
Hypertension	24 (3.8)	32 (5.0)
Hepatobiliary disorders		
Hepatic steatosis	15 (2.3)	8 (1.3)
Blood and lymphatic system disorders		
Anaemia	29 (4.5)	22 (3.4)
Psychiatric disorders		
Insomnia	26 (4.1)	21 (3.3)
Reproductive system and breast disorders		
Benign prostatic hyperplasia	14 (2.2)	11 (1.7)

Note: Treatment-emergent events are those that occurred after the first dose and up to 2 days after the last dose of study medication

a Of these subject, investigator-reported ischemic strokes in 2 rivaroxaban subjects and in 5 warfarin subjects were adjudicated as not "ischemic stroke" by the CEC. The event rate of adjudicated ischemic stroke is provided in Table 9-8.

CEC=Clinical Endpoint Committee; MedDRA=Medical Dictionary for Regulatory Activities

Bleeding related AEs

In Study 11702 (EINSTEIN DVT) the incidence of treatment emergent bleeding events was the same for rivaroxaban, 139 (8.1%) subjects, as for enoxaparin/VKA 138 (8.1%) subjects. The pattern of bleeding events was also similar for the two treatment groups. There was an indication that subjects with poorer renal function had an increased risk of bleeding related AEs: creatinine clearance < 50 ml/min versus >= 80 ml/ min HR (95% CI) 3.952 (1.637 to 9.545). Study PH-36338 was an analysis of multiple bleeding events in Study 11702 DVT (EINSTEIN DVT). Of 412 subjects that had bleeding events in the rivaroxaban group 301 (73.1%) had one event, 77 (18.7%) had two, 22 (5.3%) had three, eight (1.9%) had four, and four (1.0%) had five. Of 379 subjects that had bleeding events in the enoxaparin/VKA group 272 (71.8%) had one event, 68 (17.9%) had two, 20 (5.3%) had three, eleven (2.9%) had four, four (1.1%) had five and four (1.1%) had more than five.

In Study 11899 (MRR-00273), treatment emergent bleeding events were reported in 108 (18.1%) subjects in the rivaroxaban group and 66 (11.2%) in the placebo. Major bleeding

events were reported in four (0.7%) subjects in the rivaroxaban group and none in the placebo (Table 22). Study PH-36346 provided a post hoc analysis of uterine bleeds reported in Study 11702 (EINSTEIN DVT) and 11899 (EINSTEIN Extension). The Kaplan-Meier plot indicated an approximate doubling of risk for uterine bleed in the rivaroxaban group compared with the enoxaparin/VKA group (Figure 17).

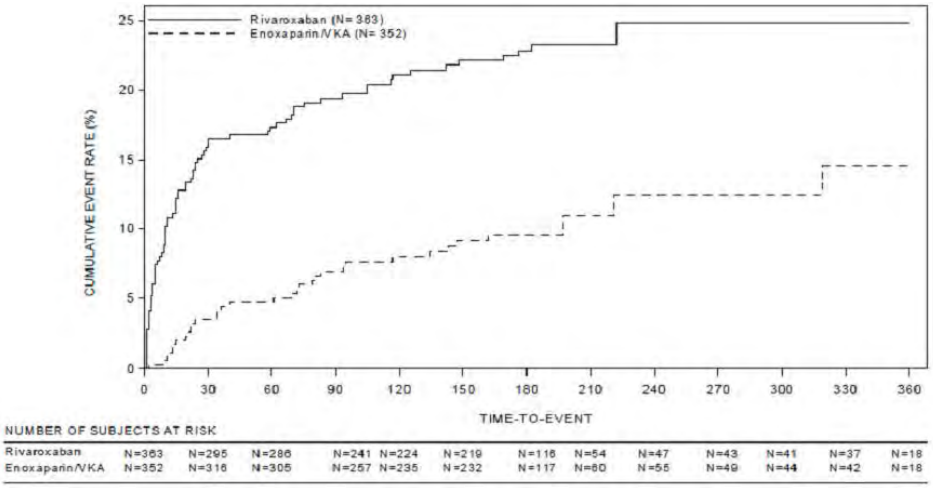
Table 22: Incidence rates of treatment emergent bleeding events (Study 11899 (MRR-00273)).

Endpoint/ components	Rivaroxaban 20 mg o.d. (N=598) n (%)	Placebo (N=590) n (%)
Any bleeding event	104 (17.4%)	63 (10.7%)
Any major or clinically relevant non-major bleeding event	36 (6.0%)	7 (1.2%)
Major bleeding event	4 (0.7%)	0
Fall in hemoglobin ≥ 2 g/dL	4 (0.7%)	0
Transfusions ≥ 2 units	2 (0.3%)	0
Any clinically relevant non-major bleeding event	32 (5.4%)	7 (1.2%)
Surgical site	1 (0.2%)	0
Skin (other than injection site)	4 (0.7%)	2 (0.3%)
Urogenital	9 (1.5%)	0
Gastrointestinal	1 (0.2%)	0
Nasal	8 (1.3%)	1 (0.2%)
Rectal	6 (1.0%)	2 (0.3%)
Ear	1 (0.2%)	0
Uterus	3 (0.5%)	2 (0.3%)
Anal	1 (0.2%)	0
Any non major bleeding event (clinically relevant or not)	101 (16.9%)	63 (10.7%)
Any trivial bleeding event	75 (12.5%)	56 (9.5%)
Trivial bleeding events occurring in at least 1% of subjects (any treatment group)		
Skin (other than injection site)	37 (6.2%)	37 (6.3%)
Gingival	12 (2.0%)	3 (0.5%)
Nasal	17 (2.8%)	10 (1.7%)
Conjunctival	8 (1.3%)	0
Uterus	5 (0.8%)	6 (1.0%)

Note: Incidences are based on the number of subjects, not the number of events. Although a subject may have had 2 or more events, the subject is counted only once in a category. The same subject may appear in different categories. Percentages calculated with the number of subjects in each group as denominator. Treatment-emergent was defined as occurring after the first dose and up to 2 days after the last dose of study drug.

o.d. = once daily

Figure 17: Kaplan-Meier cumulative rate of treatment emergent major or clinically relevant non major or trivial uterus bleedings (population: safety, only females with age lower than 55) (Study PH-36346).



In Study 11223 (MRR-00150), bleeding events were slightly more frequent in the higher dose rivaroxaban groups, suggesting a dose dependent increase in risk (Table 23).

Table 23: Incidence rates of all bleeding events (safety population) (Study 11223 (MRR-00150)).

Bleeding event	BAY 59-7939 10 mg bid (N=119) n (%)	BAY 59-7939 20 mg bid (N=117) n (%)	BAY 59-7939 40 mg od (N=121) n (%)	BAY 59-7939 30 mg bid (N=121) n (%)	VKA / enoxaparin (N=126) n (%)
Any event	6 (5.0%)	11 (9.4%)	14 (11.6%)	13 (10.7%)	8 (6.3%)
Major bleeding	2 (1.7%)	2 (1.7%)	2 (1.7%)	4 (3.3%)	0 (0.0%)
Fatal bleeding	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Clin overt bleeding[b]	2 (1.7%)	2 (1.7%)	2 (1.7%)	2 (1.7%)	0 (0.0%)
Clin overt bleeding[c]	2 (1.7%)	0 (0.0%)	1 (0.8%)	2 (1.7%)	0 (0.0%)
Clin overt bleeding[d]	1 (0.8%)	2 (1.7%)	1 (0.8%)	3 (2.5%)	0 (0.0%)
Non-major bleeding	4 (3.4%)	9 (7.7%)	12 (9.9%)	11 (9.1%)	8 (6.3%)

a Bleeding events starting more than 2 days after last study medication intake were not considered.
b Associated with a fall in Hb of ≥2 g/dL.
c Leading to transfusion of ≥2 units blood.
d Warranting treatment cessation.

BAY 59-7939 = rivaroxaban

In Study 11528 (MRR-00223) bleeding events were reported in 31 (23.0%) subjects in the rivaroxaban 20 mg once daily group, 29 (21.6%) in the 30 mg daily, 29 (21.3%) in the 40 mg daily and in 38 (27.7%) subjects in the heparin/VKA groups. There was a higher rate of clinically important bleeding events in the heparin/VKA group (Table 24).

Table 24: Incidence rates of clinically relevant bleeding events (major or clinically relevant non major bleedings) (safety population) (Study 11528 (MRR-00223)).

Bleeding event	BAY 59-7939 20 mg od (N=135)	BAY 59-7939 30 mg od (N=134)	BAY 59-7939 40 mg od (N=136)	(LMW) heparin/ VKA (N=137)
Any event	31 (23.0%)	29 (21.6%)	29 (21.3%)	38 (27.7%)
Major bleeding	1 (0.7%)	2 (1.5%)	0 (0.0%)	2 (1.5%)
Fatal bleeding	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.7%)
Critical bleeding	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.5%)
Intracranial	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.7%)
Rectal	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.7%)
Clinically overt bleeding associated with a fall in hemoglobin ≥2 mg/dL	1 (0.7%)	1 (0.7%)	0 (0.0%)	1 (0.7%)
Clinically overt bleeding leading to blood transfusion ≥2 units of blood	1 (0.7%)	2 (1.5%)	0 (0.0%)	1 (0.7%)
Non-major bleeding	30 (22.2%)	27 (20.1%)	29 (21.3%)	36 (26.3%)
Any clinically relevant non-major bleeding	7 (5.2%)	6 (4.5%)	3 (2.2%)	10 (7.3%)

BAY 59-7939 = rivaroxaban

In Study 11630 (R-8570) ROCKET-AF, bleeding related TEAE was reported in 2298 (32.32%) subjects in the rivaroxaban group and in 2256 (31.66%) subjects in the VKA group. With regard to CEC adjudicated bleeding events, in the rivaroxaban group there was a lower risk of bleeding related death and critical organ bleeding but a greater risk for a drop in haematocrit and transfusion (Table 25). Gastrointestinal haemorrhage was reported in 100 (1.41%) subjects of the rivaroxaban group and in 70 (0.98%) subjects in the VKA group. Of the warfarin subjects who had intracranial haemorrhages, the majority of subjects had their last INR either in, or below, the TTR.

Table 25: HR and 95% CI for time to the first occurrence of bleeding events (adjudicated by CEC) while on treatment (up to last dose plus 2 days) (Study 39039039AFL3001: Safety Analysis Set).

	------ Rivaroxaban ------		-------- Warfarin -------			
	N= 7111	Event Rate	N= 7125	Event Rate	---- Rivaroxaban vs. Warfarin ---	
Parameter	n (%)	(100 Pt-yr)	n (%)	(100 Pt-yr)	Hazard Ratio (95% CI)	p-value
Principal Safety Endpoint(a)	1475 (20.74)	14.91	1449 (20.34)	14.52	1.03 (0.96,1.11)	0.442
Major	395 (5.55)	3.60	386 (5.42)	3.45	1.04 (0.90,1.20)	0.576
Hemoglobin Hematocrit Drop	305 (4.29)	2.77	254 (3.56)	2.26	1.22 (1.03,1.44)	0.019*
Transfusion	183 (2.57)	1.65	149 (2.09)	1.32	1.25 (1.01,1.55)	0.044*
Critical Organ Bleeding(b)	91 (1.28)	0.82	133 (1.87)	1.18	0.69 (0.53,0.91)	0.007*
Death	27 (0.38)	0.24	55 (0.77)	0.48	0.50 (0.31,0.79)	0.003*
Non-major Clinically Relevant	1185 (16.66)	11.80	1151 (16.15)	11.37	1.04 (0.96,1.13)	0.345
Minimal	258 (3.63)	2.35	226 (3.17)	2.03	1.16 (0.97,1.39)	0.102

Note: (a) Principal Safety Endpoint is the composite of Major and Non-Major clinically relevant bleeding event.
Note: (b) Critical organ bleeding are cases where CEC bleeding site=intracranial, intraspinal, intraocular, pericardial, intra-articular, intramuscular with compartment syndrome or retroperitoneal.
Note: Minimal events are not included in the principal safety endpoint.
Note: Hazard ratio (95% CI) and p-value from Cox proportional hazard model with treatment group as a covariate.
Note: p-value (two-sided) for superiority of Rivaroxaban versus Warfarin in hazard ratio.
Note: All analysis are based on the time to the first event.
Note: Hemoglobin hematocrit drop = a fall in hemoglobin of 2 g/dL or more.
Note: Transfusion = a transfusion of 2 or more units of packed red blood cells or whole blood.
Note: * Statistically significant at nominal 0.05 (two-sided).

In Study 12620 (A49701), bleeding related TEAEs were reported in 328 (51.3%) subjects in the rivaroxaban group and 283 (44.3%) in the warfarin. Adjudicated major bleeding events were reported in 26 (4.1%) subjects in the rivaroxaban group and 30 (4.7%) in the warfarin (Table 26). Non major clinically relevant bleeding events were reported in 119 (18.6%) subjects in the rivaroxaban group and 99 (15.5%) in the warfarin (Table 26). In the rivaroxaban group, there were increased numbers of subjects reporting epistaxis, gingival bleeding and rectal bleeding.

Table 26: Incidence of treatment emergent bleeding events as adjudicated by the CEC (population: subjects valid for safety analyses) (Study 12620 (A49701)).

Bleeding event category / bleeding site	Rivaroxaban (N=639) n (%)	Warfarin (N=639) n (%)
Adjudicated major bleeding events or non-major clinically relevant bleeding events	138 (21.6)	124 (19.4)
Adjudicated major bleeding events	26 (4.1)	30 (4.7)
A fall in hemoglobin of 2 g/dL or higher	13 (2.0)	17 (2.7)
Critical site	13 (2.0)	13 (2.0)
A transfusion of 2 or more units of packed red blood cells or whole blood	4 (0.6)	6 (0.9)
A fatal outcome	1 (0.2)	3 (0.5)
Bleeding site		
Gastrointestinal – upper (hematemesis or melena)	6 (0.9)	12 (1.9)
Intracranial	5 (0.8)	10 (1.6)
Intraarticular	4 (0.6)	1 (0.2)
Intraocular/retinal	3 (0.5)	2 (0.3)
Epistaxis	2 (0.3)	2 (0.3)
Gastrointestinal – lower	1 (0.2)	3 (0.5)
Hematoma	1 (0.2)	2 (0.3)
Intramuscular (with compartment syndrome)	1 (0.2)	0 (0.0)
Macroscopic (gross) hematuria	1 (0.2)	0 (0.0)
Rectal	1 (0.2)	0 (0.0)
Skin (ecchymosis other than instrumented site)	1 (0.2)	0 (0.0)
Other	0 (0.0)	1 (0.2)
Adjudicated non-major clinically relevant bleeding events	119 (18.6)	99 (15.5)
Bleeding site		
Epistaxis	35 (5.5)	10 (1.6)
Subconjunctival or other ocular	13 (2.0)	22 (3.4)
Skin (ecchymosis other than instrumented site)	14 (2.2)	20 (3.1)
Macroscopic (gross) hematuria	16 (2.5)	11 (1.7)
Gingival	19 (3.0)	4 (0.6)
Hematoma	6 (0.9)	13 (2.0)
Rectal	10 (1.6)	7 (1.1)
Hemoptysis	6 (0.9)	4 (0.6)
Gastrointestinal – upper (hematemesis or melena)	6 (0.9)	2 (0.3)
Gastrointestinal – lower	3 (0.5)	3 (0.5)
Puncture site	2 (0.3)	4 (0.6)
Bleeding associated with non-cardiac surgery	1 (0.2)	1 (0.2)
Intramuscular (with compartment syndrome)	1 (0.2)	1 (0.2)
Intraocular/retinal	2 (0.3)	0 (0.0)
Intraarticular	0 (0.0)	1 (0.2)
Other	7 (1.1)	11 (1.7)

Note: Treatment-emergent events are those that occurred after the first dose and up to 2 days after the last dose of study medication. Incidences are based on the number of subjects, not the number of events. Although a subject may have had 2 or more events, the subject is counted only once in a category. The same subject may appear in different categories.

Report PH-36398 was an analysis of the management of subjects with non fatal major bleeding that was severe in intensity in Study 11630 and Study 11620. In general, the subjects underwent investigations to determine the source of bleeding, and most were found to have underlying conditions that predisposed them to a complication of bleeding while on anticoagulant therapy. Treatment of the underlying condition resulted in resolution of the cause of bleeding in most cases, both with rivaroxaban and with warfarin. Where no source of bleeding could be identified, most events resolved with temporary or permanent discontinuation of study medication. Supportive care with blood transfusions of packed red blood cells, and/or fresh frozen plasma led to resolution in most major and severe bleeding events for both warfarin and rivaroxaban.

Study 11390 was a Phase 2 dose finding study conducted in Japanese subjects with AF. The study was discontinued because five of 11 subjects treated at a dose of 20 mg twice daily discontinued due to bleeding related AEs. None of the events were SAEs (serious adverse events).

Study 11866 was a Phase 2 dose finding study conducted in 102 Japanese subjects with AF. The study examined rivaroxaban 10 mg, 15 mg, and 20 mg once daily in comparison with warfarin. The incidence of any bleeding event was 7.7%, 16.0%, 4.2% and 3.7% in the rivaroxaban 10 mg, 15 mg, 20 mg and warfarin groups, respectively.

Serious Adverse Events (SAEs) and Deaths

SAEs

In Study 11702 (EINSTEIN DVT) treatment emergent SAEs were reported in 207 (12.0%) subjects in the rivaroxaban group and 233 (13.6%) in the enoxaparin/VKA. The pattern of SAEs was similar for the two treatment groups (Table 27).

Table 27: Incidence of treatment emergent SAEs (at least 1% in any treatment group) by MedDRA preferred term (Study 11702 (EINSTEIN DVT)).

MedDRA system organ class (Primary term)	Rivaroxaban N=1718 (100%)	Enox/VKA N=1711 (100%)
ANY EVENT	207 (12.0%)	233 (13.6%)
Gastrointestinal disorders	27 (1.6%)	31 (1.8%)
Infections and infestations	28 (1.6%)	48 (2.8%)
Investigations	8 (0.5%)	20 (1.2%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	47 (2.7%)	42 (2.5%)
Nervous system disorders	18 (1.0%)	17 (1.0%)
Vascular disorders	10 (0.6%)	19 (1.1%)

Notes: Incidences are based on the number of subjects, not the number of events. Although a subject may have had 2 or more clinical AEs, the subject is counted only once in a category. The same subject may appear in different categories. Percentages calculated with the number of subjects in each group as denominator. Sorted first by System Organ Class (alphabetical order). Treatment-emergent AEs were defined as AEs occurring after randomization and up to 2 days after the last dose of study drug.

Study 11899 (MRR-00273), SAEs were reported in 52 (8.7%) subjects in the rivaroxaban group and 46 (7.8%) in the placebo. The pattern of SAEs was similar for the two treatment groups (Table 28).

Table 28: Incidence of treatment emergent SAEs (at least 1% in any treatment group) by MedDRA SOC (Study 11899 (MRR-00273)).

MedDRA system organ class (Primary term)	Rivaroxaban 20 mg o.d. (N=598) n (%)	Placebo (N=590) n (%)
ANY EVENT	52 (8.7%)	46 (7.8%)
Cardiac disorders	9 (1.5%)	7 (1.2%)
Gastrointestinal disorders	10 (1.7%)	6 (1.0%)
Infections and infestations	8 (1.3%)	7 (1.2%)
Neoplasms benign, malignant and unspecified (including cysts and polyps)	2 (0.3%)	6 (1.0%)

Note: Incidences are based on the number of subjects, not the number of events. Although a subject may have had 2 or more clinical AEs, the subject is counted only once in a category. Treatment-emergent AE is defined as AE occurring after the first dose and up to 2 days after the last dose of study drug.
Source: Table 14.3.1/21
o.d. = once daily, MedDRA = Medical Dictionary for Regulatory Activities, SOC = system organ class

Study 11223 (MRR-00150), SAEs were reported in 19 (16.0%) subjects in the 10 mg twice daily group, in 25 (21.4%) in the 20 mg twice daily, in 21 (17.4%) in the 40 mg once daily, in 18 (14.9%) in the 30 mg twice daily and 21 (16.7%) in the enoxaparin/VKA groups. There was no apparent pattern of SAEs with rivaroxaban (Table 29).

Table 29: Incidence rates (≥2% in any treatment group) of SAEs by MedDRA SOCs and preferred terms (safety population) (Study 11223 (MRR-00150)).

Adverse event[c]	BAY 59-7939 10 mg bid (N=119) n (%)	BAY 59-7939 20 mg bid (N=117) n (%)	BAY 59-7939 40 mg od (N=121) n (%)	BAY 59-7939 30 mg bid (N=121) n (%)	VKA / enoxaparin (N=126) n (%)
Any event	15 (13%)	21 (18%)	15 (12%)	15 (12%)	17 (13%)
Blood and lymphatic system disorders	3 (3%)	1 (<1%)	1 (<1%)	0 (0%)	0 (0%)
Cardiac disorders	1 (<1%)	2 (2%)	1 (<1%)	2 (2%)	1 (<1%)
Atrial fibrillation	1 (<1%)	2 (2%)	1 (<1%)	0 (0%)	0 (0%)
Gastrointestinal disorders	3 (3%)	2 (2%)	0 (0%)	3 (2%)	0 (0%)
Gastrointestinal hemorrhage	1 (<1%)	0 (0%)	0 (0%)	3 (2%)	0 (0%)
General disorders and administration site conditions	1 (<1%)	1 (<1%)	3 (2%)	0 (0%)	1 (<1%)
Edema peripheral	0 (0%)	0 (0%)	2 (2%)	0 (0%)	0 (0%)
Infections and infestations	3 (3%)	5 (4%)	3 (2%)	0 (0%)	5 (4%)
Investigations	1 (<1%)	1 (<1%)	2 (2%)	0 (0%)	7 (6%)
ALT increased	0 (0%)	1 (<1%)	0 (0%)	0 (0%)	3 (2%)
AST increased	0 (0%)	1 (<1%)	0 (0%)	0 (0%)	2 (2%)
Neoplasms benign, malignant and unspecified (incl. cysts/polyps)	3 (3%)	4 (3%)	0 (0%)	1 (<1%)	1 (<1%)
Renal and urinary disorders	2 (2%)	1 (<1%)	1 (<1%)	0 (0%)	0 (0%)
Hydronephrosis	2 (2%)	0 (0%)	1 (<1%)	0 (0%)	0 (0%)
Reproductive system and breast disorders	0 (0%)	2 (2%)	1 (<1%)	1 (<1%)	0 (0%)
Respiratory, thoracic and mediastinal disorders	2 (2%)	3 (3%)	4 (3%)	3 (2%)	1 (<1%)
Pulmonary embolism	1 (<1%)	1 (<1%)	3 (2%)	2 (2%)	0 (0%)
Vascular disorders	3 (3%)	4 (3%)	0 (0%)	4 (3%)	1 (<1%)
Deep vein thrombosis	2 (2%)	2 (2%)	0 (0%)	3 (2%)	1 (<1%)

a Incidence rate = # of events / # at risk, where:
# of events = # of subjects reporting the event after start of treatment.
at risk = # of subjects in reference population.
b Only TEAEs which occurred up to 2 days after the last dose of study medication are included.
c Given are the serious adverse events that occurred in at least 2% of subjects in any treatment group
at SOC level (primary terms) or primary preferred term level (the latter written in Italics).

BAY 59-7939 = rivaroxaban

In Study 11528 (MRR-00223) SAEs were reported in 19 (14.1%) subjects in the rivaroxaban 20 mg once daily group, 18 (13.4%) in the 30 mg, 14 (10.3%) in the 40 mg and 21 (15.3%) in the heparin/VKA. The rates of SAEs were similar for the four treatment groups (Table 30).

Table 30: Incidence rates (≥2% in any treatment group) of treatment emergent SAEs by MedDRA preferred term (safety population) (Study 11528 (MRR-00223)).

MedDRA system organ class Preferred term (primary term)	BAY 59-7939 20 mg od (N=135)	BAY 59-7939 30 mg od (N=134)	BAY 59-7939 40 mg od (N=136)	(LMW) heparin/ VKA (N=137)
Any event	19 (14%)	18 (13%)	14 (10%)	21 (15%)
Cardiac disorders	3 (2%)	3 (2%)	0 (0%)	0 (0%)
General disorders and administrative site conditions	2 (2%)	1 (1%)	0 (0%)	2 (2%)
Infections and infestations	3 (2%)	0 (0%)	2 (1%)	5 (4%)
Injury, poisoning and procedural complications	3 (2%)	4 (3%)	1 (1%)	3 (2%)
Neoplasms benign, malignant, and unspecified (including cysts and polyps)	2 (1%)	6 (4%)	3 (2%)	5 (4%)
Respiratory, thoracic, and mediastinal disorders	3 (2%)	2 (1%)	3 (2%)	2 (1%)
Vascular disorders	2 (2%)	2 (2%)	1 (1%)	6 (4%)
Deep vein thrombosis	0 (0%)	0 (0%)	0 (0%)	3 (2%)

BAY 59-7939 = rivaroxaban

In Study 11630 (R-8570) ROCKET-AF, SAEs were reported in 2649 (37.25%) subjects in the rivaroxaban group and 2720 (38.18%) in the warfarin. The pattern of SAEs was similar for the two treatment groups (Table 31).

Table 31: Incidence of the 15 most frequent treatment emergent SAEs based on the rivaroxaban treatment group by preferred term (Study 39039039AFL3001: Safety Analysis Set).

Preferred Term	Rivaroxaban (N=7111) n (%)	Warfarin (N=7125) n (%)
Total no. subjects with treatment- emergent serious adverse events	2489 (35.00)	2598 (36.46)
Cardiac failure	261 (3.67)	292 (4.10)
Cardiac failure congestive	158 (2.22)	193 (2.71)
Atrial fibrillation	145 (2.04)	155 (2.18)
Pneumonia	141 (1.98)	170 (2.39)
Gastrointestinal haemorrhage	80 (1.13)	60 (0.84)
Angina unstable	70 (0.98)	87 (1.22)
Sudden death	67 (0.94)	61 (0.86)
Anaemia	64 (0.90)	27 (0.38)
Chronic obstructive pulmonary disease	55 (0.77)	52 (0.73)
Syncope	54 (0.76)	37 (0.52)
Haematuria	53 (0.75)	42 (0.59)
Upper gastrointestinal haemorrhage	51 (0.72)	31 (0.44)
Transient ischaemic attack	44 (0.62)	67 (0.94)
Cellulitis	38 (0.53)	58 (0.81)
Epistaxis	37 (0.52)	39 (0.55)

Study 12620 (A49701), SAEs were reported in 179 (28.0%) subjects in the rivaroxaban group and 183 (28.6%) in the warfarin. The pattern of SAEs was similar for the two treatment groups (Table 32).

Table 32: Incidence (≥0.4% in either treatment group) of treatment emergent SAEs (population: subjects valid for safety analyses) (Study 12620 (A49701)).

MedDRA system organ class Preferred term	Rivaroxaban (N=639) n (%)	Warfarin (N=639) n (%)
Any event	151 (23.6)	155 (24.3)
Cardiac disorders	30 (4.7)	29 (4.5)
Cardiac failure	12 (1.9)	11 (1.7)
Atrial fibrillation	4 (0.6)	2 (0.3)
Cardiac failure chronic	3 (0.5)	3 (0.5)
Cardiac failure congestive	2 (0.3)	3 (0.5)
Gastrointestinal disorders	21 (3.3)	34 (5.3)
Colonic polyp	5 (0.8)	9 (1.4)
Gastric ulcer haemorrhage	3 (0.5)	2 (0.3)
Periodontitis	1 (0.2)	3 (0.5)
Gastrointestinal haemorrhage	0 (0.0)	4 (0.6)
Ileus	0 (0.0)	4 (0.6)
Diverticulum intestinal haemorrhagic	0 (0.0)	3 (0.5)
Nervous system disorders	21 (3.3)	33 (5.2)
Ischaemic stroke	9 (1.4)	18 (2.8)
Epilepsy	4 (0.6)	1 (0.2)
Convulsion	0 (0.0)	3 (0.5)
Infections and infestations	29 (4.5)	22 (3.4)
Pneumonia	14 (2.2)	10 (1.6)
Gastroenteritis	3 (0.5)	1 (0.2)
Injury, poisoning and procedural complications	19 (3.0)	11 (1.7)
Spinal compression fracture	4 (0.6)	2 (0.3)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	13 (2.0)	14 (2.2)
Gastric cancer	2 (0.3)	4 (0.6)
Prostate cancer	3 (0.5)	0 (0.0)
Eye disorders	12 (1.9)	9 (1.4)
Cataract	9 (1.4)	7 (1.1)
Respiratory, thoracic and mediastinal disorders	13 (2.0)	6 (0.9)
Interstitial lung disease	2 (0.3)	3 (0.5)
Asthma	3 (0.5)	1 (0.2)
Musculoskeletal and connective tissue disorders	7 (1.1)	6 (0.9)
General disorders and administration site conditions	5 (0.8)	7 (1.1)
Sudden death	4 (0.6)	2 (0.3)
Renal and urinary disorders	5 (0.8)	5 (0.8)
Metabolism and nutrition disorders	5 (0.8)	4 (0.6)
Diabetes mellitus	4 (0.6)	1 (0.2)
Hepatobiliary disorders	3 (0.5)	3 (0.5)
Vascular disorders	3 (0.5)	3 (0.5)
Blood and lymphatic system disorders	2 (0.3)	4 (0.6)
Anaemia	1 (0.2)	3 (0.5)
Ear and labyrinth disorders	2 (0.3)	3 (0.5)

Note: Treatment-emergent events are those that occurred after the first dose and up to 2 days after the last dose of study medication

Deaths

Study 11702 (EINSTEIN DVT); there were 41 (2.4%) deaths reported in the rivaroxaban group and 52 (3.0%) in the enoxaparin/VKA group. The profile of deaths was similar for the two treatment groups (Table 33).

