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Human Medicines Development and Evaluation

Assessment report

Xarelto

Rivaroxaban

Procedure No. EMEA/H/C/000944/II/0018

Note

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

7 Westferry Circus ● Canary Wharf ● London E14 4HB ● United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7418 8613
E-mail info@ema.europa.eu **Website** www.ema.europa.eu

1. Scientific discussion

The studies included in this application have been performed according the GCP standards.

The pharmacokinetics (PK) and pharmacodynamics (PD) of rivaroxaban 15mg and 20 mg tablets have been characterised and reported in previous submissions including the exposure and exposure – response in the indications DVT (deep vein thrombosis) and PE (pulmonary embolism).

In this application, one additional food effect study (Japanese breakfast meal) and one additional drug interaction study (rifampicin) are submitted (EINSTEIN CYP). PK exposure was not obtained in the phase III studies supporting the indications. However, measurements to prothrombin time (PT) was obtained and analysed. The simulations to exposure in patients in moderate/severe renal impairment are also reviewed.

The proposed indication for treatment of PE is based on one pivotal phase III study, study 11702 PE with support from studies 11702 DVT in treatment of DVT (comparison against enoxaparin and VKA) and 11899 in continued treatment of VTE after 6 to 14 months of anticoagulant treatment (comparison against placebo. These latter two studies supported the previous application for treatment of DVT.

1.1. Clinical pharmacology aspects

The pharmacokinetics (PK) and pharmacodynamics (PD) of rivaroxaban 15 mg and 20 mg tablets have been characterised and reported in previous submissions including the exposure and exposure-response in the indications (VTE and PE) under consideration.

In this submission one additional food effect study (Japanese breakfast meal) and one additional drug-drug interaction study (rifampicin) is covered (EINSTEIN CYP). PK exposure was not obtained in the phase III studies supporting the indications. However, measurements of prothrombin time (PT) was obtained and analysed. The simulations of exposure to rivaroxaban in patients with moderate/severe renal impairment were also reviewed.

1.1.1. Pharmacokinetics

1.1.1.1. Food effect study (s*tudy 15921)*

1.1.1.1.1. Methods – analysis of data submitted

Plasma rivaroxaban concentrations were measured using a fully validated high performance liquid chromatography assay with tandem mass spectrometric detection (HPLC-MS/MS).

For the analysis of the food interaction study standard non-compartmental analysis, NCA, was employed. The study was analysed using population modelling in NONMEM.

The method used for statistical analysis of the food interaction study was considered appropriate by the CHMP.

For calculation of the difference between test and reference treatment in the food interaction study ANOVA was employed. The method used for statistical analysis of the food interaction study was considered appropriate.

This was a single-center, randomized, open-label, two-fold cross-over study to investigate the effect of a Japanese meal on the safety, tolerability, and PK of a 15-mg immediate-release rivaroxaban tablet given orally in the morning to 12 healthy young Japanese male subjects. (Study 15921 / A57650, Module 5.3.1.2) The Japanese breakfast contained ca. 17 % proteins, 53 % carbohydrates, 30 % fat with an energy content of 900 kcal in total. Rich pharmacokinetic sampling up to 72 hours after dose was performed.

1.1.1.1.2. Results

One subject did not complete both treatment periods, thus 11 subjects contributed with data for the pharmacokinetic evaluation. Key PK parameters are summarized in Table 1.

Table 1: PK parameters in plasma of rivaroxaban following administration of the 15-mg tablet under fasting and fed conditions [geometric mean/%CV (range); all subjects valid for PK, n=11] (Study 15921)