Table 33: Incidence of all post randomisation deaths by adjudicated cause (Study 11702 (EINSTEIN DVT)).

Cause of deaths as assessed by CIAC	Rivaroxaban N=1718 (100%)	Enox/VKA N=1711 (100%)
Any event	41 (2.4%)	52 (3.0%)
Not adjudicated	0	1 (<0.1%)
Pulmonary embolism	1 (<0.1%)	0
Bleeding	2 (0.1%)	5 (0.3%)
Cancer	27 (1.6%)	20 (1.2%)
Septicaemia	0	2 (0.1%)
Unexplained death [a] and PE cannot be ruled out	3 (0.2%)	6 (0.4%)
Ischemic stroke	1 (<0.1%)	4 (0.2%)
Other vascular event	1 (<0.1%)	1 (<0.1%)
Infectious disease	3 (0.2%)	9 (0.5%)
Other respiratory failure	0	1 (<0.1%)
Cachexia	1 (<0.1%)	0
Pneumonia	0	1 (<0.1%)
Renal failure	1 (<0.1%)	0
Diabetic coma	1 (<0.1%)	0
Suicide	0	1 (<0.1%)
Liver disease	0	1 (<0.1%)

[a] typographical error corrected; the original text in the database was "unexplained PE and PE cannot be ruled out".

Notes: For any subject that died the central independent adjudication committee had to class the death based on a pre-defined list of choices. Treatment groups for the safety population are displayed as study treatment administered (not as randomized).

Study 11899 (MRR-00273), a single (0.2%) death was reported in the rivaroxaban group (cardiac arrest) and there were two (0.3%) deaths in the placebo group (pulmonary embolism, infectious disease).

Study 11223 (MRR-00150), five (4.2%) deaths were reported in the 10 mg twice daily group, four (3.4%) in the 20 mg twice daily, two (1.7%) in the 40 mg once daily, two (1.7%) in the 30 mg twice daily, and in one (0.8%) in the enoxaparin/VKA groups. The deaths appeared to be related to underlying conditions.

Study 11528 (MRR-00223), 4 (3.0%) deaths occurred in the rivaroxaban 20 mg group, and 9 (6.7%) in the 30 mg, 4 (2.9%) in the 40 mg and 5 (3.6%) in the enoxaparin/VKA groups. The deaths appeared to be related to underlying disease.

Study 11630 (R-8570) ROCKET-AF, overall, death was reported for 446 (6.27%) in the rivaroxaban group and 512 (7.19%) in the warfarin. From first dose to last dose plus 30 days, there were 369 (5.19%) deaths in the rivaroxaban group and 431 (6.05%) in the warfarin group. The pattern of deaths was similar for the two treatment groups (Table 34).

Table 34: Summary of deaths (adjudicated by CEC) (from first dose to last dose plus 30 days) by primary cause and death cause subclass (Study 39039039AFL3001: Safety Analysis Set).

Primary Cause Of Death Death Cause Sub-Class	Rivaroxaban (N=7111) n (%)	Warfarin (N=7125) n (%)	Total (N=14236) n (%)
Total no. subjects Who Died	369 (5.19)	431 (6.05)	800 (5.62)
Vascular	272 (3.83)	316 (4.44)	588 (4.13)
Sudden or Unwitnessed Death	134 (1.88)	146 (2.05)	280 (1.97)
Congestive Heart Failure / Cardiogenic Shock	50 (0.70)	49 (0.69)	99 (0.70)
Intracranial Hemorrhage	23 (0.32)	37 (0.52)	60 (0.42)
Non-hemorrhagic Stroke	26 (0.37)	27 (0.38)	53 (0.37)
Myocardial Infarction	14 (0.20)	17 (0.24)	31 (0.22)
Other Vascular	11 (0.15)	18 (0.25)	29 (0.20)
Hemorrhage, Not Intracranial	4 (0.06)	11 (0.15)	15 (0.11)
Dysrhythmia	7 (0.10)	5 (0.07)	12 (0.08)
Pulmonary Embolism	2 (0.03)	3 (0.04)	5 (0.04)
Atherosclerotic Vascular Disease (Excluding Coronary)	1 (0.01)	3 (0.04)	4 (0.03)
Non-vascular	72 (1.01)	84 (1.18)	156 (1.10)
Infection	19 (0.27)	27 (0.38)	46 (0.32)
Malignancy	15 (0.21)	16 (0.22)	31 (0.22)
Respiratory Failure	13 (0.18)	15 (0.21)	28 (0.20)
Sepsis	14 (0.20)	10 (0.14)	24 (0.17)
Accidental/trauma	3 (0.04)	7 (0.10)	10 (0.07)
Other Non-vascular	2 (0.03)	4 (0.06)	6 (0.04)
Renal Failure	3 (0.04)	3 (0.04)	6 (0.04)
Suicide	2 (0.03)	2 (0.03)	4 (0.03)
Liver Failure	1 (0.01)	0	1 (0.01)
Unknown	25 (0.35)	31 (0.44)	56 (0.39)

Note: Percentages calculated with the number of subjects in each group as denominator.
Note: This summary includes all deaths.
Note: In the current database some deaths have multiple primary causes of death or sub-classifications of death.

Study 12620 (A49701), death was reported for 14 (2.2%) subjects in the rivaroxaban group and 12 (1.9%) in the warfarin. On treatment, death was reported for seven (1.1%) subjects in the rivaroxaban group and five (0.8%) in the warfarin. The causes of death were similar for the two treatment groups.

Laboratory findings

Study 11702 (EINSTEIN DVT), significantly fewer subjects in the rivaroxaban group had elevations in SGPT/ALT >3x ULN: 25 (1.5%) subjects compared with 62 (3.8%) in the enoxaparin/VKA, difference (%) (95% CI) -2.3% (-3.4% to -1.2%). Apart from this, the profile of laboratory abnormalities was similar for the two treatment groups.

Study 11899 (MRR-00273), elevation in AST (aspartate aminotransferase) >3x ULN was reported in seven (1.2%) subjects in the rivaroxaban group and three (0.5%) in the placebo. Elevation in ALT >3x ULN was reported in eleven (1.9%) subjects in the rivaroxaban group and three (0.5%) in the placebo.

Study 11223 (MRR-00150), elevations in AST and ALT occurred more frequently in the enoxaparin/VKA group.

Study 11528 (MRR-00223), the rates of clinically significant laboratory abnormalities for the four treatment groups were similar.

Study 11630 (R-8570) ROCKET-AF, clinically significant abnormalities in ALT and bilirubin occurred in the same frequency in both treatment groups. Treatment emergent thrombocytopenia was reported in 34 (0.48%) subjects in the rivaroxaban group and 63 (0.88%) in the warfarin.

In Study 12620 (A49701), the pattern of laboratory test abnormalities was similar for the two treatment groups.

Study PH-35310 was an integrated analysis of liver safety for rivaroxaban based on data from Studies 10942, 10944, 10945 and 11527 (prevention of VTE in subjects undergoing elective hip or knee replacement) and Studies 11223 and 11528 (treatment of VTE in subjects diagnosed with DVT). A total of 3146 subjects were treated with rivaroxaban in these studies. The rates of subjects with elevation in AST >3x ULN increased from 3.3% with the 5 mg dose up to 6.8% with the 60 mg dose.

Study PH-36382 was an integrated analysis of liver safety for rivaroxaban based on data from Study 11223 and Study 11528 (treatment of VTE). The incidence of treatment emergent elevation of ALT >3x ULN was 17 (2.1%) of 813 subjects in the rivaroxaban group and 25 (10.6%) of 236 in the enoxaparin/VKA, HR (95% CI) 0.188 (0.101 to 0.347).

Study PH-36329 was an explorative analysis of prothrombin time measured by Neoplastin reagent in subjects treated with rivaroxaban in Study 11702 DVT (EINSTEIN DVT). The data were presented as extensive tabulations of summary statistics. There did not appear to be any significant difference in PT between subjects with and without bleeding but hypothesis tests were not performed on the data.

Safety in special populations

Study PH-36333 was a pooled analysis of the effect of rivaroxaban on bleedings and efficacy for selected subgroups in Studies 11223 and 11528. The subgroups of interest were subgroups defined by age (subjects aged ≥75 years), gender, body weight (<60 kg), calculated CrCl ≤50 mL/min, active malignancy at baseline, and use of NSAIDs during the treatment period. There was no significant effect of these variables on the risk of deterioration or major bleeding events. The rates of adjudicated efficacy and bleeding outcomes observed in the Phase 2 Studies 11223 and 11528 did not indicate a need for dose adaptation with subjects above 75 years of age, a low body weight or moderate renal impairment (that is, calculated CrCl 30-50 mL/min) for the Phase 3 studies that investigated a total daily dose of 20 mg of rivaroxaban.

Immunological events

In Study 11630 (R-8570) ROCKET-AF, treatment emergent hypersensitivity reactions were reported in 12 (0.17%) subjects in the rivaroxaban group and six (0.08%) in the warfarin group (Table 35).

Table 35: Incidence of treatment emergent hypersensitivity (SMQ) by body system and preferred term (Study 39039039AFL3001: Safety Analysis Set).

Body System Or Organ Class Preferred Term	Rivaroxaban (N=7111) n (%)	Warfarin (N=7125) n (%)
Total no. subjects with treatment emergent hypersensitivity(SMQ) adverse Events	12 (0.17)	6 (0.08)
Skin and Subcutaneous Tissue Disorders	5 (0.07)	5 (0.07)
Toxic Skin Eruption	2 (0.03)	0
Cutaneous Vasculitis	1 (0.01)	0
Erythema Multiforme	1 (0.01)	0
Exfoliative Rash	1 (0.01)	2 (0.03)
Dermatitis Exfoliative	0	1 (0.01)
Dermatitis Exfoliative Generalised	0	1 (0.01)
Stevens-Johnson Syndrome	0	1 (0.01)
Vascular Disorders	5 (0.07)	1 (0.01)
Circulatory Collapse	5 (0.07)	1 (0.01)
Immune System Disorders	2 (0.03)	0
Anaphylactic Reaction	1 (0.01)	0
Anaphylactic Shock	1 (0.01)	0

Safety related to drug-drug interactions and other interactions

Study PH-36306 (Module 5, Section 5.4.5.3) was an analysis of the effect of rivaroxaban (BAY 59-7939) on bleedings and efficacy with selected co medication categories in Study 11702 DVT (EINSTEIN DVT) and Study 11899 (EINSTEIN EXTENSION). Comedication with NSAID did not increase the risk of bleeding with rivaroxaban compared with warfarin HR (95% CI) 0.977 (0.646 to 1.477). Co medication with NSAID did not increase the risk of bleeding with rivaroxaban compared with warfarin HR (95% CI) 0.890 (0.550 to 1.440). Clopidogrel or ticlopidine did not significantly increase the risk of bleeding with rivaroxaban compared with warfarin: HR (95% CI) 1.755 (0.482 to 6.386).

Study R-8571 was an additional analysis of data from Study 11630 that examined drug interactions. There was no apparent effect upon the primary efficacy outcome measure of concomitant medication with NSAIDs, aspirin, thienpyridines or CYP3A4 inhibitors. Concomitant medication with thienpyridines increased the risk of major bleeding event in the rivaroxaban group from 3.57/100/year to 4.76/100/year; and aspirin increased the incidence from 3.03/100/year to 4.56/100/year.

Discontinuation due to AEs

In Study 11702 (EINSTEIN DVT), DAE (AE leading to discontinuation) occurred for 85 (4.9%) subjects in the rivaroxaban group and 81 (4.7%) in the enoxaparin/VKA (Table 36).

Table 36: Incidence of AEs resulting in permanent discontinuation of study drug (for at least five subjects in any treatment group) by MedDRA SOC (Study 11702 (EINSTEIN DVT)).

MedDRA system organ class Preferred term (Primary term)	Rivaroxaban N=1718 (100%)	Enox/VKA N=1711 (100%)
ANY EVENT	85 (4.9%)	81 (4.7%)
Blood and lymphatic system disorders	7 (0.4%)	4 (0.2%)
Anaemia	5 (0.3%)	2 (0.1%)
Gastrointestinal disorders	11 (0.6%)	11 (0.6%)
Infections and infestations	5 (0.3%)	8 (0.5%)
Investigations	6 (0.3%)	4 (0.2%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	18 (1.0%)	19 (1.1%)
Nervous system disorders	10 (0.6%)	5 (0.3%)
Renal and urinary disorders	5 (0.3%)	3 (0.2%)
Reproductive system and breast disorders	5 (0.3%)	1 (<0.1%)
Respiratory, thoracic and mediastinal disorders	8 (0.5%)	7 (0.4%)
Skin and subcutaneous tissue disorders	4 (0.2%)	5 (0.3%)
Vascular disorders	6 (0.3%)	5 (0.3%)

Notes: Incidences are based on the number of subjects, not the number of events. Although a subject may have had 2 or more clinical AEs, the subject is counted only once in a category. The same subject may appear in different categories. Percentages calculated with the number of subjects in each group as denominator. Sorted first by System Organ Class (alphabetical order) then by Preferred Term (alphabetical order).

Study 11899 (MRR-00273), DAE was reported for 39 (6.5%) subjects in the rivaroxaban group and 20 (3.4%) in the placebo. DAE was more commonly due to a bleeding event or elevation in AST/ALT in the rivaroxaban group (Table 37).

Table 37: Incidence of AEs resulting in permanent discontinuation of study drug (for at least two subjects in any treatment group) by MedDRA SOC (Study 11899 (MRR-00273)).

MedDRA system organ class Preferred term (Primary term)	Rivaroxaban 20 mg o.d. (N=598) n (%)	Placebo (N=590) n (%)
ANY EVENT	39 (6.5%)	20 (3.4%)
Cardiac disorders	6 (1.0%)	2 (0.3%)
Atrial fibrillation	3 (0.5%)	1 (0.2%)
Gastrointestinal disorders	9 (1.5%)	2 (0.3%)
Abdominal pain upper	2 (0.3%)	0
Gastrointestinal haemorrhage	2 (0.3%)	0
Immune system disorders	2 (0.3%)	0
Infections and infestations	2 (0.3%)	0
Injury, poisoning and procedural complications	2 (0.3%)	1 (0.2%)
Investigations	4 (0.7%)	1 (0.2%)
Alanine aminotransferase increased	2 (0.3%)	0
Aspartate aminotransferase increased	2 (0.3%)	1 (0.2%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	3 (0.5%)
Nervous system disorders	3 (0.5%)	4 (0.7%)
Headache	2 (0.3%)	0
Renal and urinary disorders	3 (0.5%)	1 (0.2%)
Haematuria	3 (0.5%)	0
Reproductive system and breast disorders	2 (0.3%)	0
Skin and subcutaneous tissue disorders	3 (0.5%)	1 (0.2%)
Vascular disorders	2 (0.3%)	3 (0.5%)
Thrombophlebitis superficial	0	2 (0.3%)

Notes: Incidences are based on the number of subjects, not the number of events. Although a subject may have had 2 or more clinical AEs, the subject is counted only once in a category. The same subject may appear in different categories. Percentages calculated with the number of subjects in each group as denominator. Sorted first by System Organ Class (alphabetical order) then by Preferred Term (alphabetical order).

Source: Table 14.3.1/25

o.d. = once daily, MedDRA = Medical Dictionary for Regulatory Activities, SOC = system organ class

Study 11223 (MRR-00150), DAE occurred for nine (7.6%) subjects in the 10 mg twice daily group, 18 (15.4%) in the 20 mg twice daily, six (5.0%) in the 40 mg once daily, nine (7.4%) in the 30 mg twice daily and one (0.8%) in the enoxaparin/VKA. There was no apparent pattern in the conditions leading to discontinuation in the rivaroaxaban group.

Study 11528 (MRR-00223), DAE occurred for nine (6.7%) subjects in the rivaroxaban 20 mg once daily group, eight (6.0%) in the 30 mg, seven (5.1%) in the 40 mg and six (4.4%) in the heparin/VKA. There was no apparent difference between the groups in the pattern of AEs leading to discontinuation.

In Study 11630 (R-8570) ROCKET-AF, DAE was reported for 1118 (15.72%) subjects in the rivaroxaban group and 1082 (15.19%) in the warfarin. There were more subjects in the rivaroxaban group discontinuing because of gastrointestinal haemorrhage, anaemia, renal failure and elevated ALT (Table 38).

Table 38: Incidence of the 15 most frequent post baseline AEs leading to permanent study medication discontinuation based on the rivaroxaban treatment group by preferred term (Study 39039039AFL3001: Safety Analysis Set).

Dictionary-Derived Term	Rivaroxaban (N=7111) n (%)	Warfarin (N=7125) n (%)
Total no. subjects with post baseline adverse events leading to permanent study medication discontinuation	1118 (15.72)	1082 (15.19)
Sudden death	68 (0.96)	63 (0.88)
Gastrointestinal haemorrhage	47 (0.66)	27 (0.38)
Epistaxis	35 (0.49)	24 (0.34)
Cardiac failure	34 (0.48)	33 (0.46)
Haematuria	33 (0.46)	24 (0.34)
Anaemia	31 (0.44)	12 (0.17)
Cardiac failure congestive	25 (0.35)	25 (0.35)
Upper gastrointestinal haemorrhage	22 (0.31)	13 (0.18)
Renal failure	19 (0.27)	6 (0.08)
Liver function test abnormal	18 (0.25)	13 (0.18)
Gingival bleeding	16 (0.23)	4 (0.06)
Ischaemic stroke	16 (0.23)	21 (0.29)
Melaena	16 (0.23)	6 (0.08)
Myocardial infarction	15 (0.21)	19 (0.27)
Alanine aminotransferase increased	14 (0.20)	7 (0.10)
Rectal haemorrhage	14 (0.20)	11 (0.15)
Transient ischaemic attack	14 (0.20)	13 (0.18)

In Study 12620 (A49701), DAE was reported for 84 (13.1%) subjects in the rivaroxaban group and 96 (15.0%) in the warfarin. DAE due to ischaemic stroke was less common in the rivaroxaban group: eight (1.3%) subjects compared with 21 (3.3%) (Table 39).

Table 39: Incidence (≥0.4% in either treatment group) of AEs resulting in permanent discontinuation of study drug (population: subjects valid for safety analyses) (Study 12620 (A49701)).

MedDRA system organ class Preferred term	Rivaroxaban (N=639) n (%)	Warfarin (N=639) n (%)
Any event	84 (13.1)	96 (15.0)
Nervous system disorders	21 (3.3)	35 (5.5)
Ischaemic stroke	8 (1.3)	21 (3.3)
Gastrointestinal disorders	10 (1.6)	10 (1.6)
Gastric ulcer haemorrhage	3 (0.5)	2 (0.3)
Gastrointestinal haemorrhage	0 (0.0)	4 (0.6)
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	9 (1.4)	7 (1.1)
Prostate cancer	3 (0.5)	0 (0.0)
Cardiac disorders	5 (0.8)	8 (1.3)
Renal and urinary disorders	7 (1.1)	6 (0.9)
Haematuria	4 (0.6)	2 (0.3)
Respiratory, thoracic and mediastinal disorders	5 (0.8)	5 (0.8)
Interstitial lung disease	1 (0.2)	4 (0.6)
Blood and lymphatic system disorders	2 (0.3)	5 (0.8)
Anaemia	0 (0.0)	4 (0.6)
Skin and subcutaneous tissue disorders	3 (0.5)	4 (0.6)
Vascular disorders	3 (0.5)	4 (0.6)
Infections and infestations	3 (0.5)	3 (0.5)
Hepatobiliary disorders	3 (0.5)	3 (0.5)
Investigations	2 (0.3)	4 (0.6)
Musculoskeletal and connective tissue disorders	1 (0.2)	3 (0.5)

Pooled analyses of safety data

The sponsor also provided reports of pooled analyses of data that were used to inform the Clinical Reports.

Study PH-35415 was a technical report describing the definitions and statistical approaches underlying an integrated analysis of rivaroxaban Studies 11354 (RECORD 1), 11355 (RECORD 4), 11356 (RECORD 3) and 11357 (RECORD 2) with regard to efficacy and safety. No data were presented in the report and no analyses were described.

Study PH-35843 was an additional safety analyses of VTE prevention Phase 3 rivaroxaban studies in subjects undergoing total hip replacement or total knee replacement: 11354 (RECORD 1), 11355 (RECORD 4), 11356 (RECORD 3) and 11357 (RECORD 2). The study included a total of 12206 subjects who had taken at least one dose of rivaroxaban. The study focused on haemorrhagic adverse events, rhabdomyolysis/myopathy and serum creatinine. Haemorrhagic adverse events were reported in 189 (3.10%) subjects in the rivaroxaban group and 168 (2.75%) in the enoxaparin. Rhabdomyolysis/myopathy was reported in 148 (2.39%) subjects in the rivaroxaban group and 171 (2.76%) in the enoxaparin. There was no apparent difference between rivaroxaban and enoxaparin in serum creatinine, reported as mean (SD) of ULN: 0.91 (0.29) for rivaroxaban and 0.91 (0.43) for enoxaparin.

Study PH-36312 was an additional safety report for Studies 11702 DVT (EINSTEIN DVT) and 11899 (EINSTEIN EXTENSION). The report only presented data for each study separately and did not perform any pooled analysis of the study results.

Study R-8572 and Study R-8599 were additional tabulations of data which the sponsor had prepared for the Integrated Summary of Safety. There was no text in the documents describing any analyses of the data, but the tabulations were provided.

Study PH-36320 was a pooled analysis of safety of rivaroxaban in 1516 subjects who received at least one dose of rivaroxaban or placebo in 59 Phase 1 clinical trials. TEAEs were reported by 506 (37.9%) of 1335 subjects treated with rivaroxaban and 49 (27.1%) of 181 subjects treated with placebo. TEAEs were reported in 187 (38.0%) subjects at doses <10 mg, 37 (37.4%) at 10 mg, 141 (43.4%) at 15 mg, 122 (35.7%) at 20 mg and 49 (27.1%) at >20 mg. The most frequently reported TEAEs were: headache 174 (13.0%) subjects, nasopharyngitis 50 (3.7%) and diarrhoea 33 (2.5%). There were no deaths. SAEs were reported by ten subjects.

Study R-8568 was a global pharmacovigilance analysis of Study 11630 (ROCKET) and Study 12620 (J-ROCKET). The profile of TEAEs was similar for rivaroxaban and warfarin. Treatment emergent haemorrhagic events were reported in 2298 (32.32%) of the rivaroxaban group and 2256 (31.66%) of the warfarin.

Study PH-36319 was a pooled analysis of liver safety aspects of rivaroxaban in the 1516 subjects who received at least one dose of rivaroxaban or placebo in the 59 Phase 1 clinical trials. There were 256 subjects treated with rivaroxaban included in the analysis and in that population one (0.4%) subject had ALT >3x ULN, one (0.4%) had AST >3x ULN and one (0.4%) had GGT (gamma glutamyl transpeptidase) >3x ULN.

Study R-8569 was an integrated summary of liver safety that examined all studies of rivaroxaban and post marketing data up to 15 September 2010. Overall, the incidence of post baseline elevation in ALT >3x ULN was 371 (2.51%) of 14798 subjects treated with rivaroxaban and 305 (2.34%) of 13014 subjects treated with comparator, HR (95% CI) 1.04 (0.89 to 1.21) p=0.033. The incidence in ROCKET and J-ROCKET of post baseline elevation in ALT >3xULN was 217 (2.85%) of 7618 subjects treated with rivaroxaban and 217 (2.84%) of 7646 subjects treated with comparator: HR (95% CI) 1.01 (0.84 to 1.22) p=0.929. The incidence in ODIXa-DVT (11223), EINSTEIN (11528), EINSTEIN DVT AND EINSTEIN PE was 78 (1.77%) of 4415 subjects treated with rivaroxaban and 137 (3.66%) subjects treated with comparator, HR (95% CI) 0.41 (0.31 to 0.55) p=0.009.

Study PH-36355 was an integrated summary of the management of major and severe bleeding in the clinical trials with rivaroxaban for the prophylaxis of DVT and PE in patients undergoing elective total hip replacement or total knee replacement surgery (RECORD Program) and also the use of rivaroxaban for treatment of VTE and prevention of recurrent DVT and PE (EINSTEIN program). The recommendations for management of severe bleeding arising from the sponsor's analysis of the data are:

Should bleeding occur, management of the haemorrhage may include the following steps:

- Identify and treat the underlying cause of the bleeding
- Where no source of bleeding can be identified, delay of next rivaroxaban administration or discontinuation of treatment as appropriate. Rivaroxaban has a terminal half life between 5 and 13 h (see Pharmacokinetic properties). Management should be individualised according to the severity and location of the haemorrhage. A specific agent to reverse the anti coagulant effect of rivaroxaban is not yet available. Because of high plasma protein binding, rivaroxaban is not expected to be dialysable. Protamine sulfate and vitamin K are not expected to affect the anticoagulant activity of rivaroxaban.
- Appropriate symptomatic treatment, for example, mechanical compression, surgical interventions, fluid replacement and haemodynamic support, blood product (packed red cells or fresh frozen plasma, depending on associated anaemia or coagulopathy) or platelets.
- If life threatening bleeding cannot be controlled by the above measures, administration of one of the following procoagulants may be considered:
- activated prothrombin complex concentrate (APCC)
- prothrombin complex concentrate (PCC)
- recombinant factor VIIa.

Post marketing experience

Post marketing data

There were no additional post marketing data provided in the submission.

Risk management plan

The RMP summarised exposure to rivaroxaban for the two new indications. A total of 3074 subjects were exposed to rivaroxaban for the indication of VTE. A total of 1658 subjects were exposed to the dosing regimen proposed by the sponsor. There were 213 males and 223 females over the age of 75 years were treated for this indication. A total of 108 subjects with hepatic impairment, and 13 subjects with severe renal failure were also treated for the indication of VTE.

Exposure for the indication of SPAF (stroke prevention in atrial fibrillation) was a total of 7935 subjects. A total of 5661 subjects were treated with rivaroxaban 20 mg once daily and 1997 with 15 mg once daily. There were 1608 males and 1314 females over the age of 75 years. There were 511 subjects with hepatic impairment and five with severe renal failure.

Total patient exposure for the indication of prevention of VTE following elective hip or knee replacement since 2008 (year of first launch) was 435,000 patients.

The Important Identified Risks were:

- Haemorrhage

Important Potential Risks were:

- Increase in liver enzymes, including bilirubin
- Symptomatic liver Impairment

Identified drug interactions:

- Ketoconazole
- Ritonavir
- Clarithromycin
- Erythromycin
- Fluconazole
- Rifampicin
- Acetylsalicylic acid
- Naproxen
- Clopidogrel
- Enoxaparin
- Warfarin

The sponsor proposes the following approaches to pharmacovigilance:

- Routine pharmacovigilance
- Continued collection of AE data from sponsored clinical trials
- Prescription event monitoring study
- Post marketing observational study
- Drug utilisation cohort studies in European databases

Evaluation of the data contained in the submission did not identify any additional risks that should be included in the RMP.

Evaluator's overall conclusions on clinical safety

The profile of TEAEs was similar for rivaroxaban and for VKA. There were similar rates of renal failure and pancreatitis. There was a slightly higher rate of minor bleeding events (for example, epistaxis and gingival bleeding) with rivaroxaban than with VKA. There were fewer subjects with elevation of ALT with rivaroxaban than with VKA.

The incidence and pattern of bleeding events was similar for rivaroxaban and VKA. The incidence of minor bleeding events was slightly higher with rivaroxaban. The incidence of uterine bleeding with rivaroxaban was double that of VKA in Study 11899. In Study 11630 and Study 12620, more serious bleeding events were more common with VKA. In Study 11630, poor INR control in the VKA group did not appear to contribute to intracranial haemorrhage. The observation of an increased risk of bleeding related AEs in subjects with poorer renal function in the EINSTEIN DVT study supports a reduction in dose for subjects with renal failure.[11]

The sponsor provided two reports describing the management of subjects treated with rivaroxaban who presented with significant bleeding events. These reports indicate the management of bleeding events in subjects treated with rivaroxaban should be:

- Identify and treat the underlying cause of the bleeding.
- Where no source of bleeding can be identified, delay of next rivaroxaban administration or discontinuation of treatment as appropriate. Rivaroxaban has a

[11] Sponsor comment: "No dose reduction is not required as stated in the approved Product Information for patients with moderate renal impairment for this indication."

terminal half life between 5 and 13 h (see Pharmacokinetic properties). Management should be individualised according to the severity and location of the haemorrhage. A specific agent to reverse the anti coagulant effect of rivaroxaban is not yet available. Because of high plasma protein binding, rivaroxaban is not expected to be dialysable. Protamine sulfate and vitamin K are not expected to affect the anticoagulant activity of rivaroxaban.