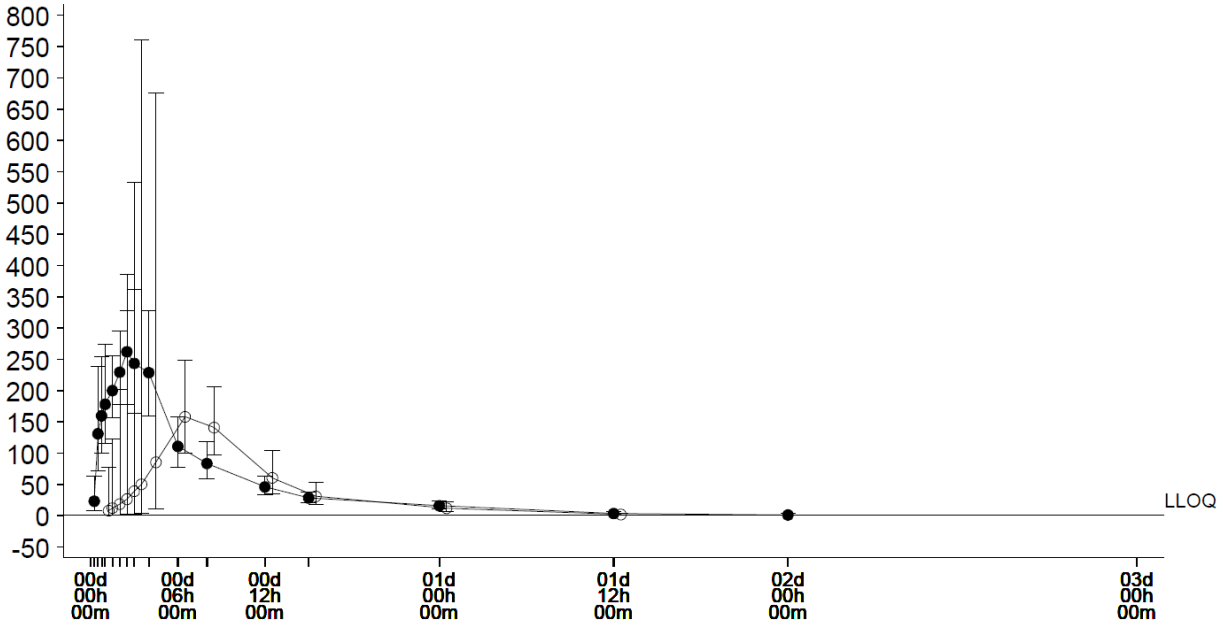
Parameter	Unit	n	Rivaroxaban 15 mg without food	n	Rivaroxaban 15 mg with food
AUC	µg*h/L	11	2065 / 27.23 (1202 – 2836)	11	1934 / 16.24 (1498 – 2405)
C_{max}	µg/L	11	289.0 / 31.67 (160.5 – 520.9)	11	268.2 / 23.75 (169.4 – 372.6)
t_{max}[a]	h	11	2.500 (0.75 – 3.00)	11	4.000 (2.50 – 12.00)
$t_{½}$	h	11	6.898 / 33.96 (4.066 – 10.68)	11	5.854 / 28.94 (3.674 – 9.606)

a Median (range)

An analysis of variance (ANOVA) estimated the LS means ratios [90% CI] of AUC and Cmax (food/fasted) to 0.939 [0.806 to 1.094] and 0.937 [0.727 to 1.208] respectively. It can be noted that the lower limit of the 90% confidence interval for Cmax was below 0.8.

In Figure 1 the geometric mean (sd) of observed plasma concentration vs. time profiles following fasting (solid circles) and fed (open circles) conditions are shown. The unit of the y-axis is µg/L and on the x-axis a combination of days and hours after dose.

Figure 1 Plasma concentrations (µg/L) of rivaroxaban after a single dose of 15 mg rivaroxaban in the fasting state and after a single dose of 15 mg rivaroxaban together with a Japanese breakfast, geometric means, n = 11, linear scale, fasting (solid circles) and fed (open circles)



1.1.1.1.3. Discussion

Absorption of rivaroxaban was slower after Japanese breakfast with tmax occurring at 4 hours compared to 2.5 hours after dose. The AUC following 15 mg rivaroxaban was not different between fasting and fed conditions based on bioequivalence criteria. However, the 90% CI for ratio of Cmax included 0.8.

Based on several specific studies, and cross study comparisons, it has previously been shown that food influences the absorption of rivaroxaban with greater absorption in the fed state compared to a fasting state. The effect is more pronounced at doses above 10 mg and it has led to recommendations in the currently approved SmPCs to administer rivaroxaban with food for indications using 15 mg or 20 mg doses but for indications using lower doses, rivaroxaban may be administered irrespective of food intake.

This new study gives somewhat contradictory results, with indications of a slightly lower absorption in the fed state compared to the fasting state, as compared to the previous data. The effect is likely not clinically relevant and there seem to be no reason from a PK perspective to put restrictions regarding food intake in the SmPC for the 15 mg dose.

Several aspects nevertheless points towards the adequacy to maintain the current wording of the SmPC for both 15 and 20 mg strengths *"The tablets are to be taken with food"* since:

1) the phase III study submitted in support of this variation included a recommendation to administer rivaroxaban with food
2) it is not known if the meal used in Study 15921 / A57650 is representative of an European meal
3) previous analyses of pooled data from phase I studies point to a slight increase in the rivaroxaban exposure when the 15-mg tablet is administered with food.

1.1.1.2. Drug interaction study

1.1.1.2.1. Methods- analysis of data submitted

Rifampicin (600 mg od), classified as strong CYP3A4 and P-gp inducer, has been shown to lead to a significant decrease in rivaroxaban elimination half-life and an approximately 50% reduction in rivaroxaban plasma exposure in healthy volunteers.

The EINSTEIN CYP cohort study was a multicenter, open-label, Phase 2 study designed to evaluate the population PK /PD of an adapted rivaroxaban dosing regimen in patients with acute, proximal DVT or acute PE and concomitant use of a strong CYP3A4 inducer (i.e. carbamazepine, phenytoin, rifampicin/rifampin, or rifabutin).