- Appropriate symptomatic treatment, for example, mechanical compression, surgical interventions, fluid replacement and haemodynamic support, blood product (packed red cells or fresh frozen plasma, depending on associated anaemia or coagulopathy) or platelets.
- If life threatening bleeding cannot be controlled by the above measures, administration of one of the following procoagulants may be considered:
  - activated prothrombin complex concentrate (APCC)
  - prothrombin complex concentrate (PCC)
  - recombinant factor VIIa.

There was no apparent difference in the frequency or pattern of SAEs between rivaroxaban and VKA, or between the different dose levels of rivaroxaban up to 30 mg twice daily. There was also a similar frequency of SAEs for rivaroxaban and placebo.

There was no apparent difference in the frequency or pattern of deaths between rivaroxaban and VKA, or between the different dose levels of rivaroxaban up to 30 mg twice daily. There was also a similar frequency of deaths for rivaroxaban and placebo.

The rate of abnormality of ALT in subjects treated with rivaroxaban was lower than for warfarin but higher than that for placebo. Elevation in ALT >3x ULN was reported in around 1.5% of the rivaroxaban subjects, 3.8% of the VKA and 0.5% of the placebo. The rate of AST >3x ULN increased with rivaroxaban dose from 3.3% with the 5 mg dose up to 6.8% with the 60 mg dose.

Concomitant medication with ASA or thienpyridines increased the risk of bleeding events. Concomitant medication with thienpyridines increased the incidence of major bleeding event in the rivaroxaban group from 3.57/100/year to 4.76/100/year; and aspirin increased the incidence from 3.03/100/year to 4.56/100/year.

List of questions

Pharmacokinetics

The Evaluator does not have any questions with regard to PK.

Pharmacodynamics

The Evaluator does not have any questions with regard to PD.

Efficacy

1. In Study 11528 the overall response rate to treatment was highest in the rivaroxaban 30 mg once daily group. Can the sponsor provide a justification as to why the 20 mg once daily dose was chosen for further development over the 30 mg once daily dose?
2. Can the sponsor provide a justification for the choice of NI margin of 2.0 used in Study 11701?

3. Can the sponsor provide a justification for the choice of NI margin of 1.46 used in Study 11630?
4. Can the sponsor provide a justification for the choice of NI margin of 2.0 used in Study 12620?
5. Has the sponsor performed an analysis/meta analysis of the effects of concomitant antithrombotic medications on efficacy?

Safety

6. In Study 11630 (R-8570) ROCKET-AF, how many subjects were treated with rivaroxaban 20 mg and how many with rivaroxaban 15 mg? Is the figure of 1474 reported in this study correct?
7. Has the sponsor performed an analysis/meta analysis of the effects of concomitant antithrombotic medications on safety?

Clinical summary and discussion

Clinical aspects

Food was demonstrated to increase the bioavailability and T_{max} for rivaroxaban. Study 011938 demonstrated that rivaroxaban AUC was increased by 39% and C_{max} by 76%. Study 011585 confirmed food increased bioavailability.

Study 012362 demonstrated dose proportionality between rivaroxaban 10 mg, 15 mg and 20 mg.

Rivaroxaban was found to be a substrate of human BCRP *in vitro* (Study PH-36090). This was proposed as a mechanism for the interaction between ritonavir and rivaroxaban.

Exposure to rivaroxaban was increased in subjects with CHF. Mean AUC and C_{max} were approximately 20% higher in subjects with CHF compared with healthy subjects (Study 012980).

Rifampicin decreased exposure to rivaroxaban and increased its clearance (Study 012680). The AUC of rivaroxaban showed a 49% decrease and C_{max} a 22% decrease after the co administration of rifampicin. The $t_{1/2}$ of rivaroxaban was halved and clearance doubled when rifampicin was co administered. Clarithromycin increased exposure to rivaroxaban and decreased its clearance (Study 012612). The ratio (90% CI), rivaroxaban rivaroxaban + clarithromycin/rivaroxaban for AUC was 1.54 (1.44-1.64) and for C_{max} was 1.40 (1.30-1.52). Omeprazole had no apparent effect on the PK of rivaroxaban (Study R-8564). Rivaroxaban had no apparent effect on the PK of warfarin (Study 010849). Fluconazole appears to decrease rivaroxaban clearance through inhibition of CYP3A4 hepatic metabolism and also Pgp/BCRP mediated active renal secretion (Study 012606). AUC was increased by 42% and C_{max} by 28%; and clearance decreased by 30%.

The population PK studies found:

- A high degree of variability in absorption (Study PPK03-002).
- Renal and hepatic failure both resulted in decreased clearance of rivaroxaban with moderately hepatically impaired subjects having a 54% decrease in clearance (Study PPK03-000130).
- CYP3A4 and Pgp inhibition decreases both renal and non renal clearance of rivaroxaban (Study 012623).

- There was a decrease in clearance with increasing age compared to a median age of 65, translating to a 38% higher drug exposure for a 90 year old subject (Study PPK03-010).
- Female subjects had 15% lower clearance of rivaroxaban (Study PPK04-009)
- Clearance decreased with age and with increasing plasma creatinine concentration; and volume of distribution increases with increasing lean body mass (Study 012143, Study AFL3001).

The effect upon PD in the PK studies with respect to the effects of food, dose proportionality, CHF, rifampicin, clarithromycin, and omeprazole were as would be expected from the effects on PK.

Factor Xa activity, HepTest and PiCT enabled discrimination between rivaroxaban and warfarin effect (Study 010849). Rivaroxaban influenced all three of these indices whereas warfarin did not. Warfarin decreased factor IIa whereas rivaroxaban did not have a significant effect on this index.

The plasma concentration response relationship for PT was described by a linear model with intercept; and an inhibitory E_{max} model described the plasma concentration effect relationship for factor Xa activity, HepTest and PTT (Study PPK03-010, Study PPK04-009, Study AFL3001).

ASA alone, or in combination with clopidogrel did not affect HepTest, aPPT, or ETP (Study 011940)

There was a trend for association of increasing C_{max} with bleeding events (Study PH-34764).

The PK data support the reduced dose used in the clinical trials for subjects with renal failure (defined as calculated CrCl between 30 and 49 mL/min, inclusive).

Benefit risk assessment

Benefits

Benefits for DVT treatment and prevention of recurrent VTE

Study 11702 (EINSTEIN DVT) demonstrated NI for rivaroxaban in comparison with enoxaparin/VKA for the indication of "treatment of deep vein thrombosis (DVT) and for the prevention of recurrent DVT and pulmonary embolism (PE)". The use of survival analysis was appropriate. The outcome measures were clinically relevant and related directly to the proposed indication. The NI margin of 2 was generous and it is not clear how it was determined,[8] but the actual upper 95% CI was less than 1.5, and the HR was less than 1. The secondary analyses and secondary efficacy outcome measures were supportive of the primary analysis. The benefit was maintained throughout the duration of the study. However, in the 30 d following cessation of treatment there was a higher rate of the primary efficacy outcome variable in the rivaroxaban group: twelve (0.8%) subjects compared with seven (0.5%) in the comparator. Although this was attributed by the sponsor to the longer duration of action of VKA it raised the question as to whether longer duration of treatment with rivaroxaban shoulkd be advised. Rivaroxaban did not result in a statistically significant improvement in mortality compared to warfarin but the incidence of all cause mortality was 38 (2.2%) subjects in the rivaroxaban group and 49 (2.9%) in the enoxaparin/VKA.

The dose of enoxaparin used in Study 11702 (EINSTEIN DVT) was consistent with the enoxaparin Product Information. The target INR range of 2 to 3 was consistent with accepted guidelines. The open label design of Study 11702 (EINSTEIN DVT) could have introduced bias, but the use of a "central independent adjudication committee for

suspected clinical outcomes that was blinded to treatment allocation" should have minimised such bias. In addition, the outcome measures were objective measures, as opposed to subjective measures such as questionnaires, and less prone to measurement bias.

A separate statistical analysis was not presented for the outcome of PE. However, PE was included in the composite primary outcome measure, which is also similar in wording to the proposed indication. The rates of PE were similar in the two treatment groups and there does not appear to be a divergence in effect for DVT and PE. Hence it is reasonable to include PE in the indication.[12]

Study 11899 (EINSTEIN DVT Extension) demonstrated superiority for rivaroxaban in comparison with placebo for extension of treatment for VTE prophylaxis. Efficacy was convincingly demonstrated for all the outcome measures. For the primary efficacy outcome measure the HR (95% CI) was 0.185 (0.087 to 0.393); for secondary outcome 1: 0.180 (0.085 to 0.383); for secondary outcome 2: 0.198 (0.096 to 0.405); and for secondary outcome 3: 0.278 (0.146 to 0.528), $p<0.0001$ for all outcome measures. The treatment effect was maintained for 12 months. Hence, although the extended duration of treatment was not standard practice the study has demonstrated benefit for extended treatment.

The dose finding studies did not give a clear indication as to the choice of rivaroxaban dose for in the Phase 3 studies. There appeared to be a plateau of effect at the rivaroxaban 20 mg twice daily dose in Study 11223. In Study 11528 the overall response rate to treatment was highest in the rivaroxaban 30 mg once daily group: 95 (77%) subjects for rivaroxaban 20 mg, 98 (82%) for 30 mg, 93 (74%) for 40 mg and 82 (69%) for heparin VKA. However, the difference in response does not appear to be sufficient to justify using the 30 mg once daily dose over the 20 mg once daily. The sponsor may have used additional data, from other studies using rivaroxaban, in determining the final dose used in the Phase 2 studies but this is not transparent.[13]

Benefits for stroke prevention in AF

Study 11630 (ROCKET AF) demonstrated superiority for rivaroxaban in comparison with VKA for the indication "prevention of stroke and systemic embolism in patients with non valvular atrial fibrillation". This was demonstrated using the predefined procedure for multiple hypothesis testing where firstly for the primary efficacy outcome measure NI was demonstrated by the PP analysis and then superiority by the ITT analysis. The HR (95%) CI was 0.79 (0.66 to 0.96), $p<0.001$ for the PP analysis and 0.79 (0.65 to 0.95), $p=0.015$, for the ITT analysis. The reduction in event rate was clinically significant: ITT analysis event rate for rivaroxaban was 1.70/100 patient years and for warfarin was 2.15/100 patient years. The outcome measures were clinically relevant and related directly to the proposed indication. Although the NI margin of 1.46 for the HR for rivaroxaban/warfarin was generous the ITT analysis subsequently proved superiority. The effect was apparent from the beginning to the end of the study. The effect was not apparent for subjects with prior stroke/TIA/non CNS systemic embolism at baseline but other than this, the primary efficacy outcome measure was not influenced by baseline characteristics. The conclusion of efficacy was supported by Major Secondary Endpoint 1 (composite of stroke, non CNS systemic embolism, and vascular death), HR (95% CI) 0.86 (0.74 to 0.99); Major Secondary Endpoint 2 (composite of stroke, non CNS systemic embolism, MI, and vascular death), 0.85 (0.85 (0.74 to 0.96); primary haemorrhagic stroke; HR (95% CI), 0.59 (0.37 to 0.93);

[12] Sponsor comment: "The indication wording claimed that rivaroxaban is to treat acute DVT and thereby prevent the recurrence of DVT and PE. The study is not designed to show that rivaroxaban independently prevents the recurrence of DVT and PE."

[13] Sponsor comment: "All data leading to a dose decision in Phase III was presented and discussed in the dossier in detail."

and non CNS systemic embolism, 0.23 (0.09 to 0.61). However, there was no significant improvement in all cause mortality or for any other secondary efficacy outcome measure. For the warfarin treatment group, only 55.16% of INR measurements were in the target range of 2 to 3. This may have influenced the results in favour of rivaroxaban, but is also fairly typical of warfarin treatment control in clinical practice.

Non CNS systemic embolism is also included in the proposed indication and the HR (95% CI) of 0.23 (0.09 to 0.61) support its inclusion. The results for stroke (except for non disabling stroke) were also in favour of rivaroxaban. Hence the separate components of the indication are supported by the data.

Study 12620 was conducted in Japanese subjects using a lower dose than that used in Study 11630 (ROCKET AF). For the primary efficacy outcome measure NI was demonstrated by the PP analysis. There were 11 events in the rivaroxaban group and 22 in the warfarin, HR (95% CI) 0.49 (0.24 to 1.00). This was supported by the ITT analysis. The margin for NI of 2 was generous, but the primary analysis had an upper 95% CI of 1. This was well within the NI margin.

Risks

The profile of TEAEs was similar for rivaroxaban and for VKA. There were similar rates of renal failure and pancreatitis. There was a slightly higher rate of minor bleeding events (for example, epistaxis and gingival bleeding) with rivaroxaban than with VKA. There were fewer subjects with elevation of ALT with rivaroxaban than with VKA.

The incidence and pattern of bleeding events was similar for rivaroxaban and VKA.[14] The incidence of minor bleeding events was slightly higher with rivaroxaban. The incidence of uterine bleeding with rivaroxaban was double that of VKA in Study 11899. In Study 11630 and Study 12620 more serious bleeding events were more common with VKA. The observation of an increased risk of bleeding related AEs in subjects with poorer renal function in the EINSTEIN DVT study supports a reduction in dose for subjects with renal failure.

The sponsor proved two reports describing the management of subjects treated with rivaroxaban who presented with significant bleeding events. These reports indicate the management of bleeding events in subjects treated with rivaroxaban should be:

- Identify and treat the underlying cause of the bleeding
- Where no source of bleeding can be identified, temporary or permanent discontinue rivaroxaban
- Give supportive care with blood transfusions of packed red blood cells, and/or fresh frozen plasma

There was no apparent difference in the frequency or pattern of SAEs between rivaroxaban and VKA, or between the different dose levels of rivaroxaban up to 30 mg twice daily. There was also a similar frequency of SAEs for rivaroxaban and placebo.

There was no apparent difference in the frequency or pattern of deaths between rivaroxaban and VKA, or between the different dose levels of rivaroxaban up to 30 mg twice daily. There was also a similar frequency of deaths for rivaroxaban and placebo.

The rate of abnormality of ALT in subjects treated with rivaroxaban was lower than for warfarin but higher than that for placebo. Elevation in ALT >3x ULN was reported in around 1.5% of the rivaroxaban subjects, 3.8% of the VKA and 0.5% of the placebo. The

[14] Sponsor comment: "This statement is not accurate: the pattern is different, for example nominal superiority for critical organ bleed and fatal bleed was shown in the rivaroxaban arm."

rate of AST >3x ULN increased with rivaroxaban dose from 3.3% with the 5 mg dose up to 6.8% with the 60 mg dose.

Concomitant medication with ASA or thienpyridines increased the risk of bleeding events. Concomitant medication with thienpyridines increased the incidence of major bleeding event in the rivaroxaban group from 3.57/100/year to 4.76/100/year; and aspirin increased the incidence from 3.03/100/year to 4.56/100/year.

Safety specification

The data did not indicate any additional risks that should be added to the Safety Specification.

Balance

The risk benefit balance is in favour of extending the indications for rivaroxaban to include:

- Prevention of stroke and systemic embolism in patients with non valvular atrial fibrillation.
- Treatment of DVT and for the prevention of recurrent DVT and PE.

Rivaroxaban appears to be equivalent in efficacy and safety to warfarin. However, from a patient's perspective warfarin has the disadvantage of requiring blood testing and closer clinical monitoring.

Conclusions

The application should be approved to extend the indications for Xarelto (rivaroxaban) to include:

- Prevention of stroke and systemic embolism in patients with non valvular atrial fibrillation.
- Treatment of DVT and for the prevention of recurrent DVT and PE.

Second round evaluation

Second round evaluation of clinical data submitted in response to questions

In response to request for information, the sponsor has provided tabulations of data from Study 11702 DVT and Study SN 11899 (EINSTEIN EXTENSION); and two protocols for post marketing studies.

The data tabulations are for subjects treated with PAI (platelet aggregation inhibitors) or ASA at baseline and provide baseline, efficacy and safety data. These tabulations are provided by the sponsor in their response.

The two post marketing protocols are for:

- An observational post authorisation modified prescription event monitoring safety study to monitor the safety and utilisation of rivaroxaban in the primary care setting in England. The study is to be conducted by the Drug Safety Research Unit (DSRU) in the UK. The study will be conducted over a 12 month time period. It will focus on haemorrhagic and thrombotic events but will also collect data on other identified and unidentified ADRs (adverse drug reactions). Patients who are prescribed rivaroxaban in a general practice setting will be entered into the study and adverse events will be elicited over a 12 month follow up period.

- An observational post authorisation safety specialist cohort event monitoring study (SCEM) to monitor the safety and utilisation of rivaroxaban in the secondary care setting in England. The study is also to be conducted by the DSRU in the UK. The study will focus on haemorrhagic and thrombotic events but will also collect data on other identified and unidentified ADRs. Patients who are prescribed rivaroxaban in by a specialist will be entered into the study and adverse events will be elicited over a 3 month follow up period.

Questions put to the sponsor:

1. It was noted that the first three commercial scale batches of the 15 mg and 20 mg tablets would be placed on stability trial to verify the shelf life. Please give an assurance that the TGA will be immediately notified of any out of specification results or untoward trends (results that are worse than those observed for the pilot scale batches).
2. Please provide a justification as to why the 20 mg once daily dose was chosen for further development over the 30 mg once daily dose?
3. Please provide a justification for the choice of NI margin of 2.0 used in Study 11702.
4. Please provide a justification for the choice of a NI margin of 1.46 used in Study 11630.
5. Please provide a justification for the choice of a NI margin of 2.0 used in Study 12620.
6. Have you performed an analysis/meta analysis of the effects of concomitant antithrombotic medications on efficacy?
7. In Study 11630 (R-8570) ROCKET-AF, how many subjects were treated with rivaroxaban 20 mg and how many with rivaroxaban 15 mg? Is the figure of 1474 reported in this study correct?
8. Have you performed an analysis/meta analysis of the effects of concomitant antithrombotic medications on safety?
9. Please provide more information about these planned studies, otherwise indicate when provision of such information is anticipated.
10. In regard to the planned drug utilisation cohort studies in European databases, please provide the planned dates for submission of interim and final data, otherwise indicate when provision of such information is anticipated.
11. Given the Australian and international post marketing exposure of Xarelto, please provide information on the occurrence and frequency of medication errors from related PSURs (Periodic Safety Update Reports).
12. Please definitively state whether a dosing card will be provided to prescribers in Australia in accordance with Australian specific registration details. If so, you should also provide detail as to how this activity will be implemented in Australia.
13. Please provide details of these plans to the TGA for review.
14. For any safety considerations raised in the clinical requests for information, please provide information that is relevant and necessary to address the issues in the RMP.

Second round benefit-risk assessment

Second round assessment of benefits

After consideration of the responses to clinical questions, the benefits of Xarelto (rivaroxaban) in the proposed usage are unchanged from those identified above.

Second round assessment of risks

After consideration of the responses to clinical questions, the benefits of Xarelto (rivaroxaban) in the proposed usage are unchanged from those identified above.

Second round assessment of benefit-risk balance

The benefit-risk balance of Xarelto (rivaroxaban), given the proposed usage, is favourable.

Second Round Recommendation Regarding Authorisation

The application should be approved to extend the indications for Xarelto (rivaroxaban) to include:

- Prevention of stroke and systemic embolism in patients with non valvular atrial fibrillation.
- Treatment of DVT and for the prevention of recurrent DVT and PE.

V. Pharmacovigilance findings

Risk management plan

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

Safety specification

The sponsor provided a summary of ongoing safety concerns which are shown at Table 40.

Table 40: Summary of ongoing safety concerns for rivaroxaban.

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

CrCl, creatinine clearance; CYP3A4, cytochrome P450 3A4; DVT, deep vein thrombosis; PE, pulmonary embolism; P-gp, P-glycoprotein

OPR reviewer's comment:

In the SS (Safety Specification) of the RMP, it is stated that:

> *No data are available to support appropriate dosing, safety or efficacy in this population (subjects aged < 18 years). In order to address the issues relating to drug exposure and safety, a Paediatric Investigational Plan and the corresponding timelines for development were submitted to the Paediatric Committee (PDCO) of the European Medicines Agency (EMA). This was approved at the September 2009 PDCO*

meeting. For VTE treatment, a Phase 1 single dose study with rivaroxaban in a paediatric population is ongoing; and

It is recognised that prescribers may make use of rivaroxaban in a paediatric population, either in a population undergoing major orthopaedic surgery, in those receiving conservative treatment of fractures by plaster cast, in those being treated for acute thrombosis, or in those with AF.

Reports of paediatric exposure to rivaroxaban will be reviewed as part of Bayer Schering Pharma's (BSP's) ongoing routine safety surveillance practices. Relevant cases will be discussed in the PSUR.

Consequently, it is recommended that the sponsor should consider including the important missing information 'Paediatric population', as an ongoing safety concern. The relevant sections of the RMP should be amended accordingly.

Pharmacovigilance plan

The sponsor proposes routine pharmacovigilance activities, consistent with the published activities,[15] to monitor all the specified ongoing safety concerns.

The sponsor states that there will be specific SAE follow up using SAE questionnaires:

- For the important identified risk 'Haemorrhage' and the important missing information 'Patients with severe renal impairment (CrCl < 30 mL/min)' and 'Patients receiving concomitant systemic inhibitors of CYP3A4 or Pgp other than azole antimycotics (for example, ketoconazole) and HIV protease inhibitors (for example, ritonavir)', to include the presence or absence of co morbidities and concomitant medications that are associated with an increased risk of bleeding, clotting parameters and anticoagulant therapy, questions to include type of surgery, time after surgery to first dose, etcetera.
- For the important potential risk 'Increases in liver enzymes, including bilirubin', to collect data for SAE reports of significant liver enzyme elevations as well as clinical liver disorder. These questionnaires systematically collect data relating to past medical history, and outcome and diagnostic procedures supporting the diagnosis.

The sponsor has provided copies of the Liver Injury, Cerebral Haemorrhage and Bleeding (Spontaneous Report) questionnaires in an annex of the RMP.

In addition, the sponsor states that for the important potential risk 'Increases in liver enzymes, including bilirubin':

- Relevant liver related events will be sent to external liver experts (Hepatic Event Assessment Committee) for evaluation and assessment;
- The established Liver Advisory Panel will evaluate aggregate data; and
- Data will be collected on symptomatic liver impairment.

To further monitor the important identified risk 'Haemorrhage' and the important missing information 'Patients receiving concomitant systemic inhibitors of CYP3A4 or Pgp other than azole antimycotics (for example, ketoconazole) and HIV protease inhibitors (for example, ritonavir)' and 'Pregnant or breast feeding women', the sponsor proposes to conduct a Modified Prescription Event Monitoring (MPEM) study, the aim of which is to

[15] European Medicines Agency, "ICH Topic E 2 E Pharmacovigilance Planning (Pvp), Step 5: Note for Guidance on Planning Pharmacovigilance Activities (CPMP/ICH/5716/03)", June 2005, Web, accessed 7 August 2012 <http://www.emea.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002818.pdf>.

proactively capture safety and drug utilisation data in the post marketing phase of licence approval of rivaroxaban as prescribed to patients by general practitioners (GPs) in primary care in England. The second, based in secondary care, will proactively monitor the short term safety and drug utilisation of rivaroxaban as prescribed to patients for medical conditions requiring anticoagulation by specialists in this setting with a particular focus on obtaining information on patients who stop taking rivaroxaban prior to transfer of care to their GP.

The sponsor's correspondence, dated 28 October 2011, provided full draft protocols for these two studies, dated July 2011 and September 2011, respectively. It is assumed these updated documents will replace the outline of the protocols/synopses of these planned studies initially provided in an annex of the RMP.

The duration of the MPEM study, which uses an observational cohort design, will be dependent on the level of prescribing of rivaroxaban by GPs in England. Randomisation will not be required. The study will start upon notification of the date of market launch in England (to be confirmed, expected to be November 2011). At 12 months, cohort accrual will be examined to determine the proportions of patients initiated in primary care compared to secondary care (based on response to relevant question on treatment initiation on the questionnaire). Patients will be observed for a minimum of 12 months to evaluate use of rivaroxaban, with data captured using a two phased approach, initially after 3 months observation to gather relevant risk factor information on baseline characteristics, acute AEs associated with specific risks of interest (including any early acute haemorrhagic and hepatic outcomes), and then at 12 months observation to obtain information on time variant data such as changes in health status, disease severity, medications, and AEs with delayed onset associated with specific risks of interest. During the course of the study, selected outcomes of interest will undergo further evaluation to inform on any unusual features/manifestations, relevant risk factors, clinical course, and behaviours. The data analysis plan will include: descriptive univariate analysis to examine drug utilisation characteristics; calculation of crude incidence event rates and rate differences for the whole cohort and subsets of special populations for purposes of signal detection; qualitative case series reports and quantitative determination of time to onset using regression modelling; and self controlled methods to calculate adjusted relative risks for selected events (where feasible). The sponsor states that for this MPEM study, a sample size of 10,000 evaluable patients is desirable to detect an effect size (relative incidence rate) of at least 2.0 with power of 90% at 5% significance for analysis of major bleeding events of interest within the primary objectives for which the hypothesised background rate is uncommon (>0.1%). An interim study report will be produced in time for inclusion in the scheduled PSUR for the product or regular updates of the RMP for as long as the study continues. Examination of aggregate event data will be limited to one interim report on a study cohort of 2,500 valid patients or on the valid cohort achieved at approximately 18 months, whichever is the sooner after one year and a detailed final report based on a study cohort of 10,000 valid patients unless a decision is made to end the study early.

The second study will use an observational, population based open cohort design to study the short term (up to 12 weeks) safety and use of rivaroxaban as initiated by specialists in the secondary care setting in the immediate post marketing period. This Specialist Cohort Event Monitoring (SCEM) study aims to collect exposure and outcome data for a cohort of approximately 2,000 evaluable patients over a three year period. Randomisation will not be required. Patient recruitment into the study is anticipated to start in the first quarter of 2012 (to be confirmed) and will continue for a maximum of 36 months, or until the target sample size has been achieved (whichever is the soonest). The final cohort size, period of observation and the duration of the SCEM study will be dependent on the level of prescribing of rivaroxaban by specialists in England. The primary focus of the study will be to quantify the cumulative incidence (risk) of selected identified risks in real life clinical

practice (that is, major and minor bleeding composite outcomes which meet pre specified PP definitions) occurring in the three months observation period after treatment initiation and incident and recurrent thromboembolic complications. The study also includes several exploratory analyses to:

1. where possible, to quantify the incidence of other important identified and potential risks (not mentioned in the primary objective), other frequently and rarely reported AEs and to identify previously unrecognised ADRs; and
2. describe clinical features and management of cases of overdose, major bleeding (according to PP pre specified definition) and VTE events in the cohort exposed to rivaroxaban.

Progress reports (relevant to specialist and patient cohort accrual) will be produced in time for inclusion in the scheduled PSUR for the product (that is, every six months for the first two years after launch and then annually thereafter) or regular updates of the RMP for as long as the study continues. Examination of aggregate event data will be limited to one interim report on a study cohort of 600 evaluable patients or on the valid cohort achieved at approximately 18 months post date of first patient recruited (whichever is the soonest), and a detailed final report based on a study cohort of 2,000 evaluable patients or on the valid cohort achieved at approximately 36 months post date of first patient recruited (whichever is the soonest; unless an extension to study period is required).

To further monitor the important identified risk 'Haemorrhage' and the important missing information 'Patients receiving concomitant systemic inhibitors of CYP3A4 or Pgp other than azole antimycotics (for example, ketoconazole) and HIV protease inhibitors (for example, ritonavir)' and 'Pregnant or breast feeding women', the sponsor proposes to conduct drug utilisation cohort studies in European databases. The most relevant to Australia would appear to be the post authorisation safety study programme planned for the UK. The sponsor summarises the proposed design of a population based study to characterise the risk of bleeding associated with rivaroxaban treatment in comparison with treatment with warfarin, the most widely used VKA in routine clinical practice in the UK.

The data source for this study will be The Health Improvement Network (THIN) database in the UK. THIN includes information on over 3 million patients (approximately 5% of the UK population) that is systematically recorded by participating primary care practitioners (PCPs) as part of their routine patient care and is anonymised and sent to THIN for use in research projects. The computerised information includes demographics, details of PCP visits, referrals to specialists and hospital admissions (including diagnostic and treatment information), results of laboratory tests, and a free text section. Prescriptions issued by the PCP are recorded electronically and the indication can be ascertained by reviewing the patient's clinical history. The Read classification is used to code specific diagnoses as reasons for each consultation and a drug dictionary based on data from the MULTILEX classification is used to record prescriptions. The sponsor claims that the population included in THIN is representative of the UK as a whole in terms of age, sex and geographic distribution and this database has been validated for use in pharmacoepidemiology.