The PK/PD of an adapted rivaroxaban dosing regimen (30 mg bid in the first 3 weeks of treatment, followed by 20 mg bid) was studied in 19 patients treated for DVT or PE and who concomitantly were medicated with a strong CYP3A4 and P-gp inducer. Fifteen patients received (ethambutol, isoniazid, pyrazinamide, rifampicin) and 4 patients received phenytoin. The adapted dosing regimen in these patients led to a similar exposure and pharmacodynamics when compared to patients treated for DVT (15 mg bid in the first 3 weeks of treatment, followed by 20 mg od) without the concomitant administration of a strong CYP3A4 inducer.

1.1.1.2.2. Results

Oral clearance (CL/F) in patients included in the EINSTEIN CYP cohort was estimated to 10.8 L/h as compared to 5.67 L/h in the DVT population without strong CYP3A4 inducer comedication. In Table 1 model derived secondary PK parameters ($AUC_{0-24,ss}$, $C_{max,ss}$, $C_{min,ss}$) for the EINSTEIN CYP cohort are compared with those simulated prior to the study and parameters derived from the DVT population without CYP3A4 inducer treatment.

Table 1 Derived PK parameters in patients treated for DVT or PE with concomitant intake of a strong CYP3A4 inducer (Study 13812), B) simulated PK parameters in patients with concomitant intake of a strong CYP3A4 inducer, based on Phase II data from patients treated for DVT (Study 15539), and C) PK parameters derived from phase II data in patients treated for DVT (Study 12143). Median (5%/95% percentiles)

	A) Cohort with strong CYP3A4 inducer: actual		B) with strong CYP3A4 inducer: simulated		C) Phase II data of patients treated for DVT ~~all patients~~	
Parameter	initial treatment **30 mg bid**	extended treatment **20 mg bid**	initial treatment **30 mg bid**	extended treatment **20 mg bid**	initial treatment **15 mg bid**	extended treatment **20 mg qd**
$AUC_{0-24,ss}$ [µg*h/L]	2836 (1259/6877)	2319 (1059/5782)	3228 (1721/5921)	2714 (1447/4978)	4464 (2383/8187)	2719 (1452/4986)
$C_{max,ss}$ [µg/L]	200 (150/386)	167 (126/324)	268 (183/419)	225 (154/352)	274 (176/459)	255 (179/397)
$C_{min,ss}$ [µg/L]	42 (1/170)	35 (1/143)	34 (6/124)	29 (5/104)	99 (32/237)	26 (4/99)

The inter-individual variability (IIV) in clearance for patients treated with strong CYP3A4 inducers was estimated to 38.7% (approximate CV) which was similar to the IIV estimated (39.9%) in a model of rivaroxaban exposure based on a Phase II dose-ranging study in DVT patients.

1.1.1.2.3. Discussion

The number of patients included in the rifampicin interaction study (n=19) was small compared to the planned number of patients (n=50). However, the result did not contradict the previously established interaction potential of strong CYP3A4 inducers on the PK of rivaroxaban in healthy volunteers and point in the direction that this interaction is occurring also in patients.

These additional data in conclusion do not justify a need to amend the SmPC.

1.1.1.3. Impaired renal function

The MAH proposed the following recommendations in SmPC section 4.2 (posology) in patients with reduced renal function:

No dose adjustment is necessary in patients with mild renal impairment (creatinine clearance 50 - 80 ml/min) (see section 5.2).

In patients with moderate (creatinine clearance 30 - 49 ml/min) or severe (creatinine clearance 15 - 29 ml/min) renal impairment the following dosage recommendations apply:

- *For the prevention of stroke and systemic embolism in patients with non valvular atrial fibrillation, the recommended dose is 15 mg once daily (see section 5.2).*
- *For the treatment of DVT and prevention of recurrent DVT and PE: Patients should be treated with 15 mg twice daily for the first 3 weeks. Thereafter, the recommended dose is 15 mg once daily based on PK modelling (see sections 4.4 and 5.2).*
- ***For the treatment of PE and prevention of recurrent DVT and PE: Patients should be treated with 15 mg twice daily for the first 3 weeks. Thereafter, the recommended dose is 20 mg once daily (see section 5.2).***

Limited clinical data for patients with severe renal impairment (creatinine clearance 15 29 ml/min) indicate that rivaroxaban plasma concentrations are significantly increased therefore, Xarelto is to be used with caution in these patients. Use is not recommended in patients with creatinine clearance < 15 ml/min (see sections 4.4 and 5.2).

CHMP discussion

At present, with the additional data submitted in the application, there is a larger amount of clinical data available from the combination of studies EINSTEIN DVT and EINSTEIN PE. In both these studies, patients with a CLCR between 30 and 50 mL/min were dosed 20 mg QD. This has been extensively discussed in the assessment of the MAH responses and is considered acceptable and the proposal above accepted. The CHMP considered that the DVT posology should be in line with the PE posology for patients with moderate and severe renal impairment.