The study objectives are:

1. To provide a detailed description of patients who are prescribed oral rivaroxaban for the first time in comparison with those who are prescribed warfarin for the first time, and describe the characteristics of rivaroxaban use (including dose and duration).
2. To determine time trends in the characteristics of first time use of rivaroxaban.
3. To study the occurrence of hospitalisation or referral to a specialist from primary care for three common, well characterised bleeding events:
    a. intracranial haemorrhage,

b. gastrointestinal bleeding, and

c. genitourinary bleeding among users of rivaroxaban in comparison with users of warfarin.

All male and female patients aged 2 to 89 years who have been enrolled with a primary care physician contributing to the database for at least 1 year and who had their first prescription recorded in the database at least 1 year ago will be included. The enrolment period will start on the day after rivaroxaban receives marketing authorisation for the 'initial treatment of acute DVT and long term secondary prevention of recurrent DVT and PE' in the UK and will end 2 years after that date. The characteristics of the two study cohorts in the first year and second year of the enrolment period will be compared. To study potential adverse outcomes of treatment with rivaroxaban and warfarin, the same source population will be used as in the drug utilisation study, with the enrolment period being extended for long enough to ensure that a sufficient number of patients newly treated with rivaroxaban can be included. The sponsor states that according to a preliminary sample size calculation, based on an incidence of haemorrhagic stroke in warfarin treated patients of 5 per 1,000 person years, 10,000 rivaroxaban treated patient years and 40,000 warfarin treated patient years would be required to exclude a 50% increased risk of haemorrhagic stroke in rivaroxaban treated patients compared with warfarin treated patients with a power of 73%.

Crude incidence rates will be estimated for each of the three adverse outcomes in both cohorts. Incidence will be presented using two different methods of computing the denominator. The first one will use the number of first time users on the index date as the denominator; the second will compute the person time contribution of the study cohorts into current, recent and past use. Current use will refer to person time up to 15 days after the end of supply of the index drug, recent use will refer to person time up to 90 days after the end of current use, and past use will include all person time contribution after the end of recent use. Age and sex adjusted rate ratios with 95% CIs will be estimated for each of the three adverse outcomes comparing rivaroxaban with warfarin using Poisson regression analysis. Where numbers and data permit, adjustment will be made for some of the baseline medication and co morbidity variables described in the drug utilisation section, including indication and history of adverse outcomes (referral or hospitalisation for haemorrhagic stroke, gastrointestinal bleeding or genitourinary bleeding recorded at any time before the index date). The sponsor states that this study protocol will be approved by a research ethics committee, and the study will be conducted in accordance with Good Epidemiology Practices. The sponsor has also provided draft protocols/synopses of these planned studies in an annex of the RMP. The sponsor's correspondence, dated 28 October 2011, states that annual updates on these studies are planned throughout the study period as regards accrual of patients and their characteristics.

Final reports from the studies will be due 4 to 5 years after study start including analyses on safety outcomes. A more precise time plan for study reports will be available mid November 2011.

In regard to the currently approved VTE prevention indication, an open label post marketing observational study (XAMOS – XA0801 – Study 13802) to compare bleeding risk in standard regimen for VTE prevention in elective hip or knee replacement surgery in a real-life setting is being conducted. Data collected include type of surgery, type of anaesthesia, concomitant medication (for example, those with CYP3A4/Pgp inhibitory or inductory effect), previous renal/liver impairment, BMI (body mass index) and risk for bleeding (for example, gastrointestinal ulcers). The sponsor has provided a study protocol for this ongoing study in an annex of the RMP. In addition, final study protocols for drug utilisation database studies in the Netherlands, Germany, Denmark and the UK have also been provided in an annex of the RMP.

OPR reviewer's comment:

In principle, there is no objection to the sponsor implementing additional pharmacovigilance activities to further monitor the specified ongoing safety concerns. However, the related study protocols of the ongoing and planned studies associated with the currently approved VTE prevention indication have not been reviewed, as they are not considered to be part of the specific extension of indications sought in the application.

The draft protocols of the MPEM and the SCEM studies appear reasonable, although final protocols for these studies should be submitted to the TGA when available. These documents should be included as annexes to the next revision of the RMP.

The draft protocols of the drug utilisation cohort studies in European databases appear reasonable, although the power estimate for the THIN database study (73% to exclude 50% increase haemorrhagic stroke risk compared to warfarin) does not appear all that impressive. Nevertheless, given the actual numbers to achieve this estimated power (10,000 rivaroxaban treated patient years and 40,000 warfarin treated patient years), this is acceptable based on practical considerations. In addition, final protocols for these studies should be submitted to the TGA when available and included as annexes to the next revision of the RMP.

Risk minimisation activities

Sponsor's conclusion in regard to the need for risk minimisation activities

The sponsor has provided justification and concluded that routine risk minimisation activities for all the specified ongoing safety concerns pertaining to the extension of indications are sufficient.

OPR reviewer's comment:

The sponsor's justification and conclusion would appear to be reasonable, except that the increased potential for medication errors associated with the following has not been addressed:

- Xarelto 10 mg tablets may be taken with or without food, while 15 mg tablets and 20 mg tablets should be taken with food;
- seemingly conflicting instructions on what to do when a dose is missed, dependent on once or twice daily dosing.

The sponsor acknowledges that this increased potential for medication errors exists in the next section of this report and proposes several activities for the minimisation of medication error including a dosing card for doctors.

Potential for medication errors

The sponsor states that:

> *Rivaroxaban is available only on prescription. For the indication VTE prevention after elective hip or knee replacement surgery, patients will receive rivaroxaban after surgery, thus in a highly controlled environment. Therefore, the most likely source of any potential medication errors may occur at the point of dispensing of the medication to the patient. The appropriate labelling guidelines have been followed in order to reduce the potential for medication errors.*
>
> *Routine pharmacovigilance is in place and if it becomes apparent that adverse events are occurring as a result of medication errors (for example, including accidental ingestion or other unintended use by children), this topic will be discussed in the PSUR and respectively in an updated European Union RMP.*

For the indication "Prevention of stroke and systemic embolism in adult patients with nonvalvular atrial fibrillation", patients will receive 20 mg rivaroxaban once daily. For patients with moderate renal impairment (CrCl 30-49 mL/min), 15 mg rivaroxaban should be taken once daily. There is a possibility that patients could take the tablet twice daily rather than once daily because the 15 mg tablet is also intended for use in the treatment of DVT at a twice daily dose. This may lead to a greater risk in renally impaired patients than in patients with normal renal function because renal impairment may be associated with increased rivaroxaban exposure.

The sponsor's correspondence, dated 28 October 2011, further states that there were no reports on prescription or medication errors which would currently raise a new safety concern for patients treated with Xarelto. In addition, the sponsor has provided an assurance that upcoming PSURs will document the cumulative rate of medication errors.

The sponsor's correspondence, dated 28 October 2011, also states that the colour scheme of the current and proposed strengths is distinctively different (that is, font colours for 15 mg and 20 mg are green and orange, respectively); the brand name, active name and strength are also prominently displayed on four panels. In consideration of the initial three weeks treatment for acute DVT with 15 mg twice daily dosing, a pack containing 42 tablets for the 15 mg was developed. To enhance distinctiveness, a statement 'For the initial treatment of acute DVT (twice daily dosing)' is also introduced on the carton for 42 pack designed for twice daily dosing. To mitigate the risk of administration errors, especially for the indication of DVT treatment where twice daily dosing of 15 mg is indicated for the initial three weeks of treatment, followed by 20 mg once daily for the maintenance dose, physicians will be encouraged to write separate scripts for the initial and maintenance treatment to minimise the chances of patients having to possess two different strengths at the same time. This also gives the physician an opportunity to assess progress of patient and to educate the patient on the change of dosing regimen for the rest of the therapy. To assist the patients with administration at the correct time during the initial twice daily dosing treatment, the blister foil for 15 mg in the 42 pack is now modified to include "am" and "pm" in addition to the days of the week printed on the foil backing to facilitate patient compliance in this acute treatment phase and to facilitate twice daily dosing. Other pack sizes include a blister foil with (only) days of the week indicating once daily dosing.

OPR reviewer's comment:

It is expected that this new information will be incorporated into this part of the RMP when it is next updated.

Summary of recommendations

The OPR provides these recommendations in the context that the submitted RMP is supportive to the application; the implementation of a RMP satisfactory to the TGA is imposed as a condition of registration; and is applicable without modification in Australia unless so qualified:

- It is recommended that the sponsor should consider including the important missing information 'Paediatric population' as an ongoing safety concern. The relevant sections of the RMP should be amended accordingly.
- In principle there is no objection to the sponsor implementing additional pharmacovigilance activities to further monitor the specified ongoing safety concerns. However, the related study protocols of the ongoing and planned studies associated with the currently approved VTE prevention indication have not been reviewed, as they are not considered to be part of the specific extension of indications sought in the application.

- The draft protocols of the MPEM and the SCEM studies appear reasonable, although final protocols for these studies should be submitted to the TGA when available. These documents should be included as annexes to the next revision of the RMP.
- The draft protocols of the drug utilisation cohort studies in European databases appear reasonable, although final protocols for these studies should be submitted to the TGA when available. These documents should be included as annexes to the next revision of the RMP.
- The sponsor's justification and conclusion that routine risk minimisation activities for all the specified ongoing safety concerns pertaining to the extension of indications are sufficient would appear to be reasonable, except that the increased potential for medication errors associated with the following has not been addressed:
  - Xarelto 10 mg tablets may be taken with or without food, while 15 mg tablets and 20 mg tablets should be taken with food;
  - seemingly conflicting instructions on what to do when a dose is missed, dependent on once or twice daily dosing.
- New information provided in the sponsor's correspondence dated 28 October 2011, relating to the 'Potential for medication errors' section of the RMP, should be incorporated into this part of the RMP when it is next updated.
- New information provided in the sponsor's correspondence dated 28 October 2011, relating to the 'Risk Minimisation Plan' of the RMP, should be incorporated into this part of the RMP when it is next updated. In addition, the sponsor should provide an assurance that a copy of the prescriber guide, including the dosing card, will be provided to the TGA before distribution in Australia and include it in the RMP.
- The sponsor should propose a post market periodic schedule for the prescriber, patient and pharmacist survey testing for as long as these additional risk minimisation activities are still considered necessary and therefore continue to be implemented.
- In regard to the proposed routine risk minimisation activities, it is recommended to the Delegate that the draft product information document be revised to include corresponding eGFR (estimated glomerular filtration rate) values, as this is the more common method of reporting creatinine clearance and estimating renal function in Australia.
- In addition, both the nonclinical and clinical evaluators have recommended various amendments to the draft PI.
- In regard to the proposed routine risk minimisation activities, it is recommended to the Delegate that the draft consumer medicine information (CMI) document be revised to adequately reflect any changes made to the Australian PI as a result of the above recommendations.

VI. Overall conclusion and risk/benefit assessment

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

Quality

With regard to the drug product, the tablets are well controlled with satisfactory limits at release and expiry. Stability data were provided to support a shelf life of 3 years when

stored below 30ºC in the proposed packaging with the additional condition 'Store in the original pack until required' on the carton labels.

Administration of the 20 mg tablet after food resulted in significantly higher C_{max} values (approximately 75% increase) and a delay in T_{max}. AUC increased by 40% in the fed state. No study was provided on the effect of food on the 15 mg tablet. However, given that absorption is linear in the fasted state to 10 mg but linear in the fed state to 30 mg, a less pronounced food effect is expected for the 15 mg tablet.

There are no objections to the registration of Xarelto 15 mg and 20 mg rivaroxaban tablets with regard to chemistry, manufacturing and controls.

Nonclinical

The nonclinical evaluator noted that the data submitted were of high quality and the pivotal carcinogenicity studies were performed according to GLP standards:

- *In vitro*, rivaroxaban reduced platelet factor 4 release in sera from patients with HIT suggesting that it is a potential option for the prevention and treatment of thrombosis in patients with HIT. IV rivaroxaban was more effective than enoxaparin in a rat arterial thrombosis model, indicating its potential utility in treating arterial thrombotic disorders. However, rivaroxaban and other drugs which only inhibit factor Xa (for example, tick anti coagulant protein, fondaparinux) were shown to be less effective at inhibiting *in vitro* catheter induced clotting than drugs which inhibit thrombin as well as factor Xa (heparin and enoxaparin).
- Rivaroxaban is chemically related to the antibiotic linezolid and contains an oxazolidone moiety, which has been associated with mitochondrial toxicity via inhibition of mitochondrial protein synthesis. Both *in vitro* and *in vivo* testing failed to provide evidence that rivaroxaban has effective bacteriostatic action or is an inhibitor of mitochondrial protein synthesis. It was concluded that rivaroxaban would not be expected to produce the effects associated with long term linezolid use.
- Combination of rivaroxaban with the anti inflammatory drugs acetylsalicylic acid or diclofenac did not produce additive effects on bleeding time in the rat tail transection model. However, there was an additive effect on bleeding time when a low dose of rivaroxaban (producing a statistically insignificant increase in bleeding time) was combined with naproxen.
- Activated prothrombin complex and factor VIIa were identified as antidotes to the anticoagulant action of rivaroxaban in animal models.
- *In vitro* studies with cell lines expressing high levels of Bcrp or Pgp proteins indicated that only high doses of strong Bcrp or Pgp inhibitors are likely to produce modest decreases in the renal clearance of rivaroxaban. Potential drug interactions are extensively covered in the Product Information document.
- Two year carcinogenicity studies were performed using mice and rats of both sexes. The studies compared the incidence of neoplastic lesions in a control group with three groups receiving a daily oral dose of rivaroxaban up to 60 mg/kg. Unbound plasma rivaroxaban exposure levels in the high dose groups in mice were similar to those in humans while the exposure levels in the high dose groups in rats were up to 3.6 fold higher than those in humans. Rivaroxaban showed no carcinogenic potential in either species.

Nonclinical recommendations and conclusions:

- No issues of clinical concern were noted in the studies presented.

- There are no objections on nonclinical grounds to the registration of rivaroxaban (Xarelto) for the proposed indications.
- The RMP presents an appropriate overview of the toxicological findings.

Clinical

The contents of the submission have been outlined earlier. The clinical evaluator has recommended that the extensions of indication sought by the sponsor should be approved.

Pharmacology

Pharmacokinetics

Food was demonstrated to increase the bioavailability and T_{max} for rivaroxaban. Study 011938 demonstrated that rivaroxaban AUC was increased by 39% and C_{max} by 76%. Study 011585 confirmed food increased bioavailability.

Study 012362 demonstrated dose proportionality between rivaroxaban 10 mg, 15 mg and 20 mg.

Rivaroxaban was found to be a substrate of human BCRP *in vitro* (Study PH-36090). This was proposed as a mechanism for the interaction between ritonavir and rivaroxaban.

Exposure to rivaroxaban was increased in subjects with CHF. Mean AUC and C_{max} were approximately 20% higher in subjects with CHF compared with healthy subjects (Study 012980).

Rifampicin decreased exposure to rivaroxaban and increased its clearance (Study 012680). The AUC of rivaroxaban showed a 49% decrease and C_{max} a 22% decrease after the co-administration of rifampicin. The $t_{1/2}$ of rivaroxaban was halved and clearance doubled when rifampicin was co administered. Clarithromycin increased exposure to rivaroxaban and decreased its clearance (Study 012612). The ratio (90% CI), rivaroxaban rivaroxaban + clarithromycin/rivaroxaban for AUC was 1.54 (1.44-1.64) and for C_{max} was 1.40 (1.30-1.52). Omeprazole had no apparent effect on the PK of rivaroxaban (Study R-8564). Rivaroxaban had no apparent effect on the PK of warfarin (Study 010849). Fluconazole appears to decrease rivaroxaban clearance through inhibition of CYP3A4 hepatic metabolism and also Pgp/BCRP mediated active renal secretion (Study 012606). AUC was increased by 42% and C_{max} by 28%; and clearance decreased by 30%.

The population PK studies found:

- A high degree of variability in absorption (Study PPK03-002).
- Renal and hepatic failure both resulted in decreased clearance of rivaroxaban with moderately hepatically impaired subjects having a 54% decrease in clearance (Study PPK03-000130).
- CYP3A4 and Pgp inhibition decreases both renal and non renal clearance of rivaroxaban (Study 012623).
- There was a decrease in clearance with increasing age compared to a median age of 65, translating to a 38% higher drug exposure for a 90 year old subject (Study PPK03-010).
- Female subjects had 15% lower clearance of rivaroxaban (Study PPK04-009)
- Clearance decreased with age and with increasing plasma creatinine concentration; and volume of distribution increased with increasing lean body mass (Study 012143, Study AFL3001).

Pharmacodynamics

The effect upon PD in the PK studies with respect to the effects of food, dose proportionality, CHF, rifampicin, clarithromycin, and omeprazole were as would be expected from the effects on PK.

Factor Xa activity, HepTest and PiCT enabled discrimination between rivaroxaban and warfarin effect (Study 010849). Rivaroxaban influenced all three of these indices whereas warfarin did not. Warfarin decreased factor IIa whereas rivaroxaban did not have a significant effect on this index.

The plasma concentration response relationship for PT was described by a linear model with intercept; and an inhibitory E_{max} model described the plasma concentration effect relationship for factor Xa activity, HepTest and PTT (Study PPK03-010, Study PPK04-009, Study AFL3001).

ASA alone, or in combination with clopidogrel did not affect HepTest, aPPT, or ETP (Study 011940).

There was a trend for association of increasing C_{max} with bleeding events (Study PH-34764).

Efficacy

Efficacy data for treatment of DVT and prevention of recurrent DVT and of PE

Study 11702 (EINSTEIN DVT) was a multicentre, randomised, open label, parallel group, active controlled, event driven NI study. Subjects had to have a confirmed symptomatic proximal DVT without symptomatic PE. The study treatments were *either* rivaroxaban 15 mg bd for 3 weeks followed by 20 mg once daily OR enoxaparin 1 mg/kg bd, VKA (acenocoumarol or warfarin) to achieve a target INR of 2.5 (range 2.0-3.0) with enoxaparin continued until INR ≥ 2.0. Treatment duration was for 3, 6 or 12 months as determined by the investigator prior to randomisation. The sponsor is requested to clarify in detail the criteria used by the investigator to determine the treatment duration. Were they in any way mandated by the study protocol? Also in its pre Advisory Committee on Prescription Medicines (ACPM) response, the sponsor is requested to provide the numbers (percentages) in each treatment group who were treated for 3, 6 or 12 months.

The primary efficacy outcome was symptomatic recurrent VTE which was the composite of recurrent DVT or non fatal or fatal PE. There were a number of secondary efficacy variables. The study was designed as a NI study with the criterion for NI being that the upper bound of the 95% CI for the HR was to be < 2.0. The sample size calculation estimated that 88 events would be required to give a power of 90% to demonstrate NI of rivaroxaban with a two sided α of 0.05. The clinical evaluator has not stated what sample size was required to achieve this power. Therefore, the sponsor is requested to clarify the sample size required and provide a detailed justification in support of the validity of the study if the PP population of 3096 subjects was less than the projected sample size.

A total of 3459 subjects were enrolled and 3449 were randomised. Included in the ITT analysis were 3449 subjects (1731 on rivaroxaban and 1718 on enoxaparin/VKA. There were 1960 males (56.8%) and 1489 females (43.2%) and the age range was 18 to 97 years. The treatment groups were matched in terms of demographic characteristics, risk factors for thromboembolism, prior medical conditions, prior anti thrombotic medications and concomitant anti thrombotic medication.

NI was demonstrated for rivaroxaban in comparison with enoxaparin/VKA for the primary efficacy variable, the HR [95% CI] being 0.680 [0.443, 1.042] for the ITT population and 0.698 [0.444, 1.097] for the PP population, p < 0.0001 (Table 41).

Table 41: Summary of results for primary efficacy outcome (Study 11702 (EINSTEIN DVT)).

Population	ITT	ITT on treatment	PP (on treatment)
Incidence rate of primary efficacy outcome			
Rivaroxaban group	36/1731 (2.1%)	34/1718 (2.0%)	32/1525 (2.1%)
Enox/VKA group	51/1718 (3.0%)	49/1705 (2.9%)	46/1571 (2.9%)
Cox's proportional hazard model for rivaroxaban vs. enox/VKA			
Hazard ratio	0.680	0.671	0.698
Confidence interval	0.443-1.042	0.433-1.039	0.444-1.097
p-value for non-inferiority	<0.0001	<0.0001	<0.0001
p-value for superiority	0.0764	0.0737	0.1191

Notes: p-value and hazard ratio estimates based on stratified proportional hazards model, with stratification based on intended treatment duration. The asymptotic one-sided p-value for non-inferiority was calculated based on the log-hazard ratio estimated for rivaroxaban versus comparator, on its standard error and on the log of the non-inferiority margin of 2.0.

The results for the secondary efficacy variables were supportive of the primary efficacy result.

The benefit was maintained throughout the study. However, in the 30 days following cessation of treatment, there was a higher rate of the primary efficacy outcome variable in the rivaroxaban group (12; 0.8%) compared with the comparator group (7; 0.5%). This effect was attributed to the longer duration of action of VKA. However, the clinical evaluator did wonder whether a longer duration of treatment with rivaroxaban should be advised. The sponsor is asked to comment on this.

Study 11899 (Einstein Extension), the extension of EINSTEIN study, was a multicentre, randomised, placebo controlled, double blind, parallel group, event driven superiority study and included subjects who had completed 6-14 months of treatment with either rivaroxaban or VKA and either coming from the Einstein DVT study or outside of the study.

The study treatments were rivaroxaban 20 mg once daily or placebo once daily. Treatment duration was for 6 or 12 months, determined for each subject prior to randomisation. The study was terminated once a total of at least 30 confirmed recurrent thromboembolic events had been reached.

The primary efficacy outcome measure was composite of recurrent DVT or non fatal or fatal PE. The power assumptions required approximately 650 subjects per treatment group.

A total of 1200 subjects were enrolled, 1197 randomised, 693 males (57.9%) and 503 females (42.1%). The age range was 18 to 96 years. The treatment groups were matched with regard to demographic characteristics, risk factors for thromboembolism, and in the proportions of each group who received concomitant anti thrombotic agents.

Superiority was demonstrated for the primary efficacy outcome measure and for all three secondary efficacy measures.

Study 11223 was a multicentre, randomised, open label, parallel group, comparator controlled, dose finding study which included men and women of at least 18 years of age with an acute symptomatic proximal DVT.

The study treatments were rivaroxaban 10 mg bd, 20 mg bd, 40 mg once daily, 30 mg bd or enoxaparin 1 mg/kg bd subcutaneously for 5-7 days, discontinued once INR was in the range 2-3 for two consecutive days on VKA.

The primary efficacy outcome measure was the response to treatment as determined by CCUS after three weeks of treatment. A positive response was defined as:

- an improvement in the CCUS score by 4 score points compared to baseline; or

- the absence of any confirmed symptomatic recurrence; or
- extension of DVT or of symptomatic PE or of any VTE related death up to Day 21.

There were a number of secondary efficacy outcome measures.

The study included 613 subjects randomised to treatment, at least 120 in each treatment group. There were 368 males (61%) and 236 females (39%) and the age range was from 10 to 91 years. The treatment groups were matched according to demographic characteristics. The results for the CCUS score and the CCUS score plus VTE events suggested a plateauing of effect at the 20 mg bd dose.

Study 11528 was a multicentre, randomised, open label, parallel group, comparator controlled, dose finding study whose subjects had a confirmed acute symptomatic DVT without concomitant symptomatic PE.

The study treatments were rivaroxaban 20 mg once daily, 30 mg once daily, 40 mg once daily or heparin (unfractionated or tinzaparin or enoxaparin at one of two dose levels) followed by VKA. Treatment duration was for 12 weeks.

The primary efficacy outcome measure was the composite of symptomatic recurrent DVT or symptomatic fatal and non fatal PE at 12 weeks and deterioration in thrombotic burden, as assessed by complete compression ultrasound or perfusion lung scan from baseline to 12 weeks. There were secondary efficacy measures.

The study included 543 subjects, at least 130 in each treatment group. There were 277 males (51.1%), 265 females (48.9%) and the age range was from 18 to 94 years.

Overall response to treatment was highest for the rivaroxaban 30 mg od group with 98/119 (82%) improved, followed by rivaroxaban 20 mg od with 95/123 (77%) improved, then rivaroxaban 40 mg od with 93/126 (74%) improved and finally heparin/VKA with 82/119 (69%) improved.

Efficacy data for prevention of stroke in AF

Study 11630 (ROCKET AF) was a multicentre, randomised, double blind, double dummy, parallel group, active comparator, event driven, NI study in men or women aged at least 18 years with non valvular AF (that is, AF in the absence of rheumatic mitral valve disease, a prosthetic heart valve or mitral valve repair). The study treatments were:

- rivaroxaban 20 mg once daily (15 mg once daily in moderate renal impairment) + warfarin placebo once daily titrated to a target sham INR of 2 to 3; or
- warfarin once daily titrated to a target INR of 2 to 3 + rivaroxaban placebo once daily.

All subjects were required to have periodic INR testing regardless of treatment allocation.

The primary efficacy outcome measure was the composite of stroke and non CNS systemic embolism. There were a number of secondary endpoints. The criterion for NI was that the upper bound of the 95% CI for the HR for rivaroxaban/warfarin had to be <1.46 and there was a pre defined procedure for multiple hypothesis testing. Assuming a total duration of enrolment of approximately 1.5 years, a warfarin treatment group event rate of 2.3% per patient year and a yearly dropout rate of 14%, the total number of randomised subjects was estimated to be ~14,000.

There were 14,269 subjects randomised to treatment with the ITT population consisting of 7,131 subjects on rivaroxaban (5,637 on 20 mg od and 1,474 on 15 mg od) and 7,133 on warfarin. In the ITT population, there were 8,604 males (60.32%) and 5,660 females (39.68%). The treatment groups were matched for baseline demographic variables, risk factors and concomitant medication.

For the primary efficacy outcome measure NI was demonstrated by the per-protocol analysis and superiority by the ITT analysis with the HR [95% CI] being 0.79 [0.66, 0.96], p

< 0.001 for the PP analysis and 0.79 [0.65, 0.95], p = 0.015 for the ITT analysis. Efficacy was also demonstrated for the major secondary endpoint 1 (composite of stroke, non CNS systemic embolism and vascular death) and the major secondary endpoint 2 (composite of stroke, non CNS systemic embolism, MI and vascular death) but not for all cause mortality (Table 42). The effect was not apparent for subjects with a prior stroke/TIA/non CNS systemic embolism at baseline compared to those without but apart from this, the primary efficacy outcome measure was not influenced by baseline characteristics.

Table 42: Hierarchical testing – event rate, HR and 95% CI for time to the first occurrence of efficacy endpoints (adjudicated by CEC) (Study 11630 (R-8570) ROCKET AF).

	----- Rivaroxaban ----		------ Warfarin ------			
Population / Data Scope - Analysis - Endpoint	n/N	Event Rate (100 pt-yr)	n/N	Event Rate (100 Pt-yr)	Rivaroxaban vs. Warfarin Hazard Ratio (95% CI)	p-value
Per Protocol/on-treatment - Non-inferiority						
- Primary Efficacy Endpoint	188/6958	1.71	241/7004	2.16	0.79 (0.66,0.96)	<0.001[*a]
Safety/on-treatment - Superiority						
- Primary Efficacy Endpoint	189/7061	1.70	243/7082	2.15	0.79 (0.65,0.95)	0.015[*b]
- Major Secondary Efficacy Endpoint 1	346/7061	3.11	410/7082	3.63	0.86 (0.74,0.99)	0.034[*b]
- Major Secondary Efficacy Endpoint 2	433/7061	3.91	519/7082	4.62	0.85 (0.74,0.96)	0.010[*b]
- All Cause Mortality	208/7061	1.87	250/7082	2.21	0.85 (0.70,1.02)	0.073[b]
ITT/regardless of treatment exposure - Superiority						
- All Cause Mortality	621/7081	4.58	667/7090	4.92	0.93 (0.84,1.04)	0.204[b]

Note: Primary Efficacy Endpoint is the composite of stroke and non-CNS systemic embolism.
Note: Major Secondary Efficacy Endpoint 1 is the composite of stroke, non-CNS embolism, and vascular death.
Note: Major Secondary Efficacy Endpoint 2 is the composite of stroke, non-CNS embolism, myocardial infarction and vascular death
Note: Event Rate 100 pt-yr: number of events per 100 patient years of follow up.
Note: On treatment is the period between the date of the first double-blind study medication to the date of the last double-blind study medication administration plus 2 days.
Note: Regardless of treatment exposure is the period of time from the date of the first double-blind study medication up to and including the Follow-up Visit for subjects who completed the study and data up to and including the last study contact for those who prematurely discontinued.
Note: Hazard Ratio (95% CI) and p-value from the Cox proportional hazard model with treatment as a covariate.
[a] p-value (one-sided) for non-inferiority of rivaroxaban versus warfarin by a non-inferiority margin of 1.46 in hazard ratio.
[b] p-value (two-sided) for superiority of rivaroxaban versus warfarin in hazard ratio.
[*] Statistically significant at 0.025 (one-sided) for non-inferiority and 0.05 (two-sided) for superiority.
Note: Per Protocol, safety and ITT refer to per protocol, safety, and ITT excluding site 042012.