In conclusion, the proposed wording for the moderate renal impairment was subsequently amended as follows:

In patients with moderate (creatinine clearance 30 - 49 ml/min) or severe (creatinine clearance 15 - 29 ml/min) renal impairment the following dosage recommendations apply:

- For the prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation, the recommended dose is 15 mg once daily (see section 5.2).
- For the treatment of DVT, ***treatment of PE*** and prevention of recurrent DVT and PE: Patients should be treated with 15 mg twice daily for the first 3 weeks.

Thereafter, the recommended dose is 20 mg once daily. ***A reduction of the dose from 20 mg once daily to 15 mg once daily should be considered if the patient's assessed risk for bleeding outweighs the risk for recurrent DVT and PE. The recommendation for the use of 15 mg is based on PK modelling and has not been studied in this clinical setting (see sections 4.4, 5.1 and 5.2).***

1.1.2. Pharmacodynamics

1.1.2.1. Introduction

The linear prothrombin time (PT)/rivaroxaban plasma concentration relationship in DVT Treatment EXT patients in phase II supported the use of PT in exposure-driven safety/efficacy analyses in PE patients. Therefore, PT measurements at baseline (before first rivaroxaban dose), and at steady-state trough (approximately 12 hours post-dosing for b.i.d. or 24 hours post-dosing for o.d.) and peak (2 to 4 hours after tablet intake), were scheduled for all patients enrolled in the phase III DVT and PE studies (11702).

1.1.2.2. Relationship between plasma concentration and effect

The relation between rivaroxaban exposure and effect on factor Xa activity and prothrombin time was not evaluated in PE patients since PK was not obtained. However, PE patients exhibited predictable PT Neoplastin® values at baseline, and at steady-state peak and trough when treated with 15 mg b.i.d. and 20 mg rivaroxaban o.d. The 5/95 percentiles for PT at maximum effect, 2 - 4 h after tablet intake, ranged from 17 to 31 sec for 15 mg b.i.d. and from 15 to 30 sec for 20 mg o.d. in this patient population. These ranges are very similar to PT values observed in DVT Treatment EXT patients whose 5/95 percentiles for PT at maximum effect, 2 to 4 h after tablet intake, ranged from 16 to 33 sec for 15 mg b.i.d. and from 15 to 30 sec for 20 mg o.d.

When analyzing PT Neoplastin® data and their relation to important patient covariates, the previously established increases in PT values were observed for increasing age, decreasing body weight or worsening renal function (assessed via creatinine clearance).

CHMP discussion

The pharmacodynamic response was in line with the previously established PK/PD relation between PT and rivaroxaban plasma concentration.

1.1.3. Overvall conclusion on clinical pharmacology

Rivaroxaban is a competitive, selective, and direct oral factor Xa inhibitor. Activation of factor X to factor Xa plays a central role in the cascade of blood coagulation. Inhibition of factor Xa would be expected to inhibit the amplified burst of thrombin generation induced when the coagulation system is activated both when the activation is initiated by the internal ("surface activation") or external route (tissue factor and factor VIIa).

In phase I dose escalation studies, factor Xa was inhibited in a dose-dependent way over the complete dose range closely following the pharmacokinetic profiles of rivaroxaban. The other global clotting tests PT, aPTT, and Heptest were also affected in a dose-dependent way. The 10 mg dose of rivaroxaban resulted in a maximal reduction of the factor Xa activity by 33% (SD 5.1%), and a maximal prolongation of PT of 38%. The 20 mg dose of rivaroxaban resulted in a maximal reduction of the factor Xa activity by 55%, and a maximal prolongation of PT of 98%. All pharmacodynamic parameters

investigated in phase I trials correlated closely with the plasma concentrations. Rivaroxaban has no influence on antithrombin III levels or factor II, thus supporting the direct mechanism of inhibition of factor Xa in humans.

Results of investigations of the ETP (endogenous thrombin potential) have shown that single doses of 5 and 30 mg rivaroxaban influence the intrinsic and extrinsic pathway of the coagulation system. A dose-dependent influence is noted on lag-time, time to peak, peak level and total amount of the endogenous thrombin over time curve.

Another study identified a prolonged influence of rivaroxaban beyond 24 h on the peak level of the ETP as well as lag time suggesting that pharmacological effects may be present beyond 24 hours after doses of 20 mg.

With regards to secondary pharmacology effects, it can be noted that neither preclinical data nor the dedicated QT study indicated that rivaroxaban affects QT to any clinically relevant extent.

The food effect study results did not justified amendment to the SmPC nor the rifampicin study data. However the information related to moderate renal impairment was amended further request of the CHMP and additional analysis of the overall EINSTEIN PE and DVT data.

From a clinical point of view, the clinical pharmacology of rivaroxaban has been well characterised.

1.2. Clinical Efficacy aspects

The current application for treatment of Pulmonary embolism and prevention of recurrent deep vein thrombosis and pulmonary embolism is based on one phase III pivotal study (11702PE) in PE and supportive study in PE (study 11899). The data previously assessed for the treatment of DVT from study (11702 DVT) previously assessed in application (EMEA/H/C/00944/X10) could also be considered supportive but not discussed in this report.

The following table provides an overview of the phase II and III studies supporting the current application.

Table 3 Overview of pertinent clinical studies in phase II and phase III

Study number Primary indication	Design	Rivaroxaban regimen and treatment duration	Comparator and treatment duration	Number of rivaroxaban subjects	Number of subjects with comparator treatment
Phase II trials					
13238 (report A50672) Acute proximal DVT or acute PE and using strong CYP3A4 inducer	open-label, non controlled	30 mg b.i.d. for 3 weeks followed by 20 mg b.i.d. 3 months	none	25 VFS 19 PK	not applicable
Phase III trials					
11702 PE (report A53042) Acute symptomatic PE with or without symptomatic DVT	multicenter, randomized, open-label, event-driven non-inferiority study for efficacy	15 mg b.i.d. for 3 weeks followed by 20 mg o.d. 3, 6 or 12 months [a]	enoxaparin b.i.d. overlapping with and followed by VKA 3, 6 or 12 months [a]	2420 R 2419 ITT 2412 VFS 2224 PP	2413 R 2413 ITT 2405 VFS 2238 PP
11702 DVT [b] (report MRR-00292) Acute symptomatic proximal DVT without symptomatic PE	multicenter, randomized, open-label, event-driven non-inferiority study for efficacy	15 mg b.i.d. for 3 weeks followed by 20 mg o.d. 3, 6 or 12 months [a]	enoxaparin b.i.d. overlapping with and followed by VKA 3, 6 or 12 months [a]	1731 R 1731 ITT 1718 VFS [c] 1525 PP	1718 R 1718 ITT 1711 VFS [c] 1571 PP
11899 [b] (report MRR-00273) Continued treatment of VTE after 6 to 14 months of anticoagulant treatment	multicenter, randomized, double-blind, event-driven superiority study for efficacy	20 mg o.d. 6 or 12 months [a]	placebo 6 or 12 months [a]	602 R 602 ITT 598 VFS 550 PP	595 R 594 ITT 590 VFS 554 PP

PK=valid for pharmacokinetic analysis; PP=per protocol population; R=randomized; VFS=valid for safety population; VKA=vitamin K antagonist

[a] based on the risk profile of the subject, and local preferences; decision made by the investigator at the time of randomization

[b] Studies 11702 DVT and 11899 were presented in detail in a previous filing.

Notes: In all studies, study outcomes were assessed by an independent central adjudication committee that was unaware of treatment allocation.

1.2.1. Dose response studies

1.2.1.1. Introduction

Two dose response studies (11223 and 11528) were performed in patients with acute DVT.

Thrombus scores were evaluated with compression ultrasonography (CUS) in study 11223 and with CUS and perfusion lung scintigraphy (PLS) in study 11528.

Table 4 Dose response studies in treatment of VTE

Study number/ primary indication	Design	Rivaroxaban regimen and treatment duration	Comparator and treatment duration	Number of subjects randomized to rivaroxaban	Number of subjects randomized to enoxaparin/VKA treatment
Supportive phase II trials					
11223 (MRR-00150) acute symptomatic DVT without symptomatic PE	randomized, partially blinded (double-blind for rivaroxaban and open-label for the comparator), parallel-group	10 mg b.i.d., 20 mg b.i.d., 30 mg b.i.d. and 40 mg o.d. 12 weeks	Enoxaparin b.i.d. overlapping with and followed by VKA 12 weeks	487 R 478 VFS 431 ITT [a] 419 PP	126 R 126 VFS 112 ITT 109 PP
11528 (MRR-00223) acute symptomatic DVT without symptomatic PE	randomized, partially blinded (double-blind for rivaroxaban and open-label for comparator), parallel-group	20 mg, 30 mg and 40 mg o.d. 12 weeks	(LMW) heparin overlapping with and followed by VKA 12 weeks	406 R 405 VFS 368 ITT [a] 348 PP	137 R 137 VFS 119 ITT 101 PP

1.2.1.2. Results

No clear dose response relationship could be established for efficacy parameters in any of the studies. In study 11223 a 30% improvement in CUS thrombus score was observed in 53, 48, 38, 52 and 40% in the 10mg b.i.d, 20mg b.i.d, 40mg o.d., 30mg b.i.d and enoxaparin/VKA groups, respectively. In study 11528 the overall improvement rates based on CUS, PLS and symptomatic DVT were 77, 82, 74 and 69% in the 20mg o.d., 30mg o.d., 40 mg o.d. and the enoxaparin/VKA groups, respectively. The lack of a clear relationship between dose and efficacy response are commonly seen in dose finding studies within this area.

The doses applied in the phase III studies in DVT and PE were rivaroxaban 15 mg twice daily in the acute phase for a total of 3 weeks followed by rivaroxaban 20 mg once daily. In the pivotal study in PE a dose confirmation exercise was performed.