In those centres where subjects treated with warfarin were in the TTR 65.54% to 100% of the time, NI of rivaroxaban in comparison with warfarin was still demonstrated with the HR [95% CI] being 0.74 [0.49, 1.12]. Overall for the warfarin treatment group, only 55.16% of INR measurements were in the target range of 2.0 to 3.0.

Study 12620 was a supportive, randomised, double blind, double dummy, parallel group study in Japanese subjects with non valvular AF. The study treatments were rivaroxaban 15 mg once daily (10 mg once daily in moderate renal impairment) versus warfarin. A lower rivaroxaban dose was chosen for Japanese patients because pop PK modelling had shown steady state exposure levels about 20-30% higher in Japanese patients compared with those in Caucasian patients.

The primary efficacy outcome measure was the composite of adjudicated stroke and non CNS systemic embolism. There were secondary endpoints similar to those in the pivotal study. The study was designed as a NI study with a margin of 2 for the upper bound of the 95% CI for the HR.

A total of 1,439 subjects were screened with 1280 randomised to treatment, 640 in each ITT group. For the primary efficacy outcome measure, NI was demonstrated by the PP analysis. There were 11 events in the rivaroxaban group (11/637) and 22 in the warfarin (22/637) with a HR [95% CI] = 0.49 [0.24, 1.00]. The major secondary efficacy endpoint results were supportive of the primary result.

Safety

In the efficacy studies there were 3,212 subjects exposed to rivaroxaban for the indication of 'treatment of DVT and for the prevention of recurrent DVT and PE' and 7,551 subjects exposed for the indication of 'prevention of stroke and systemic embolism in patients with non valvular AF'.

Overall, the profile of TEAEs was similar for rivaroxaban and for VKA. In the pivotal DVT study, 11702 (EINSTEIN DVT), TEAEs were reported in 62.7% of subjects in the rivaroxaban group and 63.1% in the enoxaparin/VKA group. Menorrhagia was more common in the rivaroxaban group (2.9%) than in the enoxaparin/VKA group (1.1%). There were fewer hepatic AEs in the rivaroxaban group (4.8%) than in the enoxaparin/VKA group (9.4%). In the pivotal non valvular AF study, 11630 (ROCKET AF), TEAEs were reported in 81.44% of subjects in the rivaroxaban group versus 81.54% in the warfarin group. The most frequently reported AEs for rivaroxaban were epistaxis (10.14%), peripheral oedema (6.12%) and dizziness (6.09%) and for warfarin were epistaxis (8.55%), nasopharyngitis (6.39%) and dizziness (6.30%). Treatment emergent renal failure was reported in 3.70% subjects in the rivaroxaban group and 3.96% in the warfarin group. Treatment emergent pancreatitis was reported in 0.30% subjects in the rivaroxaban group and 0.32% in the warfarin group.

In Study 11702 (EINSTEIN DVT) the incidence of treatment emergent bleeding events was the same for rivaroxaban (8.1%) as for enoxaparin/VKA (8.1%). The pattern of bleeding events was also similar for the two treatment groups. There was an indication that subjects with poorer renal function had an increased risk of bleeding related AEs. In Study 11630 (ROCKET AF), bleeding related TEAEs were reported in 32.32% of subjects in the rivaroxaban group versus 31.66% in the VKA group. In the rivaroxaban group there was a lower risk of bleeding related death and critical organ bleeding but a greater risk of a drop in haematocrit and transfusion. GI haemorrhage was reported in 1.41% of the rivaroxaban group and 0.98% of the VKA.

There was no apparent difference in either the frequency or the pattern of SAEs between the rivaroxaban and the VKA groups or between the different dose levels of rivaroxaban up to 30 mg bd. There was also a similar frequency of SAEs for rivaroxaban and placebo.

There was no apparent difference in either the frequency or the pattern of deaths between rivaroxaban and VKA or between the different dose levels of rivaroxaban up to 30 mg bd. There was also a similar frequency of deaths for rivaroxaban and placebo.

In Study 11702 (EINSTEIN DVT) significantly fewer subjects in the rivaroxaban group (1.5%) had elevations in ALT >3x ULN compared with the enoxaparin/VKA group (3.8%). In Study 11630 (ROCKET AF), clinically significant abnormalities in ALT and bilirubin occurred with very similar frequencies in both treatment groups although the rate of death with ALT >3x ULN within 30 days of the death was lower in the rivaroxaban group (11/7111, 0.15%) than in the warfarin group (19/7125, 0.27%). From an integrated analysis of liver safety, the rates of subjects with elevations in AST >3x ULN increased from 3.3% with the 5 mg dose up to 6.8% with the 60 mg dose.

Concomitant treatment with thienopyridines increased the risk of a major bleeding event in the rivaroxaban group from 3.57/100/year to 4.76/100/year while aspirin increased the incidence from 3.03/100/year to 4.56/100/year.

Rates of discontinuation due to AEs were roughly comparable between active comparator groups. In Study 11630 (ROCKET AF), there were more subjects in the rivaroxaban group discontinuing because of GI haemorrhage (0.66% versus 0.38%), anaemia (0.44% versus 0.17%), renal failure (0.27% versus 0.08%) and elevated ALT (0.20% versus 0.10%). The sponsor is requested to give a summary of the seriousness and/or severity of the cases in each treatment group for each of these AEs.

First round evaluation

First round risk-benefit balance

The clinical evaluator was of the opinion that the risk-benefit balance was in favour of extending the indications for rivaroxaban to prevention of stroke and systemic embolism in patients with non valvular atrial fibrillation AND treatment of DVT and for the prevention of recurrent DVT and PE.

Clinical questions asked as part of the consolidated list of questions

The clinical evaluator asked a number of questions the most important of which related to the choice of the 20 mg once daily dose (rather than the 30 mg once daily) and the choice of the various NI margins. The choice of the 20 mg once daily dose was the result of post hoc analyses from two studies of asymptomatic changes on repeat ultrasound. In answer to the questions about the choice of NI margins, the sponsor provided justifications on purely statistical grounds without discussing the clinical significance of the choices. For each NI margin choice, particularly for those in the pivotal studies, the sponsor is requested to give detailed justifications for those choices which demonstrate the clinical significance of each. In answer to a question as to whether a meta analysis had been conducted of the effects of concomitant anti thrombotic medications on safety, the sponsor replied that such an analysis had been undertaken. For subjects treated for the DVT indication, the event rate for bleeding in rivaroxaban treated subjects also treated with aspirin or clopidogrel was 22.7/100 PY compared with 15.4/100 PY in subjects treated with rivaroxaban alone. In subjects treated for the indication of stroke prevention in AF, the event rate for the major safety bleeding endpoint was 18.5/100 PY in concomitant aspirin users compared with 13.1/100 PY in concomitant non users.

Second round evaluation

Second round evaluation of clinical data submitted in response to questions

After the second round evaluation, the clinical evaluator was still of the opinion that the risk-benefit balance was still favourable for rivaroxaban in relation to the indications sought and the evaluator recommended approval.

Risk management plan

The OPR evaluator is of the opinion that the submitted RMP is supportive of the application and has recommended that the implementation of a RMP satisfactory to the TGA should be imposed as a specific condition of registration. The OPR evaluator has made a number of recommendations in their report. The Delegate supports all recommendations made by the OPR. The Delegate notes in particular the recommendation that the draft product information document be revised to include corresponding eGFR values, as the latter is the more common method of reporting creatinine clearance and estimating renal function in Australia, certainly as a first step. The Delegate would very much like to hear the views of both the sponsor and of the ACPM regarding this issue.

To further monitor the important identified risk: 'Haemorrhage' and the important missing information: 'Patients receiving concomitant systemic inhibitors of CYP3A4 or Pgp other than azole antimycotics (for example, ketoconazole) and HIV protease inhibitors (for example, ritonavir)' and 'Pregnant or breast feeding women' the sponsor proposes to conduct a MPEM study, the aim of which is to proactively capture safety and drug utilisation data in the post marketing phase of licence approval of rivaroxaban as

prescribed to patients by GPs in primary care in England. The second, based in secondary care, will proactively monitor the short term safety and drug utilisation of rivaroxaban as prescribed to patients for medical conditions requiring anticoagulation by specialists in this setting, with a particular focus on obtaining information on patients who stop taking rivaroxaban prior to transfer of care to their GP. The latter will be a SCEM study.

There appears to be a third post registration study planned or rather series of studies. These are to be drug utilisation studies employing European databases, the most relevant of which will be a UK study which will use THIN as its data source. The main aim of this population based study will be to characterise the risk of bleeding associated with rivaroxaban treatment in comparison with treatment with warfarin, the most widely used VKA in routine clinical practice in the UK.

In its pre ACPM response, the sponsor is asked to identify precisely each of the foregoing studies and give a brief description of each in terms of objectives and design.

Risk/benefit discussion

Delegate considerations

Study 11702 (EINSTEIN DVT) demonstrated NI for rivaroxaban in comparison with enoxaparin/VKA for the indication of 'treatment of DVT and for the prevention of recurrent DVT and PE'. The outcome measures were clinically relevant and related directly to the proposed indication. As noted by the clinical evaluator, the NI margin of 2 was generous and while there was a detailed statistical justification of why this value was chosen, the sponsor appears not at all to have addressed the clinical relevance and/or justification for the choice of this value. The sponsor has been requested to present a critical appraisal of this issue in its pre ACPM response. For the primary efficacy endpoint, the estimate of the HR was less than 1 and the upper bound of the 95% CI was in fact less than 1.1, for both the PP and ITT analyses. The sponsor has also been asked to clarify the precise sample size required to achieve the pre defined power of the study and to provide a detailed justification of the validity of the study if this sample size was in fact greater than the 3,096 subjects who were available for the PP analysis, the latter being the preferred analysis for a NI study.

For Study 11702, the results for the secondary efficacy outcome measures were supportive of the primary analysis. While the benefit appeared to maintained throughout the duration of the study, in the 30 days following cessation of treatment there was a higher rate of the primary efficacy endpoint in the rivaroxaban group, 12 (0.8%) compared with 7 (0.5%) in the comparator arm. The latter finding has been attributed by the sponsor to the longer duration of action of VKA. Was this longer duration of action of VKA ever taken into account in the design of the study? The clinical evaluator has noted that this result raises the question of whether a longer duration of treatment with rivaroxaban should be advised and the sponsor has been asked to comment. The Delegate has already asked the sponsor a number of questions about the treatment duration. In the light of this observed difference in the rate of the primary efficacy endpoint in the 30 days following cessation of treatment (which, by the way, the Delegate assumes to represent an overall analysis), the sponsor is requested to calculate the rate of the primary efficacy endpoint in the 30 days following cessation of treatment in each of the comparator treatment groups for each separate duration of treatment, that is, for the group of patients who were treated for 3 months, for the group of patients who were treated for 6 months and finally for the group of patients who were treated for 12 months. As well, the sponsor is requested to carry out a comparison of the principal baseline demographic and disease characteristics for each of the comparator treatment groups for each separate duration of treatment, that is, for the group of patients who were treated for 3 months, for the group of patients who were treated for 6 months and finally for the group of patients who were

treated for 12 months. Finally, the sponsor is requested to calculate the rate of the primary efficacy endpoint at treatment cessation, that is, as per the primary analysis, in each of the comparator treatment groups for each separate duration of treatment, that is, for the group of patients who were treated for 3 months, for the group of patients who were treated for 6 months, and finally for the group of patients who were treated for 12 months.

In relation to Study 11702, did the sponsor conduct any analysis of the results stratified by time in the TTR as it did for the ROCKET AF study? The sponsor is requested to provide, for Study 11702, the numbers/percentages of patients in the VKA treatment arm whose INR values were maintained within the TTR, at least 50% of the time, at least 60% of the time, at least 70% of the time, at least 80% of the time and at least 90% of the time.

For Study 11702, a separate statistical analysis was not presented for the outcome of PE, the numbers of such events being very low. Given that the rates of PE were similar in the comparator treatment groups, the Delegate agrees that it is reasonable to include PE in the indication although the ACPM will be asked for advice on this issue.

Study 11899 (EINSTEIN Extension) included subjects who had completed 6 months treatment with either rivaroxaban or VKA in EINSTEIN DVT and continued on either rivaroxaban or placebo. Treatment duration was for 6 or 12 months and was determined for each subject prior to randomisation. The sponsor is requested to clarify in detail the criteria used by the investigator to determine the treatment duration. Were they in any way mandated by the study protocol?

For Study 11899, the sponsor is requested to critically compare the principal baseline demographic and disease characteristics of the study population of Study 11702, EINSTEIN DVT and that of Study 11899, Extension of EINSTEIN DVT and highlight any significant differences between those two study populations.

The power assumptions of Study 11899, EINSTEIN Extension, required approximately 650 subjects per treatment group, yet only 1197 patients were randomised. The sponsor is to justify in detail why this shortfall of over 100 subjects does not undermine the validity of the study results.

For Study 11899, EINSTEIN DVT, efficacy was demonstrated for all outcome measures and the treatment effect was maintained for 12 months.

Study 11630 (ROCKET AF) demonstrated firstly NI and then superiority for rivaroxaban in comparison with VKA for the indication 'prevention of stroke and systemic embolism in patients with non valvular atrial fibrillation'. The outcome measures were clinically relevant and related directly to the proposed indication. As noted by the clinical evaluator, the NI margin of 1.46 for the HR for rivaroxaban/warfarin was generous but the upper bound of the corresponding 95% CI was 0.96, clearly less than 1.46 and in fact less than 1.0. Nonetheless, the sponsor has been asked to provide a detailed clinical, as opposed to statistical, justification for the choice of 1.46 as the pre defined NI margin. Also it must be clearly understood that, for the warfarin treatment group, only 55.16% of INR measurements were within the target range of 2.0 to 3.0. While it may be difficult to achieve consistent and optimal INR control on warfarin, the lack of high levels of such optimal control does mean that one does not really know how well rivaroxaban achieves its effect when warfarin works at its best. This is also presumably the case for the DVT/PE studies, although this is to be clarified by the sponsor.

The profile of TEAEs was similar for rivaroxaban and for VKA. There were similar rates of renal failure and pancreatitis, although in ROCKET AF it was noted that the rate of discontinuations because of renal failure was higher for rivaroxaban (0.27%) than it was for VKA (0.08%). There was a slightly higher rate of minor bleeding events (for example, epistaxis and gingival bleeding) with rivaroxaban than with VKA. From EINSTEIN DVT, there was an indication that subjects with poorer renal function had an increased risk of

bleeding-related AEs. In Study 11630 (ROCKET AF), bleeding related TEAEs were reported in 32.32% of subjects in the rivaroxaban group versus 31.66% in the VKA group. In the rivaroxaban group there was a lower risk of bleeding related death and critical organ bleeding but a greater risk of a drop in haematocrit and transfusion. GI haemorrhage was reported in 1.41% of the rivaroxaban group and 0.98% of the VKA. In Study 11702 (EINSTEIN DVT) significantly fewer subjects in the rivaroxaban group (1.5%) had elevations in ALT >3x ULN compared with the enoxaparin/VKA group (3.8%). In Study 11630 (ROCKET AF), clinically significant abnormalities in ALT and bilirubin occurred with very similar frequencies in both treatment groups although the rate of death with ALT >3x ULN within 30 days of the death was lower in the rivaroxaban group (11/7111, 0.15%) than in the warfarin group (19/7125, 0.27%). Also in ROCKET AF more subjects in the rivaroxaban group (0.20%) discontinued because of an elevated ALT than in the warfarin group (0.10%).

Indication

While the clinical evaluator has not recommended any amendment to the wording of the indications, the Delegate is strongly of the opinion that each indication must be modified to remind practitioners that in the target populations studied, the warfarin/VKA treatment was not always working or allowed to work at an optimal level. Granted, such optimal levels are difficult to achieve in clinical practice but there has to be a clear, open and accurate acknowledgement of this deficiency in the PI and in the view of the Delegate, such acknowledgement must first occur within the Indications. This was clearly an issue which exercised the minds of the decision makers at the US FDA (Food and Drug Administration). Thus in line with the indication in the US PI, the Delegate requests the indications be amended to the following:

> "*Prevention of stroke and systemic embolism in patients with non valvular AF; there are limited data on the relative effectiveness of Xarelto and warfarin for this indication when warfarin therapy is optimally controlled*
>
> *Treatment of DVT and for the prevention of recurrent DVT and PE; there are limited data on the relative effectiveness of Xarelto and warfarin for this indication when warfarin therapy is optimally controlled.*"

Summary

While the Delegate is minded to agree with the clinical evaluator that rivaroxaban appears to be equivalent in efficacy and safety to warfarin for the indications sought by the sponsor, the Delegate has asked a large numbers of questions of the sponsor. All of these questions must be satisfactorily answered by the sponsor and any final approval will be contingent upon this. The issue of fundamental importance to this submission is that to do with how well or how optimally warfarin/VKA was allowed to work as a comparator and there must be clear, open, detailed and accurate discussion of the issue within the PI.

Outcome

I propose to approve this submission by Bayer Australia Ltd to register Xarelto tablets (containing rivaroxaban 15 mg or 20 mg) based on the safety and efficacy of the product having been satisfactorily established for the indication below, for the reasons stated above in the Risk/Benefit Discussion.

> *"Prevention of stroke and systemic embolism in patients with non valvular AF; there are limited data on the relative effectiveness of Xarelto and warfarin for this indication when warfarin therapy is optimally controlled*
>
> *Treatment of DVT and for the prevention of recurrent DVT and PE; there are limited data on the relative effectiveness of Xarelto and warfarin for this indication when warfarin therapy is optimally controlled."*

This approval will be contingent upon the provision, by the sponsor, of satisfactory answers to all questions asked of the sponsor in this Request for ACPM Advice and also upon amendment of the PI document to the satisfaction of the TGA.

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

1. The implementation of the RMP as follows:
    a. DVT indication: version 5, dated 17 November 2010, and any subsequent updated versions as agreed with the Office of Product Review
    b. SPAF indication: version 6, dated 21 December 2010, and any subsequent updated versions as agreed with the OPR
2. Conditions of registration specifying the lodgement with the OPR of the TGA: first, of the study protocols and secondly of the final study reports as evaluable data when available of all post authorisation studies mentioned in the RMP evaluation, namely the MPEM study, the SCEM study, the UK study which will use THIN as its data source and finally the open label post marketing observational study (XAMOS – XA0801 – Study 13802).

The sponsor should address the following issues in the pre ACPM response:

- An update to the registration status (with dates) for this submission of Xarelto (rivaroxaban) in the USA, Europe/UK, Switzerland, Canada and New Zealand including any withdrawals, rejections or deferrals.
- The sponsor has been asked a number of questions and to provide a number of clarifications concerning Study 11702 (EINSTEIN DVT).
- The sponsor has been asked a number of questions and to provide a number of clarifications concerning Study 11899, Extension of EINSTEIN DVT.
- The sponsor has been asked a number of questions and to provide a number of clarifications concerning Study 11630 (ROCKET AF).
- If not already dealt with in answer to the questions above, the sponsor has been asked to address in critical detail the issue of the clinical significance, as opposed to the purely statistical significance, of each chosen NI margin.
- The sponsor has been requested to summarise the seriousness and/or severity of the cases in ROCKET AF for which more subjects in the rivaroxaban group discontinued than in the warfarin/VKA group. This is in relation to the AEs of GI haemorrhage, anaemia, renal failure and elevated ALT.
- The sponsor is asked to comment on the recommendation of the RMP evaluator that the draft PI be revised to include, where relevant, eGFR values.
- The sponsor has been asked to identify precisely each of the post authorisation studies discussed by the RMP evaluator and to give a brief description of each in terms of objectives and design.

Advisory committee considerations

The ACPM, having taking into account the submitted evidence of pharmaceutical efficacy, safety and quality, as well as the sponsor's response to these documents, agreed with the Delegate and considered this product to have a positive benefit-risk profile for the indication to include:

> *Prevention of stroke and systemic embolism in patients with non valvular atrial fibrillation and at least one additional risk factor for stroke*
>
> *Treatment of DVT and for the prevention of recurrent DVT and PE.*

In considering this application, the ACPM expressed concern about the end points and their validity in the comparative studies, expressing a view that it is the clinical impact of variations of INR that should be the outcome measure and not the variability of INR itself.

The ACPM noted that rivaroxaban was shown to be no more effective than well controlled use of the comparator; however rivaroxaban exposes the patient to major and potentially catastrophic adverse events. In particular, the ACPM advised that there is inadequate assessment of the clinical context across a range of situations, citing the inappropriateness of a set 24 h cessation prior to surgery, the critical need for assessment of hepatic and renal clearance and dosage adjustment; the risks of urgent unplanned surgery; routine dosing adjustments in aged or low body weight patients.

The ACPM supported the amendments proposed by the Delegate to the PI and CMI and advised the inclusion addition of:

- a clear statement in the 'Contraindications and Dosage and Administration' sections to alert prescribers and consumers to the significant safety risks for patients with renal impairment. In providing this advice, the ACPM noted the current absence of guidelines/standards for measuring and determining renal function thresholds.
- a strong statement in the 'Precautions' section to ensure awareness of the significant risks of irreversible bleeding, the absence of any measure of clinical effect, of antidote therapy, and the clinical impact particularly in regard to urgent unplanned surgery. The ACPM expressed concern that the PI has this critical issue inappropriately under the heading 'Overdosage'.
- statements in the 'Clinical Trials' section to reflect a more accurate account of the comparative efficacy with the current anticoagulant standard therapy to reflect the evidence that there is no increased efficacy over well controlled therapy with warfarin.
- a statement to emphasise that the drug interaction profile is not fully defined and the caution required for concomitant administration with other drugs.

The ACPM supported the Delegate in requiring a specific condition of registration to include a significant focus on the strengthening and sponsor commitment to full implementation of the RMP to ensure:

- accurate and balanced communication of the fact that while this product has the benefit of not requiring monitoring, there is the inherent risk that the effect in normal, or indeed overdose situations is not reversible in a timely fashion.
- rigorous enforcement of prescriber education for awareness of significant risks to population groups and consideration of precautions prior to prescribing.
- rigorous commitment to patient awareness of and access to CMI.
- a focus on prescribers' participation in pharmacovigilance and reporting all patient bleeds for analysis and data collection.

The ACPM advised that the implementation by the sponsor of the recommendations outlined above to the satisfaction of the TGA, in addition to the evidence of efficacy and safety provided would support the safe and effective use of these products.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Xarelto tablets (oral administration) containing rivaroxaban 15 mg and 20 mg. The approved indication reads as follows:

Xarelto is indicated for (1) the prevention of stroke and systemic embolism in patients with non valvular atrial fibrillation and at least one additional factor for stroke, and (2) the treatment of deep vein thrombosis (DVT) and for the prevention of recurrent DVT and pulmonary embolism.

Specific conditions of registration applying to these therapeutic goods:

1. That the sponsor take all necessary steps to implement the RMP version 5 (dated 17 November 2010) for the DVT indication and version 6 (dated 21 December 2010) for the Stroke Prevention in AF indication and any subsequent updated versions as agreed with the OPR.
2. That the sponsor is to ensure always that in both the PI and RMP there is accurate and balanced reporting of the fact that while rivaroxaban has the benefit of not requiring routine laboratory monitoring, there is always the inherent risk that the effect of the medicine is not reversible in a timely fashion when urgently required and that this risk applies to the normal situation and not just to situations involving overdose.
3. That the sponsor is to take all necessary steps to enforce rigorously all elements of prescriber education as outlined in the RMP, particularly with regard to making prescribers aware of the significant risks applying to particular patient population groups and with regard to having prescribers actively consider all precautions prior to prescribing. With respect to this condition of registration, the sponsor is required to lodge with the OPR a report every 3 months summarising the success or otherwise of these particular aspects of the prescriber education program. In these reports particular attention is to be paid to any problems encountered in making prescribers aware of these factors. The first report is to be lodged no later than 3 months after the date of the approval letter and subsequent reports are to be lodged at 3 monthly intervals, the final report to be lodged 12 months after the first, making five reports in all.
4. That the sponsor is take all necessary steps to raise patient awareness of and access to the CMI leaflet and that information about the availability of the latter must always be an element of any prescriber education program. Furthermore, if there is to be any initiative such as a prescriber familiarisation plan then copies of the CMI leaflet along with the Product Information document must be provided to those prescribers.
5. That, if there is any initiative such as a prescriber familiarisation program or a patient familiarisation program involving the enrolment of patients for the purpose of commencing them on rivaroxaban, then:
    a. All patients involved must be provided with the latest version of the CMI leaflet
    b. There must be a focus on obtaining the participation of prescribers in pharmacovigilance monitoring, particularly the reporting of all events of bleeding in a patient with the aim of accurate data collection for analysis
    c. The OPR is to be informed immediately upon the actual commencement of such a program and to be given a 3 monthly report of this program. This report is to be combined with the report outlined above and is subject to the same timetable and lodgement requirements as the latter report.
6. That the sponsor is required to submit to the TGA, as evaluable data within the context of category 1 applications, the final clinical study reports, of each of the following as soon as they are available:
    a. The Phase 1, open label, two way crossover study in healthy subjects to determine the effect of multiple doses of omeprazole on the pharmacokinetics, pharmacodynamics and safety of a single dose of rivaroxaban

b. The Phase 1, open label, non randomised, sequential, two treatment period study to explore the pharmacodynamic changes when transitioning from rivaroxaban to warfarin

c. The study for the Einstein-PE evaluation examining the effect of the oral direct factor Xa inhibitor rivaroxaban in patients with acute symptomatic deep vein thrombosis or pulmonary embolism

d. The Einstein CYP cohort study (Study 13238), namely the study examining the effect of the oral direct factor Xa inhibitor rivaroxaban in patients with acute symptomatic deep vein thrombosis or pulmonary embolism using a strong CYP 3A4 inducer.

Attachment 1. Product Information

The following Product Information was approved at the time this AusPAR was published. For the current Product Information please refer to the TGA website at www.tga.gov.au.

Therapeutic Goods Administration

PO Box 100 Woden ACT 2606 Australia
Email: info@tga.gov.au Phone: 1800 020 653 Fax: 02 6232 8605
www.tga.gov.au
Reference/Publication #

PRODUCT INFORMATION

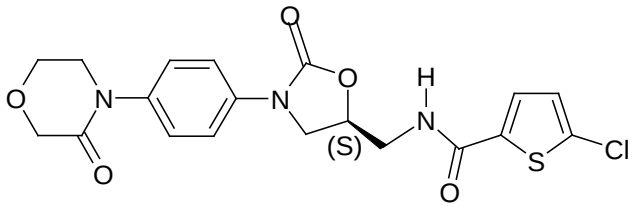
XARELTO® (rivaroxaban)

NAME OF THE MEDICINE

Xarelto (rivaroxaban) is a selective, direct acting Factor Xa inhibitor.

Rivaroxaban is 5-Chloro-N-({(5*S*)-2-oxo-3-[4-(3-oxo-4-morpholinyl)phenyl]-1,3-oxazolidin-5-yl}methyl)-2-thiophene-carboxamide. The empirical formula is $C_{19}H_{18}ClN_3O_5S$, molecular weight is 435.89 g / mole and CAS number is 366789-02-8.

Rivaroxaban has the following structural formula:



DESCRIPTION

Rivaroxaban is an odourless, non-hygroscopic white to yellowish powder. Rivaroxaban is practically insoluble in water and aqueous media in the pH range 1 to 9. An amount of approximately 5 - 7 mg/L rivaroxaban is pH-independently soluble in aqueous media at 25º C. Rivaroxaban is only slightly soluble in organic solvents (e.g. acetone, polyethylene glycol 400).

Each film-coated tablet contains 10 mg, or 15 mg or 20 mg of rivaroxaban.

In addition, each Xarelto tablet contains:

- *Tablet core:* Microcrystalline cellulose, croscarmellose sodium, lactose, hypromellose, sodium lauryl sulfate, magnesium stearate.
- *Filmcoat:* Macrogol 3350, hypromellose, titanium dioxide, iron oxide red.

PHARMACOLOGY

Pharmacodynamic properties

Pharmacotherapeutic group: Antithrombotic agent

Mechanism of Action

Rivaroxaban is a highly selective direct Factor Xa inhibitor with oral bioavailability.

Activation of Factor X to Factor Xa (FXa) via the intrinsic and extrinsic pathway plays a central role in the cascade of blood coagulation. FXa directly converts prothrombin to thrombin through the prothrombinase complex, and ultimately, this reaction leads to fibrin clot formation and activation of platelets by thrombin. One molecule of FXa is able to generate more than 1000 molecules of thrombin due to the amplification nature of the coagulation cascade. In addition, the reaction rate of prothrombinase-bound FXa increases 300,000-fold compared to that of free FXa and causes an explosive burst of thrombin

generation. Selective inhibitors of FXa can terminate the amplified burst of thrombin generation. Consequently, several specific and global clotting tests are affected by rivaroxaban. Dose dependent inhibition of Factor Xa activity was observed in humans.

Pharmacodynamic effects

Dose dependent inhibition of Factor Xa activity was observed in humans. Prothrombin time (PT) is influenced by rivaroxaban in a dose dependent way with a close correlation to plasma concentrations (r value equals 0.98) if Neoplastin® is used for the assay. Other reagents would provide different results. The readout for PT is to be done in seconds, because the INR (International Normalised Ratio) is only calibrated and validated for coumarins and cannot be used for any other anticoagulant

Table 1: 5/95 percentiles for PT (Neoplastin®) after tablet intake

	VTE Prevention in total hip and knee replacement	DVT Treatment and prevention of recurrent DVT and PE*		Stroke Prevention in Atrial Fibrillation	
Dosage	10 mg	15 mg bid	20 mg od	15 mg od	20 mg od
5/95 percentiles for PT (Neoplastin®) 2 – 4 hours after tablet intake (seconds)	13 – 25	16 – 33	15 – 30	10 – 50	14 – 40

*measurements of 5/95 percentiles for PT were recorded 1 – 4 hours after tablet intake
od = once daily, bid = twice daily

The activated partial thromboplastin time (aPTT) and HepTest® are also prolonged dose-dependently; however, they are not recommended to assess the pharmacodynamic effect of rivaroxaban. Anti-Factor Xa activity is influenced by rivaroxaban (see “Effect on Laboratory Tests”).

There is no need for monitoring of coagulation parameters while using Xarelto.

No QTc prolonging effect was observed with rivaroxaban.

Pharmacokinetic properties

Absorption and Bioavailability

Rivaroxaban is rapidly absorbed with maximum concentrations (C_{max}) appearing 2 - 4 hours after tablet intake. The absolute bioavailability of rivaroxaban is high (80-100 %) for the 10 mg dose irrespective of fasting/fed conditions. Under fed conditions Xarelto 10 mg, 15 mg and 20 mg tablets demonstrated dose-proportionality. Oral bioavailability of Xarelto 20 mg tablet is reduced to 66% under fasting conditions. When Xarelto 20 mg tablet is taken with food mean AUC is increased by 39% compared to tablet taken under fasting conditions. This indicates almost complete absorption and high oral bioavailability.

Xarelto 10 mg tablets can be taken with or without food. Intake with food does not affect rivaroxaban AUC or C_{max} at the 10 mg dose. (see DOSAGE AND ADMINISTRATION).

Xarelto 15 mg and 20 mg tablets should be taken with food (see DOSAGE AND ADMINISTRATION).

Variability in rivaroxaban pharmacokinetics is moderate with inter-individual variability (CV %) ranging from 30 % to 40 %, apart from the day of surgery and the following day when variability in exposure is high (70%) in patients who underwent hip or knee replacement.

Distribution

Plasma protein binding in human is high at approximately 92% to 95%, with serum albumin being the main binding component. The volume of distribution is moderate with V_{ss} being approximately 50 L.

Metabolism and Elimination

Of the administered rivaroxaban dose, approximately 2/3 undergoes metabolic degradation, with half then eliminated renally and the other half eliminated by the fecal route. The other 1/3 of the administered dose undergoes direct renal excretion as unchanged active substance in the urine, mainly via active secretion.

Rivaroxaban is metabolised via CYP3A4, CYP2J2 and CYP-independent mechanisms. Oxidative degradation of the morpholinone moiety and hydrolysis of the amide bonds are the major sites of biotransformation.

Based on *in vitro* investigations rivaroxaban is a substrate of the transporter proteins P-gp (P-glycoprotein) and Bcrp (breast cancer resistance protein).

Unchanged rivaroxaban is the most important compound in human plasma with no major or active circulating metabolites being present. With a systemic clearance of about 10 L/h rivaroxaban can be classified as a low-clearance drug. Elimination of rivaroxaban from plasma occurred with terminal half-lives of 5 to 9 hours in young individuals, and with terminal half-lives of 11 to 13 hours in the elderly.

Gender / Elderly (above 65 years)

Whilst elderly patients exhibited higher plasma concentrations than younger patients with mean AUC values being approximately 1.5-fold higher, mainly due to reduced (apparent) total and renal clearance, no dose adjustment is necessary (see DOSAGE AND ADMINISTRATION).

There were no clinically relevant differences in pharmacokinetics and pharmacodynamics between male and female patients (see DOSAGE AND ADMINISTRATION).

Different weight categories

Extremes in body weight (< 50 kg or > 120 kg) had only a small influence on rivaroxaban plasma concentrations (less than 25 %). No dose adjustment is necessary (see DOSAGE AND ADMINISTRATION).

Children and adolescents (from birth to 18 years)

No data are available for this patient population (see DOSAGE AND ADMINISTRATION).

Interethnic differences

No clinically relevant interethnic differences among Caucasian, African-American, Hispanic, Japanese or Chinese patients were observed regarding rivaroxaban pharmacokinetics and pharmacodynamics (see DOSAGE AND ADMINISTRATION).

Hepatic impairment

The critical aspect of liver impairment is the reduced synthesis of normal coagulation factors in the liver, which is captured by only one of the five clinical/biochemical measurements composing the Child Pugh classification system. The bleeding risk in patients may not clearly correlate with this classification scheme. Therefore, the decision to treat patients with an anticoagulant should be made independently of the Child Pugh classification.

Cirrhotic patients with mild hepatic impairment (classified as Child Pugh A) exhibited only minor changes in rivaroxaban pharmacokinetics (1.2-fold increase in rivaroxaban AUC on average), nearly comparable to their matched healthy control group. No relevant difference in pharmacodynamic properties was observed between these groups. In cirrhotic patients with moderate hepatic impairment (classified as Child Pugh B), rivaroxaban mean AUC was significantly increased by 2.3-fold compared to healthy volunteers, due to significantly impaired drug clearance which indicates significant liver disease. Unbound AUC was increased 2.6-fold. There are no data in patients with severe hepatic impairment. The inhibition of FXa activity was increased by a factor of 2.6 as compared to healthy volunteers; prolongation of PT was similarly increased by a factor of 2.1.

The global clotting test PT assesses the extrinsic pathway that comprises of coagulation Factors VII, X, V, II, and I, which are synthesised in the liver. Patients with moderate hepatic impairment were more sensitive to rivaroxaban resulting in a steeper PK/PD relationship between concentration and PT. The elevated PT at baseline and a significantly altered sensitivity in anti-coagulant activity towards rivaroxaban plasma exposure (increase in slope for PT/rivaroxaban plasma concentration relationship by more than 2-fold) in cirrhotic patients with moderate hepatic impairment indicate the decreased ability of the liver to synthesize coagulation factors. The PK/PD changes in these patients are markers for the severity of the underlying hepatic disease which is expected to lead to a subsequent increased bleeding risk in this patient group.

Therefore Xarelto is contraindicated in patients with significant hepatic disease (including moderate and severe hepatic impairment, i.e. Child-Pugh B and C) which is associated with coagulopathy leading to a clinically relevant bleeding risk. No data are available for severe hepatic impairment (Child Pugh C patients) (see DOSAGE AND ADMINISTRATION). Xarelto may be used with caution in cirrhotic patients with moderate hepatic impairment if it is not associated with coagulopathy.

Renal impairment

Rivaroxaban exposure was inversely correlated to the decrease in renal function, as assessed via creatinine clearance (CrCl) measurements. In individuals with mild (creatinine clearance 50 - 80 mL/min), moderate (creatinine clearance 30 - 49 mL/min) and severe (creatinine clearance 15-29 mL/min) renal impairment, rivaroxaban plasma concentrations (AUC) were 1.4, 1.5 and 1.6-fold increased respectively as compared to healthy volunteers (see DOSAGE AND ADMINISTRATION and PRECAUTIONS).

Corresponding increases in pharmacodynamic effects were more pronounced (see DOSAGE AND ADMINISTRATION and PRECAUTIONS) in individuals with mild, moderate or severe renal impairment; the overall inhibition of FXa activity was increased by a factor of

1.5, 1.9 and 2.0 respectively as compared to healthy volunteers. Prolongation of PT was similarly increased by a factor of 1.3, 2.2 and 2.4 respectively.

There are no data in patients with CrCl < 15 mL/min. Use is contraindicated in patients with creatinine clearance < 15 mL/min (see CONTRAINDICATIONS). Xarelto 10 mg is to be used with caution in patients with severe renal impairment creatinine clearance 15-29 mL/min. Xarelto 15 mg and 20 mg are contraindicated in patients with CrCl < 30 mL/min. (see DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS and PRECAUTIONS).

Due to the underlying disease patients with severe renal impairment are at an increased risk of both bleeding and thrombosis. The increased exposure to rivaroxaban further increases the risk of bleeding in these patients. Due to the high plasma protein binding rivaroxaban is not expected to be dialysable.

If there is a suspicion of renal impairment, the degree of renal impairment must be determined accurately. Caution must be exercised when renal function estimates are based on eGFR. In clinical trials, renal function was determined using the calculated creatinine clearance, using the Cockcroft-Gault Formula as follows:

Creatinine Clearance (mL/min)

Males: (140-age) (years) x weight (kg)

72 x serum creatinine (mg/100 mL)

Females: 0.85 x (140-age) (years) x weight (kg)

72 x serum creatinine (mg/100 mL)

CLINICAL TRIALS

Prevention of Venous Thromboembolic Events (VTE) in patients undergoing major orthopaedic surgery of the lower limbs

The RECORD clinical program was designed to demonstrate the efficacy of rivaroxaban for the prevention of venous thromboembolic events (VTE), i.e. proximal and distal deep vein thrombosis (DVT) and pulmonary embolism (PE) in patients undergoing major orthopaedic surgery of the lower limbs. Over 9,500 patients (7,050 in total hip replacement surgery and 2,531 in total knee replacement surgery) were studied in controlled randomised double-blind Phase III clinical studies, known as the RECORD-program.

RECORD 1 and 2 were conducted in patients undergoing elective total hip replacement surgery (THR) and RECORD 3 was performed in patients undergoing elective total knee replacement (TKR) surgery. Rivaroxaban has not been studied in clinical trials in patients undergoing hip fracture surgery.

Table 2: Patient demographics – RECORD studies

Study	No of patients	N (%) / Sex		Mean age ± SD (years)
RECORD 1 (THR)	2209 rivaroxaban	1971(44.5)/ male	2462 (55.5)/ female	63.2 ± 11.4

Study	No of patients	N (%) / Sex		Mean age ± SD (years)
	2224 enoxaparin			
RECORD 2 (THR)	1228 rivaroxaban 1229 enoxaparin	1139 (46)/ male	1318 (54)/ female	61.5 ± 13.4
RECORD 3 (TKR)	1220 rivaroxaban 1239 enoxaparin	781 (31.8)/ male	1678 (68.2)/ female	67.6 ± 9.0

The respective studies were heterogeneous with respect to their composition of participating countries (centres from Europe, North and South America, Asia and Australia). Men and women of 18 years or older scheduled for hip or knee replacement surgery could be enrolled provided that they had no active or high risk of bleeding or other conditions contraindicating treatment with low-molecular weight heparin, no significant liver disease, were not pregnant or breastfeeding, or were not using HIV protease inhibitors.

In all three pivotal studies, rivaroxaban 10 mg once daily started not earlier than 6 hours postoperatively was compared with enoxaparin 40 mg once daily started 12 hours preoperatively.

The primary efficacy analysis in all studies was based on stratified (by geographical region) risk difference between rivaroxaban and enoxaparin and corresponding 2-sided 95% confidence intervals. Efficacy was assessed in two steps; first a non-inferiority test was performed based on the per protocol population. Since non-inferiority was shown, a pre-specified superiority analysis was performed subsequently based on the modified ITT population.

In all three phase III studies (see Table 3) rivaroxaban significantly reduced the rate of total VTE (any venographically detected or symptomatic DVT, non fatal PE or death) and major VTE (proximal DVT, non fatal PE or VTE-related death), the pre-specified primary and major secondary efficacy endpoints. The results were clinically meaningful and statistically significant. Relative risk reductions in total VTE were 49% (RECORD 3) and 70% (RECORD 1) in comparison to enoxaparin and 79% (RECORD 2) in comparison to enoxaparin/placebo. Furthermore in all three studies the rate of symptomatic VTE (symptomatic DVT, non-fatal PE, VTE-related death) was lower in rivaroxaban treated patients compared to patients treated with enoxaparin.

The main safety endpoint, major bleeding, showed comparable rates for patients treated with rivaroxaban 10 mg compared to enoxaparin 40 mg.

The analysis of the pooled results of the Phase III trials corroborated the data obtained in the individual studies regarding reduction of total VTE, major VTE and symptomatic VTE with rivaroxaban 10 mg once daily compared to enoxaparin 40 mg once daily.

Table 3: Efficacy and safety results from Phase III RECORD (VTE Prevention in THR, TKR)

	RECORD 1			RECORD 2			RECORD 3		
Study Population	**4541 patients undergoing total hip replacement surgery**			**2509 patients undergoing total hip replacement surgery**			**2531 patients undergoing total knee replacement surgery**		
Treatment dosage and duration after surgery	Rivaroxaban 10 mg od 35 ± 4 days n (%)	Enoxaparin 40 mg od 35 ±4 days n (%)	p value	Rivaroxaban 10 mg od 35 ±4 days n (%)	Enoxaparin 40 mg od 12 ± 2 days n (%)	p value	Rivaroxaban 10 mg od 12± 2 days n (%)	Enoxaparin 40 mg od 12 ±2 days n (%)	p value
Total VTE	18 (1.1%)	58 (3.7%)	<0.001	17 (2.0%)	81 (9.3%)	<0.001	79 (9.6%)	166 (18.9%)	<0.001
Major VTE	4 (0.2%)	33 (2.0%)	<0.001	6 (0.6%)	49 (5.1%)	<0.001	9 (1.0%)	24 (2.6%)	0.01
Symptomatic VTE	6 (0.4%)	11 (0.7%)	--	3 (0.4%)	15 (1.7 %)	--	8 (1.0%)	24 (2.7%)	--
Major bleedings	6 (0.3 %)	2 (0.1%)	--	1 (0.1%)	1 (0.1%)	--	7 (0.6%)	6 (0.5%)	--
PE (non fatal)	4 (0.3%)	1 (<0.1%)	--	1 (0.1%)	4 (0.5%)	--	0 (0.0)	4 (0.5%)	--

	RECORD 1			RECORD 2			RECORD 3		
Death (any cause)	4 (0.3%)	4 (0.3%)	--	2 (0,2%)	6 (0.7%)	--	0 (0.0)	2 (0.2%)	--
VTE related death	0 (0%)	1 (<0.1%)	--	0 (0%)	1 (0.1%)	--	0 (0%)	0 (0%)	--

n = number of events; (%) = percentage

Prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation

The ROCKET-AF clinical program was designed to demonstrate the efficacy of Xarelto for the prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation (AF).

In the pivotal randomised, double-blind, double-dummy, parallel-group, event-driven, non-inferiority ROCKET-AF study comparing once daily oral rivaroxaban with adjusted-dose oral warfarin, 14,264 patients were assigned either to rivaroxaban 20 mg orally once daily (15 mg orally once daily in patients with CrCl 30 to 49 mL/min) or to warfarin titrated to a target INR of 2.5 (therapeutic range 2.0 to 3.0). The median time on treatment was 19 months and overall treatment duration was up to 41 months.

Patients included in the trial had non-valvular atrial fibrillation and a history of prior stroke (ischemic or unknown type), transient ischemic attack (TIA) or non-CNS systemic embolism, or two or more of the following risk factors without prior stroke:

- age ≥75 years,
- hypertension,
- heart failure or left ventricular ejection fraction ≤35%, or
- diabetes mellitus

The mean age of patients was 71 years with 44% > 75 years. The population was 60% male, 83% Caucasian, 13% Asian and 4% other. There was a history of stroke, TIA, or non-CNS systemic embolism in 55% of patients, and 38% of patients had not taken a vitamin K antagonist (VKA) within 6 weeks at time of screening. At baseline, 37% of patients were on aspirin (almost exclusively at a dose of 100 mg or less). A few patients were on clopidogrel and 11.4 % on class III antiarrythmics including amiodarone. The study included patients with co morbidities e.g. 55% secondary prevention population (prior stroke/ TIA/ Systemic embolism), hypertension 91%, diabetes 40%, congestive heart failure 63%, and prior myocardial infarction 17%. Patients with various degree of renal impairment were included in the study, see Table 4 for details.

Table 4: Baseline patient numbers for creatinine clearance groups

CrCl ml/min (degree of renal impairment)	rivaroxaban n = 7123	warfarin n = 7124
<30 (severe)	4 (0.1)	4 (0.1)
30 - 49 (moderate)	1503 (21.1)	1475 (20.7)
50 - 80 (mild)	3321 (46.6)	3414 (47.9)
> 80 (normal)	2295 (32.2)	2231 (31.3)

Exclusion criteria included:

- cardiac related conditions (haemodynamically significant mitral valve stenosis, prosthetic heart valve, planned cardioversion, transient atrial fibrillation caused by reversible disease, known presence of atrial myxoma or left ventricular thrombus and active endocarditis),
- haemorrhage risk related conditions (active internal bleeding, major surgical procedure or trauma within 30 days before randomisation, clinically significant gastrointestinal (GI) bleeding within 6 months of randomisation, history of intracranial, intraocular, spinal or atraumatic intra-articular bleeding, chronic haemorrhagic disorder, known intracranial neoplasm, arteriovenous malformation, or aneurysm)
- planned invasive procedure with potential for uncontrolled bleeding
- sustained uncontrolled hypertension (>180/100 mm Hg)
- concomitant conditions and therapies listed under CONTRAINDICATIONS as well as severe disabling stroke (modified Rankin score 4-5) or any stroke within 14 days, TIA within 3 days, >100 mg acetylsalicylic acid (ASA), anticipated need for chronic NSAIDs treatment, known HIV infection at the time of screening, significant hepatic impairment or (ALT > 3 x ULN)

The Principal Investigators were instructed to dose their patients with warfarin orally once daily, dose-adjusted to a target International Normalized Ratio [INR] of 2.5 [range 2.0 to 3.0, inclusive]. During the study, INR monitoring (using a Hemosense® point of-care INR device [INRatio®]) was to occur as clinically indicated but at least every 4 weeks. Unblinded INR measurements were not performed while subjects were on study drug, except in case of a medical emergency.

In order to maintain the integrity of the blind, local unblinded INR measurements (i.e., not using the study Hemosense INRatio® device) were discouraged for at least 3 days after subjects stopped receiving study drug (after the start of open-label VKA therapy), including when the subject discontinued study medication, or completed the study. After 3 days, VKA dosing was managed using local unblinded INR measurements.

Comparative efficacy with standard of care (warfarin) in the double blind clinical trial setting provides evidence that rivaroxaban is as effective as warfarin. There is insufficient experience to determine how Xarelto and warfarin compare when warfarin therapy is well controlled.

Unlike some other contemporary trials, these committees did not provide detailed and focused direction to the sites about their handling of individual patient INRs, since one goal of the trial was to run the study as close to usual care as possible, to maximize generalisability of the final results to standard practice.

The primary objective of the study was met, as Xarelto was shown to be non-inferior to warfarin in the primary efficacy endpoint, composite of stroke and systemic embolism (HR 0.79, 95% CI 0.66 – 0.96, $p < 0.001$). As non-inferiority was met, Xarelto was tested, as per the pre-specified analysis, for superiority in primary and secondary endpoints. Xarelto demonstrated superiority over warfarin for stroke and systemic embolism in the on treatment, safety population (HR 0.79, 95% CI 0.65 – 0.95, $p = 0.015$). Major secondary endpoints; composite of stroke, systemic embolism and vascular death and composite of stroke, systemic embolism, myocardial infarction (MI) and vascular death were also reduced significantly (see Table 5*)*.

The incidence rates for the principal safety outcome (major and non-major clinically relevant bleeding events) were similar for both treatment groups (see Table 6).

Table 5: Efficacy results from Phase III ROCKET AF (Stroke Prevention in AF)

Study Population	Patients with non-valvular atrial fibrillation (AF) ^		
Treatment Dosage	Rivaroxaban 20 mg orally od (15 mg orally od in patients with CrCl 30 to 49 mL/min) N=7061 Event Rate (100 Pt-yr)#	Warfarin titrated to a target INR of 2.5 (therapeutic range 2.0 to 3.0) N=7082 Event Rate (100 Pt-yr) #	Hazard Ratio (95% CI) p-value
Stroke and Non-CNS Systemic embolism	189 (1.70)	243 (2.15)	0.79 (0.65-0.95) 0.015*
Stroke, Non-CNS Systemic embolism and Vascular Death	346 (3.11)	410 (3.63)	0.86 (0.74-0.99) 0.034*
Stroke, Non-CNS Systemic embolism, Vascular Death and MI	433 (3.91)	519 (4.62)	0.85 (0.74-0.96) 0.010*
Stroke	184 (1.65)	221 (1.96)	0.85 (0.70 - 1.03) 0.092
Non-CNS Systemic Embolism	5 (0.04)	22 (0.19)	0.23 (0.09 - 0.61) 0.003**
All-cause Mortality	208 (1.87)	250 (2.21)	0.85 (0.70 - 1.02) 0.073[a]

^ Safety population, on treatment = All ITT subjects who take at least 1 dose of study medication after randomisation during double-blind treatment period or within 2 days after discontinuation (site 042012 was excluded for efficacy analysis)

Number of events per 100 patient years of follow up

***** Statistically significant at 0.025 (one-sided) for non-inferiority and 0.05 (two-sided) for superiority in favour of rivaroxaban

****** Statistically significant at nominal alpha = 0.05 (two sided)

a p value (two-sided) for superiority of rivaroxaban versus warfarin in hazard ratio

Table 6: Safety results from Phase III ROCKET AF (Stroke Prevention in AF)

Study Population	Patients with non-valvular atrial fibrillation (AF) ^		
Treatment Dosage	Rivaroxaban 20 mg orally od (15 mg orally od in patients with CrCl 30 to 49 mL/min) N=7111 Event Rate (100 Pt-yr) [#]	Warfarin titrated to a target INR of 2.5 (therapeutic range 2.0 to 3.0) N=7125 Event Rate (100 Pt-yr) [#]	Hazard Ratio (95% CI) p-value
Major and Non-major Clinically Relevant bleeding events	1475 (14.91)	1449 (14.52)	1.03 (0.96 - 1.11) 0.442
Major bleeding events	395 (3.60)	386 (3.45)	1.04 (0.90 - 1.20) 0.576
Death due to bleeding	27 (0.24)	55 (0.48)	0.50 (0.31,0.79) 0.003*
Critical Organ Bleeding	91 (0.82)	133 (1.18)	0.69 (0.53 - 0.91) 0.007*
Intracranial haemorrhage	55 (0.49)	84 (0.75)	0.67 (0.47–0.93) 0,019*
Haemoglobin drop	305 (2.77)	254 (2.26)	1.22 (1.03 - 1.44) 0.019*
Transfusion of 2 or more units of packed red blood cells or whole blood.	183 (1.65)	149 (1.32)	1.25 (1.01 - 1.55) 0.044*
Non-major Clinically Relevant bleeding events	1185 (11.80)	1151 (11.37)	1.04 (0.96 - 1.13) 0.345

^ Safety population, on treatment = All ITT subjects who take at least 1 dose of study medication after randomisation during double-blind treatment period or within 2 days after discontinuation (site 042012 was excluded for efficacy analysis)

[#] Number of events per 100 patient years of follow up

* Statistically significant at nominal alpha = 0.05 (two sided)

Treatment of Deep Vein Thrombosis (DVT) and prevention of recurrent DVT and Pulmonary Embolism (PE)

The EINSTEIN clinical program was designed to demonstrate the efficacy of rivaroxaban in the initial and continued treatment of acute DVT and prevention of recurrent DVT and PE. Over 4600 patients were studied in randomised controlled Phase III clinical studies (EINSTEIN DVT and EINSTEIN Extension). The overall combined treatment duration in both studies was up to 21 months.

In EINSTEIN DVT, an open label, randomised, event driven non-inferiority study, 3449 patients with acute DVT were studied for the treatment of DVT. Concomitant conditions listed under CONTRAINDICATIONS as well as subjects who had significant liver disease or ALT > 3 x ULN, bacterial endocarditis, VKA treatment indicated other than DVT and/or PE were excluded from the study.

In the ITT analysis subjects were comparable between treatment groups. About 57% of subjects were male. The race of about 77% of subjects was described as white, for about 13% as Asian, and for about 2% as black. Age ranged from 18-95 years in the rivaroxaban and from 18-97 years in the enoxaparin/VKA group, with a mean of approximately 56 years in both groups. Mean body weight was about 82 kg, with ranges from 33 to 193 kg.

Table 7: Baseline patient numbers for creatinine clearance groups

Creatinine clearance (mL/min)	Rivaroxaban n = 1525	Enox/VKA n = 1571
< 30 mL/min (severe)	6 (0.4%)	7 (0.4%)
30 - 49 mL/min (moderate)	100 (6.6%)	106 (6.7%)
50 - 80 mL/min (mild)	354 (23.2%)	361 (23.0%)
> 80 mL/min (normal)	1044 (68.5%)	1082 (68.9%)

The treatment duration was up to 12 months, assigned prior to randomisation, based on the clinical judgement of the investigator. For the initial 3 week treatment of acute DVT 15 mg of Xarelto was administered twice daily. This was followed by 20 mg of Xarelto once daily. The comparator treatment regimen consisted of enoxaparin administered for at least 5 days in combination with vitamin K antagonist treatment until the prothrombin time/international normalised ratio (PT/INR) was in therapeutic range (³ 2.0). Treatment was continued with a vitamin K antagonist dose-adjusted to maintain the PT/INR values within the therapeutic range of 2.0 to 3.0.

After randomization, subjects allocated to the comparator arm received enoxaparin twice daily for at least 5 days in combination with VKA (overlap 4 to 5 days) and continued with VKA only after the INR had been ≥ 2 for two consecutive measurements at least 24 hours apart. Warfarin and acenocoumarol were allowed as VKAs. Warfarin and acenocoumarol were to be started not later than 48 hours after randomization. VKA dosages were individually titrated and adjusted to achieve a target INR of 2.5 and maintain the INR within the therapeutic range (range 2.0-3.0) for either 3, 6 or 12 months. The INR had to be measured

initially every 2 to 3 days, and at least once monthly once stable. Each center had to specify before study start which VKA compound (warfarin or acenocoumarol) would be used during the study.

EINSTEIN Extension, a double blind, randomised, event driven superiority study included 1,197 patients with confirmed symptomatic DVT or PE. Xarelto 20 mg once daily was compared with placebo for an additional 6 to 12 months in patients who had completed initial treatment for DVT or PE for 6 to 14 months; where clinical uncertainty with respect to the need for continued anticoagulation existed. The treatment duration, assigned prior to randomisation, was based on the clinical judgement of the investigator.

Both Phase III studies used the same pre-defined primary and secondary efficacy outcomes. The primary efficacy outcome was symptomatic recurrent VTE defined as the composite of recurrent DVT or fatal or non-fatal PE. The secondary efficacy outcome was defined as the composite of recurrent DVT, non-fatal PE and all cause mortality.

EINSTEIN-DVT (see Table 8) met its principal objective, demonstrating that Xarelto was non-inferior to enoxaparin/VKA for the primary outcome of symptomatic recurrent VTE (HR of 0.68 [95% CI = 0.44 – 1.04], p <0.001). The pre-specified test for superiority was not statistically significant (p = 0.0764). The incidence rates for the principal safety outcome (major or clinically relevant non-major bleeding events), as well as the secondary safety outcome (major bleeding events), were similar for both groups (HR of 0.97 [95% CI = 0.76 – 1.22], p = 0.77 and HR of 0.65 [95% CI = 0.33 – 1.30), p = 0.21, respectively). The pre-defined secondary outcome of net clinical benefit, (the composite of the primary efficacy outcome and major bleeding events), was reported with a HR of 0.67 ([95% CI = 0.47 – 0.95], p = 0.03) in favour of Xarelto.

The relative efficacy and safety findings were consistent regardless of pre-treatment (none, LMWH, unfractioned heparin or fondaparinux) as well as among the 3, 6 and 12-month durations. In terms of other secondary outcomes, vascular events occurred in 12 patients (0.7%) in the Xarelto arm and 14 patients (0.8%) in the enoxaparin/VKA group (HR of 0.79 [95% CI = 0.36 – 1.71], p = 0.55), and total mortality accounted for 38 (2.2%) vs. 49 (2.9%) patients in the Xarelto vs. enoxaparin/VKA arms, respectively (p = 0.06).