There was a slight tendency for increased bleeding risks with increasing doses in study 11223 with somewhat more bleedings with doses equal to or above 40 mg (with an incidence of 2.5% of major bleedings and an additional 9.5% of non major bleedings) in comparison with enoxaparin/VKA (major bleedings 0%, non major 6.3%). With the dose 10 mg b.i.d. the bleeding rates were similar to those in the enoxaparin/VKA group. In study 11528 bleeding rates were similar in all treatment groups.

1.2.2. Main pivotal study (study 11702 PE)

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

Table 5 Summary of Efficacy for 11702 PE

Title: Oral direct factor Xa inhibitor rivaroxaban in patients with acute symptomatic pulmonary embolism - The EINSTEIN PE Study			
Study identifier	11702 PE		
Design	Multi-center, randomized, open-label, parallel-group, active-controlled, event-driven non-inferiority study; central independent adjudication committee for suspected clinical outcomes was blinded to treatment allocation		
	Duration of main phase: Duration of run-in phase: Duration of extension phase:		3, 6, or 12 months (determined individually for each subject by the investigator before randomization) No fixed run-in phase – the pre-randomization period of anticoagulant therapy could extend to a maximum of 48 hours Either patients were followed up for 30 days after end of their intended treatment or they were directly transferred into an extended treatment study protocol (Study 11899) and were to receive their study medication (rivaroxaban or placebo) for 6 or 12 months
Hypothesis	Non-inferiority		
Treatment groups	Overall study cohort		3 to 12 months treatment duration, 4833 patients randomized
	3 months intended treatment duration		Rivaroxaban. 127 patients randomized Enoxaparin/VKA. 122 patients randomized
	6 months intended treatment duration		Rivaroxaban. 1388 patients randomized Enoxaparin/VKA. 1387 patients randomized
	12 months intended treatment duration		Rivaroxaban. 905 patients randomized Enoxaparin/VKA. 904 patients randomized
Endpoints and definitions	Primary outcome	Recurrent VTE	The composite of recurrent DVT or non-fatal or fatal PE
	Secondary outcome	Secondary efficacy outcome	The composite of recurrent DVT, non-fatal PE and all cause mortality
	Secondary outcome	Net clinical benefit 1	The composite of recurrent DVT or non-fatal or fatal PE (the primary efficacy outcome) and major bleeding events
	Secondary outcome	Net clinical benefit 2	The composite of recurrent DVT or non-fatal or fatal PE (the primary efficacy outcome), major bleeding events, CV deaths, MIs, strokes, and non-CNS systemic embolisms
	Other endpoint	Principal safety outcome	The composite of major bleeding events and clinically relevant non-major bleeding events
	Other endpoint	Major bleeding events	Incidence of major bleeding events
	Other endpoint	Fatal bleeding events	Incidence of major bleeding events associated with fatal outcome
	Other endpoint	Non- fatal major bleeding events in a critical site	Incidence of major bleeding events in a critical site (intracranial, retroperitoneal, intraocular, pericardial, intra-articular, adrenal gland, pulmonary, abdominal)

	Other endpoint	Major bleeding event: non-fatal non critical organ bleeding	Incidence of major bleeding events occurring as overt bleeding associated with transfusion of 2 or more units of packed red blood cells or whole blood and/or associated with a decrease in hemoglobin of 2 g/dL or more
	Other endpoint	Intracranial haemorrhage	Incidence of intracranial haemorrhage
	Other endpoint	All-cause mortality	Incidences of deaths
	Other endpoint	Vascular events	Incidence of vascular events
Database lock	30 Dec 2011		

Results and analysis				
Analysis description	**Primary analysis**			
Analysis population and time point description	Intent to treat All confirmed efficacy outcomes up to the end of the intended duration of treatment irrespective of the actual treatment duration - time to the first event of the composite efficacy outcome (Cox's proportional hazard model for rivaroxaban vs. enox/VKA)			
Descriptive statistics and estimate variability	Treatment group	Rivaroxaban	Enoxaparin/VKA	
	Number of subjects	2419	2413	
	Primary efficacy outcome (composite of recurrent DVT or non-fatal or fatal PE)	Incidence rate: 2.1%	Incidence rate: 1.8%	
Analysis description	**Secondary Analyses**			
Descriptive statistics and estimate variability	Treatment group	Rivaroxaban	Enoxaparin/VKA	
	Number of subjects	2419	2413	
	Secondary efficacy outcome	Incidence rate: 4.0%	Incidence rate: 3.4%	
	Net clinical benefit 1	Incidence rate: 3.4%	Incidence rate: 4.0%	
	Net clinical benefit 2	Incidence rate: 4.5%	Incidence rate: 4.8%	
Analysis description	**Safety Analyses**			
Descriptive statistics and estimate variability	Treatment group	Rivaroxaban	Enoxaparin/VKA	
	Number of subjects	2412	2405	
	Principal safety outcome (composite of major bleeding events and clinically relevant non-major bleeding events)	Incidence rate: 10.3%	Incidence rate: 11.4%	
	Major bleeding events	Incidence rate: 1.1%	Incidence rate: 2.2%	
	Fatal bleeding events	All confirmed TE events: < 0.1%	All confirmed TE events: 0.1%	
	Non-fatal major bleeding events in a critical site	All confirmed TE events: 0.3%	All confirmed TE events: 1.1%	

	Major bleeding event: non-fatal non critical organ bleeding	All confirmed TE events: 0.7%	All confirmed TE events: 1.0%	
	Intracranial haemorrhage	All confirmed TE events: 0.1%	All confirmed TE events: 0.5%	
	All-cause mortality	Incidence rate: 2.6%	Incidence rate: 2.1%	
	Vascular events (adjudicated events)	Incidence rate: 1.5%	Incidence rate: 1.5%	

Effect estimate per comparison	Primary efficacy outcome (composite of recurrent DVT or non-fatal or fatal PE)	Comparison groups	Rivaroxaban vs. enoxaparin/VKA
		Hazard ratio	1.123
		95% confidence interval	0.749 – 1.684
		P-value, non-inferiority P-value, superiority	P = 0.0026 P = 0.5737
	Secondary efficacy outcome (recurrent DVT, non-fatal PE and all cause mortality)	Comparison groups	Rivaroxaban vs. enoxaparin/VKA
		Hazard ratio	1.156
		95% confidence interval	0.862 – 1.552
		Nominal P-value, superiority	P = 0.3333
	Net clinical benefit 1 (primary efficacy outcome and major bleeding events)	Comparison groups	Rivaroxaban vs. enoxaparin/VKA
		Hazard ratio	0.849
		95% confidence interval	0.633 – 1.139
		Nominal P-value, superiority	P= 0.2752
	Net clinical benefit 2 (the primary efficacy outcome plus major bleeding events, CV deaths, MIs, strokes, and non-CNS systemic embolisms	Comparison groups	Rivaroxaban vs. enoxaparin/VKA
		Hazard ratio	0.940
		95% confidence interval	0.724 – 1.221
		Nominal P-value, superiority	P= 0.6430
	Principal safety outcome (composite of major bleeding events and clinically relevant non-major bleeding events)	Comparison groups	Rivaroxaban vs. enoxaparin/VKA
		Hazard ratio	0.900
		95% confidence interval	0.758 – 1.069
		P-value for superiority	0.2305
	Major bleeding events	Comparison groups	Rivaroxaban vs. enoxaparin/VKA
		Hazard ratio	0.493
		95% confidence interval	0.308 – 0.789
		Nominal P-value for superiority	0.0032
Notes	All cause mortality is based on any post-randomization death. otherwise safety variables are presented as treatment emergent.		

Analysis description	For the primary efficacy analysis, the time to the first event of the composite primary efficacy outcome was analyzed using a Cox's proportional hazards model, with intended treatment duration as stratum and adjusted for the baseline presence of malignancy. The rivaroxaban-to-comparator hazard ratio was computed with two sided 95% confidence intervals (CIs). Based on this model, rivaroxaban was to be considered at least as effective as the comparator if the upper limit of the CI was less than 2.0. To account for multiple testing, a hierarchical testing procedure was pre-specified, and comprised non-inferiority and superiority testing for the primary efficacy outcome. Furthermore, if non-inferiority for the primary efficacy outcome was demonstrated, the principal safety outcome (composite of major and clinically relevant non-major bleeding events), as well as the major bleeding outcome were to be tested hierarchically. Secondary efficacy outcomes were not included in the hierarchical testing procedure.

1.2.2.1. Methods- analysis of data

Study title /objective

The phase III study 11702 PE was a multicenter, randomized, open-label, event-driven, non inferiority trial for efficacy in patients with acute symptomatic PE with or without symptomatic DVT.

The primary efficacy objective for this study was to evaluate whether rivaroxaban is at least as effective as enoxaparin / VKA (either warfarin or acenocoumarol) in the treatment of subjects with acute symptomatic PE with or without symptomatic DVT for the prevention of recurrent VTE.

The principal safety objective was the evaluation of major and clinically relevant non-major bleedings.

Inclusion/exclusion criteria

Subjects were eligible for study 11702 PE if they had objectively confirmed acute symptomatic PE with or without symptomatic DVT. The maximum treatment duration with therapeutic doses of anticoagulants prior to randomization was 36 hours (or 48 hours after protocol amendment 4) with the additional limitation that only a single dose of VKA was allowed. Subjects were potentially eligible if the diagnosis of PE was based on one of the following criteria:

- A (new) intraluminal filling defect in segmental or more proximal branches on spiral
- computed tomography (sCT) scan
- 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
- A (new) perfusion defect of at least 75% of a segment with a local normal ventilation
- result (high-probability) on ventilation / perfusion lung scintigraphy (VPLS)
- Inconclusive sCT, pulmonary angiography, or lung scintigraphy with demonstration of DVT in the lower extremities by compression ultrasound (CUS) or venography

The index event (i.e. the event for which the subject was eligible for the study) was adjudicated. The adjudication package contained films or images of one of the above tests, which were used only to confirm the initial diagnosis. A description of the procedures for these tests was provided in the diagnostic test manual. No systematic search for other sites of thrombosis was required. Adjudication was performed after randomization.