Table 8: Efficacy and safety results from Phase III EINSTEIN DVT (DVT treatment)

Study Population	**3449 patients with symptomatic acute deep vein thrombosis**	
Treatment Dosage and Duration	Xarelto 15 mg BID for 3 weeks followed by 20 mg OD 3, 6 or 12 months N=1731	Enoxaparin for 5 days followed by VKA 3, 6 or 12 months N=1718
Symptomatic recurrent VTE*	36 (2.1%)	51 (3.0%)
Symptomatic recurrent PE	20 (1.2%)	18 (1.0%)

Study Population	3449 patients with symptomatic acute deep vein thrombosis	
Treatment Dosage and Duration	Xarelto 15 mg BID for 3 weeks followed by 20 mg OD 3, 6 or 12 months N=1731	Enoxaparin for 5 days followed by VKA 3, 6 or 12 months N=1718
Symptomatic recurrent DVT	14 (0.8%)	28 (1.6%)
Symptomatic PE and DVT	1 (0.1%)	0
Fatal PE/Death where PE cannot be ruled out	4 (0.2%)	6 (0.3%)
Major bleeding events	14 (0.8%)	20 (1.2%)
All-cause Mortality	38 (2.2%)	49 (2.9%)

*p: < 0.0001 (non-inferiority), 0.076 (superiority), HR: 0.680 (0.443 - 1.042)

In the EINSTEIN-Extension study (see Table 9), Xarelto was superior to placebo for the primary efficacy outcome with a HR of 0.18 [95% CI = 0.09 – 0.39], p <0.001 (i.e. a relative risk reduction of 82%). For the principal safety outcome (major bleeding events) there was no significant difference between patients treated with Xarelto compared to placebo (p = 0.11). Therefore, the pre-defined secondary outcome of net clinical benefit, defined as the composite of the primary efficacy outcome and major bleeding events, was reported with a HR of 0.28 ([95% CI = 0.15 – 0.53], p < 0.001) in favour of Xarelto.

Table 9: Efficacy and safety results from Phase III EINSTEIN EXTENSION (Prevention of recurrent DVT and PE)

Study Population	1197 patients continued treatment and prevention of recurrent venous thromboembolism	
Treatment Dosage and Duration	Xarelto 20 mg OD 6 or 12 months N=602	Placebo 6 or 12 months N=594
Symptomatic recurrent VTE*	8 (1.3%)	42 (7.1%)
Symptomatic recurrent PE	2 (0.3%)	13 (2.2%)
Symptomatic recurrent DVT	5 (0.8%)	31 (5.2%)

Study Population	1197 patients continued treatment and prevention of recurrent venous thromboembolism	
Treatment Dosage and Duration	Xarelto 20 mg OD 6 or 12 months N=602	Placebo 6 or 12 months N=594
Fatal PE/Death where PE cannot be ruled out	1 (0.2%)	1 (0.2%)
Major bleeding events	4 (0.7%)	0 (0.0%)
All-cause mortality	38 (2.2%)	49 (2.9%)

* p: < 0.0001 (superiority), HR: 0.185 (0.087 - 0.393)

In terms of other secondary outcomes, vascular events occurred in 3 patients in the Xarelto arm and 4 patients in the placebo group (HR of 0.74 [95% CI = 0.17 – 3.3], p = 0.69), and total mortality accounted for 1 (0.2%) vs. 2 (0.3%) of patients in the Xarelto vs. placebo arms, respectively.

INDICATIONS

Xarelto is indicated for

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

Prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation and at least one additional risk factor for stroke.

Treatment of deep vein thrombosis (DVT) and for the prevention of recurrent DVT and pulmonary embolism (PE).

CONTRAINDICATIONS

Xarelto is contraindicated in patients:

- who are hypersensitive to the active substance or to any of the excipients,
- with clinically significant active bleeding (e.g. intracranial bleeding, gastrointestinal bleeding),
- with lesions at increased risk of clinically significant bleeding and patients with spontaneous impairment of haemostasis,
- with significant hepatic disease (including moderate to severe hepatic impairment, i.e. Child-Pugh B and C) which is associated with coagulopathy leading to a clinically relevant bleeding risk (see PRECAUTIONS and Pharmacokinetic properties),
- with severe renal impairment with a creatinine clearance < 30 mL/min for Xarelto 15 mg and 20 mg tablets, (Cr Cl < 15 mL/min for Xarelto 10 mg) due to increased plasma levels

which may lead to an increased risk of bleeding (see Pharmacokinetic properties and PRECAUTIONS),

- concomitantly treated with strong inhibitors of both CYP 3A4 and P-glycoprotein such as HIV protease inhibitors (e.g. ritonavir) or systemically administered azole anti-mycotics (e.g. ketoconazole) (see Interactions with Other Medicines).
- who are pregnant (see Use in Pregnancy)
- who are breast-feeding (see Use in Lactation)

PRECAUTIONS

Haemorrhagic risk

Like other anticoagulants, Xarelto increases the risk of bleeding and can cause serious or fatal bleeding. In deciding whether to prescribe Xarelto to patients at increased risk of bleeding, the risk of thrombotic events should be weighed against the risk of bleeding. Due to the pharmacological mode of action, the use of Xarelto may be associated with an increased risk of occult or overt bleeding which may result in posthaemorrhagic anaemia (see ADVERSE EFFECTS). Several sub-groups of patients as detailed below are at increased risk of bleeding. These patients are to be carefully monitored for signs of bleeding complications after initiation of treatment. Any unexplained fall in haemoglobin or blood pressure should lead to a search for a bleeding site.

Haemorrhagic complications may present as weakness, paleness, dizziness, headache, or unexplained swelling, dyspnoea, and unexplained shock.

Patients at high risk of bleeding should not be prescribed Xarelto (see CONTRAINDICATIONS).

Close clinical surveillance is recommended in presence of multiple risk factors for bleeding including pharmacokinetic factors (renal impairment, hepatic impairment, drug interactions), pharmacodynamic interactions (NSAIDs, platelet aggregation inhibitors), and general haemorrhagic risk factors (see below).

General haemorrhagic risk factors

Xarelto like other antithrombotics should be used with caution in patients with an increased bleeding risk such as:

- congenital or acquired bleeding disorders
- uncontrolled severe arterial hypertension
- active ulcerative gastrointestinal disease
- recent gastrointestinal ulcerations
- vascular retinopathy
- recent intracranial or intracerebral haemorrhage
- intraspinal or intracerebral vascular abnormalities
- shortly after brain, spinal or ophthalmological surgery
- concomitant use of medicines affecting haemostasis
- bronchiectasis or history of pulmonary bleeding
- For patients at risk of ulcerative gastrointestinal disease an appropriate prophylactic treatment may be considered.

Other risk factors

Renal impairment

Xarelto is to be used with caution in patients with moderate renal impairment (creatinine clearance 30 - 49 mL/min) receiving co-medications leading to increased rivaroxaban plasma concentrations (1.6 fold on average) (see Interactions with Other Medicines). In patients with severe renal impairment (creatinine clearance < 30 mL/min) rivaroxaban plasma levels may be significantly increased, which may lead to an increased bleeding risk. Due to the underlying disease these patients are also at an increased risk of both bleeding and thrombosis. Due to limited clinical data Xarelto 10 mg should be used with caution in patients with CrCl 15 - 29 mL/min. Xarelto 15 mg and 20 mg should not be used in patients with CrCl < 30 mL/min (see CONTRAINDICATIONS, DOSAGE AND ADMINISTRATION, PHARMACOLOGY).

No clinical data are available for patients with creatinine clearance less than 15 mL/min. Therefore use of Xarelto is contraindicated in these patients (see CONTRAINDICATIONS).

Hepatic impairment

Xarelto is contraindicated in patients with significant hepatic disease (including moderate to severe hepatic impairment, i.e. Child-Pugh B and C) which is associated with coagulopathy leading to a clinically relevant bleeding risk. Limited clinical data in patients with moderate hepatic impairment (Child Pugh B) indicate a significant increase in the pharmacological activity. Xarelto may be used in cirrhotic patients with moderate hepatic (Child Pugh B) impairment if it is not associated with coagulopathy. (see PHARMACOLOGY and CONTRAINDICATIONS).

Strong CYP 3A4 and P-gp inhibitors

Xarelto is contraindicated in patients receiving concomitant systemic treatment with azole-antimycotics (e.g. ketoconazole) or HIV protease inhibitors (e.g. ritonavir). These active substances are strong inhibitors of both CYP 3A4 and P-gp and therefore may increase rivaroxaban plasma concentrations to a clinically relevant degree which may lead to an increased bleeding risk (see CONTRAINDICATIONS and Interactions with Other Medicines). However, fluconazole, a less potent CYP3A4 and P-gp inhibitor has less effect on rivaroxaban and may be co-administered (see Table 10 and Table 11).

Concomitant medications

Non-steroidal anti-inflammatory drugs

Care should be taken if patients are treated concomitantly with non-steroidal anti-inflammatory drugs (NSAIDs) as these drugs may impact haemostasis (see INTERACTION WITH OTHER MEDICINES).

Anticoagulants

Co administration of Xarelto with other anticoagulants has not been studied in clinical trials and is not recommended, as it may lead to an increased bleeding risk (see INTERACTION WITH OTHER MEDICINES).

Platelet aggregation inhibitors

Care should be taken if patients are treated concomitantly with platelet aggregation inhibitors (e.g. clopidogrel and acetylsalicylic acid) as it may lead to an increased bleeding risk (see

INTERACTION WITH OTHER MEDICINES). For patients on antiplatelet therapy, a careful individual risk benefit assessment should be performed regarding the additional bleeding risk versus the thrombotic risk associated with the underlying diseases.

Management of bleeding

Should bleeding occur, management of the haemorrhage may include the following steps:

- Identify and treat the underlying cause of the bleeding
- Where no source of bleeding can be identified, delay of next rivaroxaban administration or discontinuation of treatment as appropriate. Rivaroxaban has a terminal half-life between 5 and 13 hours (see Pharmacokinetic properties). Management should be individualised according to the severity and location of the haemorrhage. A specific agent to reverse the anti-coagulant effect of rivaroxaban is not yet available. Because of high plasma protein binding, rivaroxaban is not expected to be dialysable. Protamine sulfate and vitamin K are not expected to affect the anticoagulant activity of rivaroxaban.
- appropriate symptomatic treatment, e.g. mechanical compression, surgical interventions, fluid replacement and haemodynamic support, blood product (packed red cells or fresh frozen plasma, depending on associated anaemia or coagulopathy) or platelets.

If life threatening bleeding cannot be controlled by the above measures, administration of one of the following procoagulants may be considered:

- activated prothrombin complex concentrate (APCC)
- prothrombin complex concentrate (PCC)
- recombinant factor VIIa.

While there is currently no experience with the use of these products in individuals receiving Xarelto, all three procoagulants have demonstrated significant reductions in rivaroxaban-induced bleeding time prolongation in nonclinical studies.

There is no experience with antifibrinolytic agents (tranexamic acid, aminocaproic acid) in individuals receiving Xarelto. There is neither scientific rationale for benefit nor experience with the systemic haemostatics desmopressin and aprotinin in individuals receiving Xarelto.

Surgery and interventions

If an invasive procedure or surgical intervention is required, based on clinical judgement of the physician, Xarelto should be stopped at least 24 hours before the intervention if possible. Individual patient factors will need to be taken into account in the decision as to how long Xarelto should be stopped prior to surgery. Consider longer duration of treatment cessation based on benefit/risk with patients at higher risk of bleeding or in cases of major surgery where complete haemostasis may be required.

A specific agent to reverse the anti-coagulant effect of rivaroxaban is not yet available. If the procedure cannot be delayed the increased risk of bleeding should be assessed against the urgency of the intervention.

Xarelto should be restarted after the invasive procedure or surgical intervention as soon as possible provided the clinical situation allows and adequate haemostasis has been established (see Metabolism and Elimination and Effect of Laboratory Tests).

Patients with prosthetic valves

Safety and efficacy of Xarelto has not been studied in patients with prosthetic heart valves. Therefore, there are no data to support that Xarelto 20 mg (15 mg in patients with moderate renal impairment) provides adequate anti-coagulation in this patient population.

Spinal / epidural anaesthesia or puncture

When neuraxial anaesthesia (spinal / epidural anaesthesia) or spinal /epidural puncture is performed, patients treated with antithrombotic agents for prevention of thromboembolic complications are at risk of developing an epidural or spinal haematoma which can result in long-term or permanent paralysis. The risk of these events may be increased by the post-operative use of indwelling epidural catheters or the concomitant use of medicinal products affecting haemostasis. The risk may also be increased by traumatic or repeated epidural or spinal puncture.

Patients should be frequently monitored for signs and symptoms of neurological impairment (e.g. numbness or weakness of the legs, bowel or bladder dysfunction). If neurological compromise is noted, urgent diagnosis and treatment is necessary. Prior to neuraxial intervention, the physician should consider the potential benefit versus the risk in anticoagulated patients or in patients to be anticoagulated for thromboprophylaxis.

An epidural catheter is not to be removed earlier than 18 hours after the last administration of Xarelto. The next Xarelto dose is to be administered not earlier than 6 hours after the removal of the catheter.

If traumatic puncture occurs the administration of Xarelto is to be delayed for 24 hours.

Hip fracture surgery

Rivaroxaban has not been studied in clinical trials in patients undergoing hip fracture surgery to evaluate efficacy and safety in these patients. Therefore, Xarelto is not recommended in these patients.

Lactose intolerance

Xarelto contains lactose. Patients with rare hereditary problems of lactose or galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take Xarelto.

Information for the Patient

A Consumer Medicine Information leaflet is available. Please advise your patient to read this information carefully.

Effects on Fertility

Rivaroxaban did not affect male or female fertility at oral doses up to 200 mg/kg/day in Wistar rats, which corresponds to 33-fold (males) and 49-fold (females) the unbound rivaroxaban AUC in humans at the maximum recommended dose.

Use in Pregnancy

Pregnancy Category C

There are no data from the use of rivaroxaban in pregnant women. Thrombolytic agents can produce placental haemorrhage and subsequent prematurity and fetal loss.

Studies in rats and rabbits were affected by the anticoagulant effects of rivaroxaban on the mother. In rats, altered placental appearance and necrosis were observed at doses ≥ 10 mg/kg/day (4 times human exposure based on unbound plasma AUC). A NOAEL in rats for embryofetal development was established at 35 mg/kg/day (17 times human exposure based on unbound plasma AUC).

In rabbits, abortions occurred at doses ≥ 10 mg/kg/day (11 times human exposure based on unbound plasma AUC), while deaths occurred at doses ≥ 40 mg/kg/day (52 times human exposure based on unbound plasma AUC). Changes in placental appearance (course, grained and/or necrotic) were also noted at doses ≥ 10 mg/kg/day. A NOAEL in rabbits for embryofetal development was established at 2.5 mg/kg/day (3 times human exposure based on unbound plasma AUC). In rats and rabbits rivaroxaban showed pronounced maternal toxicity with placental changes related to its pharmacological mode of action (e.g., haemorrhagic complications) leading to reproductive toxicity. No primary teratogenic potential was identified. Due to the intrinsic risk of bleeding and the evidence that rivaroxaban passes the placenta, Xarelto is contraindicated in pregnancy (see CONTRAINDICATIONS). Xarelto should be used in women of childbearing potential only with effective contraception.

Use in Lactation

No data on the use of rivaroxaban in nursing mothers are available. Data from animals indicate that rivaroxaban is secreted into milk. Therefore Xarelto is contraindicated during breast-feeding (see CONTRAINDICATIONS).

[^{14}C] rivaroxaban was administered orally to lactating Wistar rats (day 8 to 10 post partum) as a single oral dose of 3 mg/kg body weight. [^{14}C] rivaroxaban-related radioactivity was secreted into the milk of lactating rats only to a low extent in relation to the administered dose. The estimated amount of radioactivity excreted into milk was 2.12 % of the maternal dose within 32 hours after administration.

Paediatric Use

Xarelto is not recommended for use in children or adolescents below 18 years of age due to a lack of data on safety and efficacy (see DOSAGE AND ADMINISTRATION and Pharmacokinetic properties).

Use in Elderly

No dose adjustment is required for the elderly (>65 years of age). It should be taken into consideration that increasing age may be associated with declining renal and hepatic function. (see CONTRAINDICATIONS, PRECAUTIONS and Pharmacokinetic properties).

Different Gender and Different Weight Categories

No dose adjustment is required for these patient populations (see “Pharmacokinetic properties”).

Carcinogenicity

Testing was performed by oral dosing for 2 years at up to 60 mg/kg/day reaching unbound plasma rivaroxaban exposure levels similar to humans (mice) or up to 3.6-fold higher (rats) than in humans.

Rivaroxaban showed no carcinogenic potential in either species.

Genotoxicity

Rivaroxaban showed no genotoxicity potential in bacterial mutagenicity tests, chromosomal aberration assays in Chinese hamster cells or in an *in vivo* mouse micronucleus assay.

INTERACTIONS WITH OTHER MEDICINES

Pharmacokinetic interactions

Rivaroxaban is cleared mainly via cytochrome P450-mediated (CYP 3A4, CYP 2J2) hepatic metabolism and renal excretion of the unchanged drug, involving the P-glycoprotein (P-gp) / breast cancer resistance protein (Bcrp) transporter systems.

CYP Inhibition

Rivaroxaban does not inhibit CYP 3A4 or any other major CYP isoforms.

CYP Induction

Rivaroxaban does not induce CYP 3A4 or any other major CYP isoforms.

Effects on rivaroxaban

Strong inhibitors of both CYP3A4 and P-gp

The concomitant use of Xarelto with substances that strongly inhibit both CYP 3A4 and P-gp may lead to reduced hepatic and renal clearance and thus significantly increased systemic exposure of rivaroxaban.

Co-administration of Xarelto with the azole-antimycotic ketoconazole (400 mg od), a strong CYP 3A4 and P-gp inhibitor, led to a 2.6-fold increase in mean rivaroxaban steady state AUC and a 1.7-fold increase in mean rivaroxaban C_{max}, with significant increases in its pharmaco-dynamic effects.

Co-administration of Xarelto with the HIV protease inhibitor ritonavir (600 mg bid), a strong CYP 3A4 and P-gp inhibitor, led to a 2.5-fold increase in mean rivaroxaban AUC and a 1.6-fold increase in mean rivaroxaban C_{max}, with significant increases in its pharmacodynamic effects.

Therefore Xarelto is contraindicated in patients receiving concomitant systemic treatment with azole-antimycotics or HIV-protease inhibitors (see CONTRAINDICATIONS). However, fluconazole (400 mg once daily) considered a less potent CYP3A4 and P-gp inhibitor led to an increase in rivaroxaban AUC and C_{max} within the magnitude of normal variability (see PRECAUTIONS and Table 10, Table 11 below).

Strong inhibitors of CYP3A4 or P-gp

Drugs strongly inhibiting only one of the rivaroxaban elimination pathways, either CYP 3A4 or P-gp, increase rivaroxaban plasma concentrations to a level which is considered not clinically relevant (see Table 10, Table 11 below).

Patients with renal impairment taking P-gp and weak to moderate CYP3A4 inhibitors may have significant increases in exposure, which may increase bleeding risk.

Xarelto is to be used with caution in patients with moderate renal impairment (creatinine clearance 30 - 49 mL/min) receiving co-medications leading to increased rivaroxaban plasma concentrations (1.6 fold on average) (see PRECAUTIONS).

CYP3A4 inducers

The concomitant use of rivaroxaban with strong CYP3A4 inducers (e.g. rifampicin, phenytoin, carbamazepine, phenobarbital or St. John's Wort) may lead to reduced rivaroxaban plasma concentrations. Caution should be taken when Xarelto 15 and 20 mg tablets are co-administered with strong CYP3A4 inducers (see Table 11 below)

Table 10: Established or potential interactions which are clinically relevant

Class (effect) Examples	Effect on rivaroxaban plasma concentration	Clinical comment
Strong CYP3A4 and strong P-gp inhibitor Azole-antimycotics e.g. ketoconazole, itraconazole, voriconazole, posaconazole or HIV-protease inhibitors e.g. ritonavir	↑ rivaroxaban	Concomitant treatment with systemic azole-antimycotics or HIV-protease inhibitors is contraindicated.

Table 11: Established or potential interactions which are not clinically relevant

Class (effect) Examples	Effect on rivaroxaban plasma concentration	Clinical comment
CYP3A4 and P-gp inhibitor Fluconazole	↑ rivaroxaban	Fluconazole (400 mg once daily), considered as moderate CYP 3A4 inhibitor, led to a 1.4-fold increase in mean rivaroxaban AUC and a 1.3-fold increase in mean C_{max}. This increase is within the

Class (effect) Examples	Effect on rivaroxaban plasma concentration	Clinical comment
		magnitude of the normal variability of AUC and C_{max} and is considered not clinically relevant.
Strong CYP 3A4 and moderate P-gp inhibitor Clarithromycin	↑ rivaroxaban	500 mg bid led to a 1.5 fold increase in mean rivaroxaban AUC and a 1.4 fold increase in C_{max}. This increase, which is close to the magnitude of the normal variability of AUC and C_{max}, is considered to be not clinically relevant.
Moderate CYP3A4 and moderate P-gp inhibitor Erythromycin	↑ rivaroxaban	500 mg tid led to a 1.3-fold increase in mean rivaroxaban steady state AUC and C_{max}. This increase is within the magnitude of the normal variability of AUC and C_{max} and is considered not clinically relevant.
Other P-gp inhibitors Cyclosporine, Amiodarone, Quinidine, Diltiazem, Verapamil	↑ rivaroxaban	Theoretically, due to the inhibition of P-gp mediated renal excretion, concomitant administration with Xarelto may lead to increased plasma rivaroxaban to a level which is considered not clinically relevant.
Strong CYP 3A4 and P-gp inducer Rifampicin	↓ rivaroxaban	Led to an approximate 50 % decrease in mean rivaroxaban AUC, with parallel decreases in its pharmacodynamic effects. The decrease in rivaroxaban plasma concentration is considered not clinically relevant.
Other CYP 3A4 inducers Anticonvulsants e.g. Phenytoin, Carbamazepine, Phenobarbitone or St John's Wort	↓ rivaroxaban	Concomitant use with Xarelto may lead to a decreased plasma rivaroxaban concentration.

Pharmacodynamic Interactions

Anticoagulants

After combined administration of enoxaparin (40 mg single dose) with rivaroxaban (10 mg single dose), an additive effect on anti-Factor Xa activity was observed without any additional effects on clotting tests (PT, aPTT). Enoxaparin did not affect the pharmacokinetics of rivaroxaban. Co administration of Xarelto with other anticoagulant therapy has not been studied in clinical trials and is not recommended, as it may lead to an increased bleeding risk (see PRECAUTIONS).

Converting patients from warfarin (INR 2.0 to 3.0) to Xarelto 20 mg or from Xarelto (20 mg) to warfarin (INR 2.0 to 3.0) increased prothrombin time/INR (Neoplastin®) more than additively (individual INR values up to 12 may be observed), whereas effects on aPTT, inhibition of Factor Xa activity and endogenous thrombin potential were additive. It should be noted that the anticoagulant effect of rivaroxaban does not correlate to INR values and therefore IINR should not be used.

If it is desired to test the pharmacodynamic effects of Xarelto during the conversion period, anti-Factor Xa activity, PiCT, and HepTest can be used as these tests were not affected by warfarin. From day 4 after stopping warfarin onwards, all tests (including PT, aPTT, inhibition of Factor Xa activity and ETP) reflected only the effect of Xarelto (see DOSAGE AND ADMINISTRATION).

If it is desired to test the pharmacodynamic effects of warfarin during the conversion period, INR measurement can be used at the C_{trough} of rivaroxaban (24 hours after the previous intake of rivaroxaban) as this test is minimally affected by rivaroxaban at this time point.

No pharmacokinetic interaction was observed between warfarin and Xarelto.

Non-steroidal anti-inflammatory drugs

Bleeding time was prolonged after co-administration of naproxen (500 mg) and rivaroxaban (mean 11.3 minutes) as compared to naproxen (500 mg) alone (7.9 minutes) and rivaroxaban alone (6.1 minutes, normal range of bleeding time: 2 to 8 minutes). In the three Phase III trials (RECORD 1, 2, and 3) more than 70 % of subjects received concomitant NSAIDs with a similar risk of bleeding as compared to comparator treatment. However, due to the general impact on haemostasis, care should be taken if anticoagulated patients are treated concomitantly with NSAIDs (see PRECAUTIONS).

No clinically relevant prolongation of bleeding time was observed after concomitant administration of Xarelto (15 mg) and 500 mg naproxen. Nevertheless there may be individuals with more pronounced pharmacodynamic response (see PRECAUTIONS).

Platelet aggregation inhibitors

Clopidogrel (300 mg loading dose followed by 75 mg maintenance dose) did not show a pharmacokinetic interaction (with Xarelto 15 mg). Bleeding time was prolonged after co-administration of clopidogrel and rivaroxaban (mean 21.7 minutes) as compared to clopidogrel alone (12.7 minutes) and rivaroxaban alone (7.7 minutes, normal range of bleeding time: 2 to 8 minutes) This increase in the combined treatment group was driven by a subset of patients in whom pronounced prolongations of bleeding times were observed. These prolongations of bleeding time did not correlate to platelet aggregation, P-selectin or GPIIb/IIIa receptor levels. For patients on antiplatelet therapy, a careful individual risk benefit assessment should be

performed regarding the additional bleeding risk versus the thrombotic risk associated with the underlying diseases. (see PRECAUTIONS).

Food and dairy products

Xarelto 10 mg can be taken with or without food (see Pharmacokinetic properties).

Xarelto 15 mg and 20 mg tablets should be taken with food (see Pharmacokinetic properties).

Interactions shown not to exist

There were no mutual pharmacokinetic interactions between rivaroxaban and midazolam (substrate of CYP 3A4), digoxin (substrate of P-gp) or atorvastatin (substrate of CYP 3A4 and P-gp).

Co-administration of the H_2 receptor antagonist ranitidine, the antacid aluminium hydroxide / magnesium hydroxide, naproxen, clopidogrel or enoxaparin did not affect rivaroxaban bio-availability and pharmacokinetics.

No clinically significant pharmacokinetic or pharmacodynamic interactions were observed when rivaroxaban was co-administered with 500 mg acetylsalicylic acid (see PRECAUTIONS).

Effect on Laboratory Tests

Xarelto at recommended doses prolongs the global clotting tests prothrombin time (PT), activated partial thromboplastin time (aPTT), HepTest®, as well as the specific clotting test, anti-Factor Xa activity. PT is influenced by Xarelto in a dose-dependent manner if Neoplastin® is used for the assay. The 5/95 percentiles of PT (Neoplastin®) 2 to 4 hours after tablet intake (i.e. at the time of maximum effect) is described in Table 1 (see Pharmacodynamic effects). In case of excessive doses, the PT is expected to be outside of this range. Although aPTT, anti-Factor Xa activity and HepTest® are also prolonged dose-dependently, none of these reliably assesses the pharmacodynamic effects of Xarelto.

During any conversion period when warfarin and Xarelto are overlapped, the pharmacodynamic effects of Xarelto can be tested with the anti-Factor Xa activity, PiCT (Prothrombinase-induced Clotting Time), and HepTest® assays, as these tests were not affected by warfarin. Four days after cessation of warfarin and onwards, all tests (including PT, aPTT, anti-Factor Xa activity and ETP) only reflected the effect of Xarelto (see DOSAGE AND ADMINISTRATION and Pharmacodynamic properties).

The INR is not valid to measure the anticoagulant activity of Xarelto, and therefore should not be used. If measurement of rivaroxaban exposure is required in special clinical situations (such as suspected overdose, or emergency settings), both prothrombin time and chromogenic anti-Factor Xa assays using validated rivaroxaban calibrators and controls have the potential to assess rivaroxaban plasma concentrations gravimetrically (ng/mL or µg/L). The pharmacokinetic profile of rivaroxaban has to be taken into account when interpreting results of these tests.

Effects on ability to drive and use machines

Syncope and dizziness have been reported and may affect the ability to drive and use machines (see ADVERSE EFFECTS). Patients experiencing these adverse reactions should not drive or use machines.

ADVERSE EFFECTS

The safety of rivaroxaban has been evaluated in eight phase III studies including 16,041 patients exposed to rivaroxaban (see Table 12).

Table 12: Number of patients studied and treatment duration in Phase III studies

Indication	Number of patients	Maximum daily dose	Maximum treatment duration
Prevention of venous thromboembolism (VTE) in adult patients undergoing elective hip or knee replacement surgrey	6,097	10 mg	39 days
Treatment of DVT and prevention of recurrent DVT and PE	2,194	Day 1 – 21: 30 mg Day 22 and onwards: 20mg	21 months
Prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation	7,750	20 mg	41 months

In total about 73% of patients exposed to at least one dose of rivaroxaban were reported with treatment emergent adverse events (regardless of causality). About 24% of patients experienced adverse events considered related to treatment as assessed by investigators. In patients treated with 10 mg Xarelto undergoing hip or knee replacement surgery, bleeding events occurred in approximately 6.8% of patients and anaemia occurred in approximately 5.9% of patients. In patients treated with either 15 mg twice daily Xarelto followed by 20 mg once daily for treatment of DVT, or with 20 mg once daily for prevention of recurrent DVT and PE, bleeding events occurred in approximately 22.7% of patients and anaemia occurred in approximately 1.8% of patients.

In patients treated for prevention of stroke and systemic embolism, bleeding of any type or severity was reported with an event rate of 28 per 100 patient years, and anaemia with an event rate of 2.5 per 100 patient years.

Due to the pharmacological mode of action, the use of Xarelto may be associated with an increased risk of occult or overt bleeding from any tissue and organ which may result in posthaemorrhagic anaemia. The signs, symptoms, and severity (including possible fatal outcome) will vary according to the location and degree or extent of the bleeding and/or anaemia. The risk of bleedings may be increased in certain patient groups e.g. patients with uncontrolled severe arterial hypertension and/or taking concomitant medications affecting haemostasis (see PRECAUTIONS). Menstrual bleeding may be intensified and/or prolonged. Haemorrhagic complications may present as weakness, asthenia, paleness, dizziness, headache or unexplained swelling, dyspnoea, and unexplained shock. In some cases as a

consequence of anaemia, symptoms of cardiac ischaemia like chest pain or angina pectoris have been observed.

Known complications secondary to severe bleeding such as compartment syndrome and renal failure due to hypoperfusion have been reported for Xarelto. Therefore, the possibility of a haemorrhage is to be considered in evaluating the condition in any anticoagulated patient.

VTE Prevention in total hip and knee replacement

The safety of Xarelto has been evaluated in three Phase III studies including 4571 patients undergoing major orthopaedic surgery of the lower limbs (total hip replacement or total knee replacement) treated up to 39 days. In the population of subjects who have taken at least one dose of Xarelto 10 mg od, a total of 1191 subjects were included in the knee replacement trial with a scheduled treatment period of about 2 weeks and 3380 subjects included in the total hip replacement trials with a scheduled treatment period of about 5 weeks. The two treatment groups, rivaroxaban and enoxaparin/placebo showed very similar demographic and baseline characteristics.

The incidence of common treatment-emergent adverse reactions reported in the safety population was similar in both treatment groups for the three Phase III studies irrespective of treatment duration and for treatment period until Day 12 ± 2. The most frequently reported treatment-emergent adverse reactions in both treatment groups during both treatment periods were gastrointestinal disorders, in particular nausea; procedural complications such as post operative anaemia; and investigations, in particular related to liver function tests.

The adverse events and adverse reactions are presented within each system organ class; and should be interpreted within the surgical setting.

Adverse events and adverse reactions as reported by the investigators in the three Phase III studies are listed in Table 13 below by system organ class (in MedDRA). RECORD 1-3 trials were similar in study design and patient population, the dose regimen tested was rivaroxaban 10 mg od compare to enoxaparin 40 mg od.

Table 13: Treatment-emergent adverse events (AE) ≥1% (regardless of causality) and treatment emergent adverse reactions (ADR) starting after initiation of rivaroxaban, as reported by the investigators in patients in three Phase III studies (RECORD 1 to 3) 11354, 11357, 11356

	Xarelto (10 mg od) N = 4657		Enoxaparin/Placebo (40 mg od) N = 4692	
System Organ Clas Medical Entity / Preferred Term	AE	ADR	AE	ADR
Blood and lymphatic system disorders				
Anaemia (incl. respective lab parameters)		54 (1.16%)		55 (1.17%)

Cardiac disorders				
Hypertension	77 (1.65%)		86 (1.83%)	
Hypotension	244 (5.24%)		238 (5.07%)	
Tachycardia	74 (1.59%)		71 (1.51%)	
Procedural hypotension	47 (1.01%)		34 (0.72%)	
Endocrine disorders				
Hyperglycaemia	43 (0.92%)		53 (1.13%)	
Gastrointestinal disorders				
Nausea	517 (11.10%)	69 (1.48%)	519 (11.06%)	86 (1.83%)
Constipation	318 (6.83%)		335 (7.14%)	
Diarrhoea	106 (2.28%)		137 (2.92%)	
Dyspepsia	42 (0.90%)		51 (1.09%)	
GI and abdominal pain	89 (1.91%)		93 (1.98%)	
Vomiting	452 (9.71%)		482 (10.27%)	
General disorders and administration site conditions				
Feeling unwell	92 (1.98%)		81 (1.73%)	
Fever	430 (9.23%)		444 (9.46%)	
Headache	108 (2.32%)		108 (2.30%)	
Peripheral Oedema	202 (4.34%)		168 (3.58%)	
Unspecific pain	285 (6.12%)		295 (6.29%)	
Infections and infestations				
Urinary tract infection	82 (1.76%)		90 (1.92%)	

Injury, Poisoning and Procedural Complications				
Arthralgia	65 (1.40%)		81 (1.73%)	
Post procedural haemorrhage (incl. postoperative anaemia and wound haemorrhage)	292 (6.27%)	123 (2.64%)	279 (5.95%)	109 (2.32%)
Wound healing complications	199 (4.27%)		161 (3.43%)	
Investigations				
Increase in blood alkaline phosphatase	38 (0.82%)		57 (1.21%)	
Increase in transaminases (incl. ALT increase, AST increase)	150 (3.22%)	102 (2.19%)	208 (4.43%)	137 (2.92%)
Increased gamma-glutamyltransferase	84 (1.80%)	56 (1.20%)	126 (2.69%)	73 (1.56%)
Increased lactate dehydrogenase	45 (0.97%)		56 (1.19%)	
Musculoskeletal and connective tissue disorders				
Increased muscle tone and cramping	62 (1.33%)		39 (0.83%)	
Nervous system disorders				
Dizziness	156 (3.35%)		144 (3.07%)	
Sleep disorders	191 (4.10%)		196 (4.18%)	
Syncope	60 (1.29%)		33 (0.70%)	
Renal and urinary disorders				
Urinary retention	84 (1.80%)		84 (1.79%)	

Respiratory, thoracic and mediastinal disorders				
Dyspnoea	49 (1.05%)		58 (1.24%)	
Skin and subcutaneous tissue disorders				
Pruritus	110 (2.36%)		87 (1.85%)	
Rash	60 (1.29%)		57 (1.21%)	
Unspecific blistering	68 (1.46%)		43 (0.92%)	
Social circumstances				
Anxiety reaction	52 (1.12%)		39 (0.83%)	
Vascular disorders				
Haemorrhage	67 (1.44%)		72 (1.53%)	
Thrombocythaemia	79 (1.70%)		87 (1.85%)	
Deep vein thrombosis	198 (4.25%)		363 (7.74%)	

Less frequent Clinical Trial Adverse Drug Reactions <1% in the Phase III studies; 11354, 11357, 11356 (RECORD 1 to 3):

Blood and the Lymphatic System Disorders: Thrombocythaemia (incl. platelet count increased)

Cardiac Disorders: Tachycardia

Gastrointestinal Disorders: Constipation, diarrhoea, abdominal and gastrointestinal pain (incl. upper abdominal pain, stomach discomfort), dyspepsia (incl. epigastric discomfort), dry mouth, vomiting

General Disorders and Administration Site Conditions: Localised oedema, decreased general strength and energy (incl. fatigue, asthenia), feeling unwell (incl. malaise)

Hepatobiliary disorders: Hepatic function abnormal

Immune system Dermatitis allergic

disorders:	
Injury, Poisoning and Procedural Complications:	Wound secretion
Investigations:	Increased lipase, increased amylase, blood bilirubin increased, increased LDH, increased alkaline phosphatase, bilirubin conjugated increased (with or without concomitant increase of ALT)
Musculoskeletal, Connective Tissue and Bone Disorders:	Pain in extremity
Nervous System Disorders:	Dizziness, headache, syncope (incl. loss of consciousness)
Renal and Urinary Disorders:	Renal impairment (incl. blood creatinine increased, blood urea increased)
Skin and Subcutaneous Tissue Disorders:	pruritus (incl. rare cases of generalised pruritus), rash, urticaria (incl. rare cases of generalised urticaria), contusion
Vascular Disorders:	hypotension (incl. blood pressure decrease, procedural hypotension), haematoma (incl. rare cases of muscle haemorrhage), gastrointestinal tract haemorrhage (incl. gingival bleeding, rectal haemorrhage, haematemesis), urogenital tract haemorrhage, nose bleed

Treatment of DVT and Prevention of Recurrent VTE

The safety of Xarelto has been evaluated in two phase III trials with 2194 patients treated up to 21 months and exposed to either 15 mg Xarelto twice daily for 3 weeks followed by 20 mg once daily (EINSTEIN DVT) or 20 mg once daily (EINSTEIN Extension).

Treatment-emergent drug-related adverse events were reported by 23.3% of rivaroxaban treated subjects and by 23.0% of enoxaparin/VKA treated subjects (study 11702 DVT). The respective incidence rates for the study 11899 were 16% rivaroxaban vs. 11% placebo.

The most common treatment-emergent adverse reactions reported in patients valid for safety analysis in the two Phase III studies for DVT treatment and prevention of recurrent VTE are presented in Table 14.

Table 14: Treatment-Emergent Adverse Reactions grouped by System Organ Class occurring in > 1% of any treatment group – EINSTEIN-DVT (11702-DVT) and EINSTEIN-Extension (11899) (patients valid for safety analysis)

	EINSTEIN-DVT		EINSTEIN-Extension	
System Organ Class /PT MedDRA	**XARELTO (N = 1718) n (%)**	**ENOXAPARIN /VKA (N = 1711) n (%)**	**XARELTO (N = 598) n (%)**	**Placebo (N = 590) n(%)**
Blood and lymphatic system disorders				
Anaemia	31 (1.80%)	25 (1.46 %)	4 (0.67%)	2 (0.34%)
Eye disorders				
Conjunctival haemorrhage	12 (0.70%)	21 (1.23%)	6 (1.00%)	0
Gastrointestinal disorders				
Gingival bleeding	36 (2.10%)	28 (1.64%)	11 (1.84%)	2 (0.34%)
Rectal hemorrhage	36 (2.10%)	19 (1.11%)	4 (0.67%)	4 (0.68%)
Abdominal pain	24 (1.40%)	15 (0.88%)	2 (0.33%)	7 (1.19%)
Abdominal pain upper	18 (1.05%)	9 (0.53%)	10 (1.67%)	1 (0.17%)
Constipation	48 (2.79%)	43 (2.51%)	6 (1.00%)	5 (0.85%)
Diarrhea	54 (3.14%)	40 (2.34%)	7 (1.17%)	8 (1.36%)
Dyspepsia	18 (1.05%)	14 (0.82%)	8 (1.34%)	4 (0.68%)
Nausea	47 (2.74%)	38 (2.22%)	7 (1.17%)	6 (1.02%)
Vomiting	18 (1.05%)	22 (1.29%)	3 (0.50%)	6 (1.02%)
General disorders and administration site conditions				
Pyrexia	43 (2.50%)	38 (2.22%)	5 (0.84%)	7 (1.19%)
Oedema peripheral	41 (2.39%)	41 (2.40%)	13 (2.17%)	17 (2.88%)
Fatigue	24 (1.40 %)	15 (0.88%)	6 (1.00%)	3 (0.51%)

	EINSTEIN-DVT		EINSTEIN-Extension	
System Organ Class /PT MedDRA	**XARELTO (N = 1718) n (%)**	**ENOXAPARIN /VKA (N = 1711) n (%)**	**XARELTO (N = 598) n (%)**	**Placebo (N = 590) n(%)**
Injury, poisoning and postprocedural complications				
Wound haemorrhage	20 (1.16%)	21 (1.23%)	11 (1.84%)	7 (1.19 %)
Contusion	53 (3.08%)	68 (3.97%)	19 (3.18%)	16 (2.71%)
Investigations				
Alanine aminotransferase increased	20 (1.16 %)	52 (3.04%)	2 (0.33%)	4 (0.68%)
Musculoskeletal, connective tissue and bone disorders				
Pain in extremity	76 (4.42%)	66 (3.86%)	29 (4.85%)	35 (5.93%)
Nervous system disorders				
Headache	91 (5.30%)	68 (3.97%)	18 (3.01%)	15 (2.54%)
Dizziness	38 (2.21%)	22 (1.29%)	6 (1.00%)	8 (1.36 %)
Renal and urinary disorders				
Haematuria	39 (2.27%)	41 (2.40%)	13 (2.17%)	2 (0.34%)
Reproductive system and breast disorders				
Menorrhagia	49 (2.85%)	19 (1.11%)	5 (0.84%)	2 (0.34%)
Vaginal haemorrhage[#]	28 (1.63%)	11 (0.64%)	1 (0.17%)	5 (0.85%)
Respiratory, thoracic and mediastinal disorders				

	EINSTEIN-DVT		EINSTEIN-Extension	
System Organ Class /PT MedDRA	**XARELTO (N = 1718) n (%)**	**ENOXAPARIN /VKA (N = 1711) n (%)**	**XARELTO (N = 598) n (%)**	**Placebo (N = 590) n(%)**
Epistaxis	89 (5.18%)	74 (4.32%)	24 (4.01%)	11 (1.86%)
Haemoptysis	19 (1.11%)	17 (0.99%)	1 (0.17%)	1 (0.17%)
Skin and subcutaneous tissue disorders				
Pruritus	29 (1.69 %)	31 (1.81 %)	2 (0.33 %)	2 (0.34%)
Rash	26 (1.51%)	27 (1.58 %)	5 (0.84%)	7 (1.19%)
Vascular disorders				
Haematoma	37 (2.15%)	59 (3.45%)	7 (1.17%)	8 (1.36%)

[#] observed as very common for rivaroxaban in women <55 years in Study 11702

Less frequent ADRs ≥ 0.1% to <1% unless otherwise specified (pooled EINSTEIN-DVT and EINSTEIN-Extension)

Cardiac disorder: tachycardia

Gastrointestinal Disorders: gastrointestinal haemorrhage, haematochezia, haemorrhoidal haemorrhage, melaena, mouth haemorrage, abdominal discomfort, abdominal pain lower, dry mouth

General Disorders and Administration Site Conditions: asthenia, feeling abnormal, malaise

Hepatobiliary Disorders: hepatic function abnormal

Immune System Disorders: hypersensitivity

Injury, poisoning and postprocedural complications: postprocedural haemorrhage, traumatic haematoma, traumatic haemorrhage, subcutaneous haematoma

Investigations:	haemoglobin decreased, aspartate aminotransferase increased, liver function test abnormal, hepatic enzyme increased, transaminases increased, blood bilirubin increased, bilirubin conjugated increased (with or without concomitant increase of ALT), gamma-glutamyltransferase increased, blood alkaline phosphatase increased
Nervous System Disorders:	syncope, cerebral and intracranial haemorrhage (≥ 0.01% to <0.1%)
Reproductive system and breast disorders:	menometrorrhagia, metrorrhagia
Skin and Subcutaneous Tissue Disorders:	urticaria, ecchymosis, skin haemorrhage, dermatitis allergic (≥ 0.01% to <0.1%)
Vascular Disorders:	hypotension

Prevention of stroke and systemic embolism in patients with atrial fibrillation

In the pivotal double-blind ROCKET AF study, a total of 14,264 unique subjects with non-valvular atrial fibrillation who were at risk for stroke and non-CNS systemic embolism were randomly assigned to treatment with either rivaroxaban (7,131 subjects) or warfarin (7,133 subjects) in 45 countries. Patients received Xarelto 20 mg orally once daily (15 mg orally once daily in patients with moderate (CrCl: 30-49 mL/min) renal impairment) or warfarin titrated to a target INR of 2.5 (therapeutic range 2.0 to 3.0). The safety population included subjects who were uniquely randomised and took at least 1 dose of study medication.

In total, 14,236 subjects were included in the safety population (used for the safety analyses), with 7,111 and 7,125 subjects in rivaroxaban and warfarin groups, respectively. The median time on treatment was 19 months and overall treatment duration was up to 41 months. The mean duration of Xarelto treatment exposure was 572 days.

The treatment-emergent adverse reactions reported in patients valid for safety analysis in ROCKET AF are presented in Table 15.

Table 15: Incidence of treatment-emergent adverse reactions grouped by System Organ Class occurring >1% of any treatment group – Subjects Valid for Safety Analysis – ROCKET AF SN11630

MedDRA System organ Class Preferred Term	Rivaroxaban N = 7111 (100%)	Warfarin N = 7125 (100%)
Blood and lymphatic system disorders		
Anaemia	219 (3.08%)	143 (2.01%)

MedDRA System organ Class Preferred Term	Rivaroxaban N = 7111 (100%)	Warfarin N = 7125 (100%)
Eye disorders		
Conjunctival haemorrhage	104 (1.46)	151 (2.12)
Gastrointestinal disorders		
Diarrhoea	379 (5.33%)	397 (5.57%)
Gingival bleeding	263 (3.70%)	155 (2.18%)
Nausea	194 (2.73%)	153 (2.15%)
Constipation	163 (2.29%)	153 (2.15%)
Rectal haemorrhage	149 (2.10%)	102 (1.43%)
Abdominal pain upper	127 (1.79%)	120 (1.68%)
Vomiting	114 (1.60%)	111 (1.56%)
Dyspepsia	111 (1.56%)	91 (1.28%)
Abdominal pain	107 (1.50%)	118 (1.66%)
Gastrointestinal haemorrhage	100 (1.41%)	70 (0.98%)
General disorders and administration site conditions		
Oedema peripheral	435 (6.12%)	444 (6.23%)
Fatigue	223 (3.14)	221 (3.10)
Asthenia	125 (1.76)	106 (1.49)
Pyrexia	72 (1.01%)	87 (1.22%)
Injury, poisoning and postprocedural complications		

MedDRA System organ Class Preferred Term	Rivaroxaban N = 7111 (100%)	Warfarin N = 7125 (100%)
Contusion	196 (2.76)	291 (4.08)
Investigations		
Alanine amino transferase increased	144 (2.03)	112 (1.57)
Musculoskeletal, connective tissue and bone disorders		
Pain in extremity	191 (2.69)	208 (2.92)
Nervous system disorders		
Dizziness	433 (6.09)	449 (6.30)
Headache	324 (4.56)	363 (5.09)
Syncope	130 (1.83)	108 (1.52)
Renal and urinary disorders		
Haematuria	296 (4.16)	242 (3.40)
Respiratory tract disorders		
Epistaxis	721 (10.14)	609 (8.55)
Haemoptysis	99 (1.39)	100 (1.40)
Skin and subcutaneous tissue disorders		
Ecchymosis	159 (2.24)	234 (3.28)

MedDRA System organ Class Preferred Term	Rivaroxaban N = 7111 (100%)	Warfarin N = 7125 (100%)
Pruritus	120 (1.69)	118 (1.66)
Rash	112 (1.58)	129 (1.81)
Vascular disorders		
Haematoma	216 (3.04)	330 (4.63)
Hypotension	141 (1.98)	130 (1.82)

Less frequent ADRs ≥0.1% to <1% unless otherwise specified – ROCKET AF

Cardiac disorders: Tachycardia

Eye disorders: Eye haemorrhage, vitreous haemorrhage

Gastrointestinal Disorders: Melaena, upper gastrointestinal haemorrhage, haemorrhoidal haemorrhage, haematochezia, Mouth haemorrhage, lower gastrointestinal haemorrhage, anal haemorrhage, gastric ulcer haemorrhage, gastritis haemorrhagic, Gastric haemorrhage, haematemesis, abdominal discomfort, abdominal pain lower, dry mouth

General Disorders and Administration Site Conditions: Malaise

Hepatobiliary Disorders: Hepatic function abnormal, hyperbilirubinaemia, jaundice (≥ 0.01% to <0.1%)

Immune System Disorders: Hypersensitivity

Injury, Poisoning, and Procedural Complications: Post procedural haemorrhage, wound haemorrhage, traumatic haematoma, incision site haemorrhage, subdural haematoma, subcutaneous haematoma, periorbital haematoma

Investigations: Haemoglobin decreased, haematocrit decreased, blood bilirubin increased, liver function test abnormal, aspartat aminotransferase increased, hepatic enzyme increased, blood urine present, creatinine renal clearance decreased, blood creatinine increased,

	blood urea increased, blood alkaline phosphatase increased, lipase increased, bilirubin conjugated increased (with or without concomitant increase of ALT) (≥ 0.01% to <0.1%)
Renal and urinary disorders:	Renal impairment
Reproductive system disorders:	Vaginal haemorrhage, metrorrhagia
Musculoskeletal, Connective Tissue, and Bone Disorders:	Haemarthrosis, muscle haemorrhage (≥0.01% to <0.1%)
Nervous system disorders:	Loss of consciousness, haemorrhagic stroke, haemorrhage intracranial
Skin and Subcutaneous Tissue Disorders:	Dermatitis allergic, rash pruritic, rash erythemateous, rash generalized, pruritus generalized, urticaria, skin haemorrhage
Vascular disorders:	Haemorrhage, bleeding varicose vein

In other clinical studies, vascular pseudoaneurysm formation following percutaneous intervention has been reported.

DOSAGE AND ADMINISTRATION

VTE Prevention in total hip and knee replacement

The recommended dose of Xarelto for VTE prevention in major orthopaedic surgery of the lower limbs (elective total hip or knee replacement) is a 10 mg tablet taken once daily.

The initial dose should be taken 6 - 10 hours after surgery provided that haemostasis has been established. Xarelto may be taken with or without food.

The duration of treatment depends on the type of major orthopaedic surgery.

- For patients undergoing hip replacement surgery, a treatment duration of 5 weeks is recommended.
- For patients undergoing knee replacement surgery, a treatment duration of 2 weeks is recommended.
- Dose of 10 mg once daily and duration specified for each type of surgery is not to be exceeded.

Stroke Prevention in Atrial Fibrillation

The recommended dose is 20 mg once daily.

For patients with moderate renal impairment (Creatinine clearance: 30 – 49 mL/min), one 15 mg tablet of Xarelto should be taken once daily.

Xarelto 20 mg tablets and Xarelto 15 mg tablets should be taken with food.

DVT Treatment and prevention of recurrent DVT and PE

The recommended dose for the initial treatment of acute DVT is 15 mg Xarelto **twice daily** for the first three weeks followed by 20 mg Xarelto **once daily** for the continued treatment and the prevention of recurrent DVT and PE.

During the initial 3 weeks of acute treatment 15 mg of Xarelto should be taken twice daily.

After the initial 3 weeks treatment Xarelto should be continued at 20 mg once daily. Therapy should be continued as long as the VTE risk persists. The duration of therapy should be individualised after careful assessment of the treatment benefit against the risk for bleeding. Experience with Xarelto in this indication for more than 12 months is limited.

Xarelto 15 mg tablets and Xarelto 20 mg tablets should be taken with food.

Special Populations

Hepatic impairment

Xarelto is contraindicated in patients with significant hepatic disease (including moderate to severe hepatic impairment, i.e. Child-Pugh B and C) which is associated with coagulopathy leading to a clinically relevant bleeding risk (see CONTRAINDICATIONS). No dose adjustment is necessary in patients with other hepatic diseases (see Pharmacokinetic properties).

Limited clinical data in patients with moderate hepatic impairment (Child Pugh B) indicate a significant increase in the pharmacological activity. No clinical data are available for patients with severe hepatic impairment (Child Pugh C) (see CONTRAINDICATIONS and Pharmacokinetic properties).

Renal impairment

Prior to commencing treatment with Xarelto, an accurate assessment of renal function should be undertaken, especially if there is any suspicion that the person may have a degree of renal impairment. (See Pharmacokinetics)

No clinical data are available for patients with (CrCl < 15 mL/min). Therefore, use of Xarelto is contraindicated in patients with CrCl <15 mL/min (see CONTRAINDICATIONS).

Please refer to Table 16 below for dosing instructions for patients with renal impairment by indications.

Table 16: Dosage and administration advice for patients with reduced renal function

Indication Creatinine Clearance (CrCl)	VTE Prevention in total hip and knee replacement	Stroke Prevention in Atrial Fibrillation	DVT Treatment and prevention of recurrent DVT and PE
Normal > 80 mL/min	10 mg once daily	20 mg once daily	15 mg twice daily for 3 weeks, followed by 20 mg once daily
Mild 50 – 80 mL/min			
Moderate 30 – 49 mL/min	10 mg once daily	15 mg once daily	15 mg twice daily for 3 weeks, followed by 20 mg once daily
Severe 15 – 29 mL/min	10 mg once daily (Use with caution)	Xarelto is contraindicated	
Severe < 15 mL/min	Xarelto is contraindicated		

Patients above 65 years

Based on clinical data, no dose adjustment is required for these patient populations (see Pharmacokinetic properties).

Increasing age is associated with declining renal function.

Body weight

No dose adjustment is required for these patient populations (see Pharmacokinetic properties).

Gender

No dose adjustment is required for these patient populations (see Pharmacokinetic properties).

Children and adolescents

Xarelto is not recommended for use in children or adolescents below 18 years of age due to a lack of data on safety and efficacy.

Ethnic differences

No dose adjustment is required based on ethnic differences (see Pharmacokinetic properties).

Transition from Vitamin K Antagonists (VKA) to Xarelto:

For patients treated for prevention of stroke and systemic embolism, VKA treatment should be stopped and Xarelto therapy should be initiated once the INR is ≤ 3.0.

For patients treated for DVT and prevention of recurrent DVT and PE, VKA treatment should be stopped and Xarelto therapy should be initiated once the INR is ≤ 2.5.

The INR is not a valid measure for the anticoagulant activity of Xarelto, and therefore should not be used. The INR is only calibrated and validated for VKAs and cannot be used for any other anticoagulant. When switching patients from VKAs to Xarelto, INR values will be elevated after the intake of Xarelto but this is not indicative of the anticoagulant effect of Xarelto (see Interactions with Other Medicines).

Transition from Parenteral Anticoagulants to Xarelto:

For patients currently receiving a parenteral anticoagulant, start Xarelto 0 to 2 hours before the time of the next scheduled administration of the parenteral drug (e.g., LMWH) or at the time of discontinuation of a continuously administered parenteral drug (e.g., intravenous unfractionated heparin).

Transition from Xarelto to Parenteral Anticoagulants:

Discontinue Xarelto and give the first dose of parenteral anticoagulant at the time that the next Xarelto dose would be taken.

Transition from Xarelto to VKAs

There is a potential for inadequate anticoagulation during the transition from Xarelto to VKA. Limited clinical trial data is available to guide the process whereby patients are converted from Xarelto to VKAs.

Continuous adequate anticoagulation should be ensured during transition to an alternate anticoagulant. In patients converting from Xarelto to VKA, VKA should be given concurrently until the INR is ≥ 2.0. It should be noted that Xarelto can contribute to an elevated INR and so INR measurements made during co-administration with warfarin may not be useful for determining the appropriate dose of VKA.

For the first two days of the conversion period, standard initial dosing of VKA should be used and, after the first two days, VKA dosing should be guided by INR testing. While patients are on both Xarelto and VKA, INR should be tested just prior to the next dose of Xarelto (not earlier than 24 hours after the previous dose). Once Xarelto is discontinued INR testing may be done reliably at least 24 hours after the last dose.

Missed Dose

It is essential to adhere to the dosage schedule provided.

*Xarelto 10 mg, 15 mg, or 20 mg tablets taken **once** a day:*

If a dose is missed, the patient should take Xarelto immediately on the same day and continue on the following day with the once daily intake as before. A double dose should not be taken to make up for a missed tablet.

*Xarelto 15 mg tablets taken **twice** a day:*

If a dose is missed during the 15 mg twice daily treatment phase the patient should take the next dose immediately to ensure the intake of 30 mg total dose per day. In this case two 15 mg tablets may be taken at once. The following day the patient should continue with the regular 15 mg twice daily intake schedule as recommended.

OVERDOSAGE

Overdose following administration of Xarelto may lead to haemorrhagic complications due to its pharmacodynamic properties.

Rare cases of overdose up to 600 mg have been reported without bleeding complications or other adverse reactions. Due to limited absorption a ceiling effect with no further increase in average plasma exposure is expected at supratherapeutic doses of 50 mg or above.

A specific antidote antagonising the pharmacoceutical effect of rivaroxaban is not available.

Activated charcoal may reduce absorption of the drug if given within up to 8 hours after ingestion. In patients who are not fully conscious or have impaired gag reflex, consideration should be given to administering activated charcoal via a nasogastric tube, once the airway is protected.

Protamine sulphate and Vitamin K are not expected to affect the anticoagulant activity of rivaroxaban. Due to the high plasma protein binding rivaroxaban is not expected to be dialysable.

Contact Poisons Information Centre 131126 for advice on management.

PRESENTATION AND STORAGE CONDITIONS

Xarelto 10 mg - One tablet contains 10 mg rivaroxaban. The tablets are film-coated round, biconvex, light red immediate release tablets of 6 mm diameter marked with a Bayer cross on one side and “10” and a triangle on the other side. The tablets are supplied in packs of 3, 5, 10, 15, 30, 100 tablets.

Xarelto 15 mg - One tablet contains 15 mg rivaroxaban. The tablets are film-coated round, biconvex, red immediate release tablets of 6 mm diameter marked with a Bayer cross on one side and “15” and a triangle on the other side. The tablets are supplied in packs of 7, 14, 28, 42, 84, 98, 100 tablets.

Xarelto 20 mg - One tablet contains 20 mg rivaroxaban. The tablets are film-coated round, biconvex, brown red immediate release tablets of 6 mm diameter marked with a Bayer cross on one side and “20” and a triangle on the other side. The tablets are supplied in packs of 7, 28, 84, 98, 100 tablets.

Not all pack sizes may be marketed.

The tablets are packed in thermoformed PP/Aluminium foil blisters or PVC/PVDC/Aluminium foil blisters. Store below 30°C.

NAME AND ADDRESS OF THE SPONSOR

BAYER AUSTRALIA LIMITED
ABN 22 000 138 714

875 Pacific Highway
PYMBLE, NSW 2073

POISON SCHEDULE OF THE MEDICINE

PRESCRIPTION ONLY MEDICINE

DATE OF FIRST INCLUSION IN THE ARTG

24 November 2008

DATE OF MOST RECENT AMENDMENT

3 April 2012

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