The main exclusion criteria were

- severe renal impairment (creatinine clearance < 30 mL/min)
- significant liver disease (or alanine aminotransferase [ALT] > 3 x upper limit of normal [ULN])
- short life expectancy (< 3 months)
- active bleeding or a bleeding risk contraindicating treatment with enoxaparin or VKA
- hypertension (systolic blood pressure > 180 mmHg or diastolic blood pressure > 110 mmHg)
- concomitant use of strong CYP3A4 inhibitors or inducers.

Treatments

Subjects were randomized to receive either rivaroxaban 15 mg b.i.d. for 3 weeks followed by 20 mg o.d. or the currently recommended treatment (drugs mandated: enoxaparin followed by either warfarin or acenocoumarol). The treatment duration was 3, 6 or 12 months, determined by the investigator prior to randomization, and based on the risk profile of the subject and local practice/guidelines.

The following guidance was used:

A 3-month treatment duration is often employed for subjects with transient risk factors such as:

- Recent surgery or trauma
- Immobilization
- Use of estrogen-containing drugs
- Puerperium

A 6-month or 12-month treatment duration is often employed for subjects with idiopathic VTE, or with permanent risk factors such as:

- Active cancer
- Previous episodes of DVT / PE
- Known thrombophilic condition (e.g. deficiency of antithrombin III, protein S or C, factor V or prothrombin gene mutations, or anti-phospholipid antibodies)

The final decision to treat a subject for 3, 6, or 12 months was at the investigator's discretion and was based on the above risk assessments as well as the potential for bleeding.

Subjects allocated to the comparator group received enoxaparin b.i.d. for at least 5 days in combination with VKA (overlap 4 - 5 days) and continued with VKA only after the INR had been ≥2.0 for 2 consecutive measurements at least 24 hours apart. Warfarin and acenocoumarol were allowed as VKAs.

Outcomes/endpoints

The primary efficacy outcome was symptomatic recurrent VTE, i.e. the composite of recurrent DVT or non-fatal or fatal PE. The following definitions were applied by the CIAC to confirm a suspected episode of symptomatic recurrent DVT / PE:

1. Suspected (recurrent) DVT with one of the following findings:

- 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

- An extension of an intraluminal filling defect, or a new intraluminal filling defect or an extension of non-visualization of veins in the presence of a sudden cut-off on venography

or

2. Suspected PE with one of the following findings:

- A (new) intraluminal filling defect in segmental or more proximal branches on sCT scan
- 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
- A (new) perfusion defect of at least 75% of a segment with a local normal ventilation result (high-probability) on VPLS
- Inconclusive sCT, pulmonary angiography, or lung scintigraphy with demonstration of DVT in the lower extremity

3. Fatal PE was:

- PE based on objective diagnostic testing, autopsy
- Death which cannot be attributed to a documented cause and for which DVT / PE cannot be ruled out (unexplained death)

In the absence of objective testing, a suspected episode of DVT or PE was to be considered as confirmed if it led to a change in anticoagulant treatment at therapeutic dosages for more than 48 hours.

The secondary efficacy outcomes assessed in this study are given in the table below.

Text Table 7-1: Secondary efficacy outcomes and their components

Outcome	Description	When / where defined?
Secondary outcome	Recurrent DVT, non-fatal PE, and all cause mortality [a]	In original SAP before study start
Net clinical benefit 1	Recurrent DVT or non-fatal or fatal PE (the primary efficacy outcome) and major bleeding events	In original SAP before study start
Net clinical benefit 2	Recurrent DVT or non-fatal or fatal PE (the primary efficacy outcome), major bleeding events, CV deaths, MIs, strokes, and non-CNS systemic embolisms	In supplemental SAP (post-hoc)

[a] Composite outcome where in the primary efficacy outcome fatal PE was substituted by all cause mortality

CNS = central nervous system; CV = cardiovascular; DVT = deep vein thrombosis; MI = myocardial infarction; PE = pulmonary embolism; SAP = statistical analysis plan

Sample size

Assuming equal efficacy, a total of 88 events was calculated to give a power of 90% to demonstrate that rivaroxaban is non-inferior to the comparator, considering a relative non-inferiority margin for the hazard ratio of 2.0 (2-sided α=0.05). Based on the observation that most recurrent events occur in the first month after the initial event, an incidence rate of recurrent VTE of 2.5% at 3 months, 3% at 6 months, and 3.5 % at 12 months was expected. Hence, a mean incidence rate for the primary efficacy outcome of 3% for both treatment groups was expected and at least 1465 subjects per group were determined to be necessary. This number of subjects was to be adjusted based on the observed overall incidence rate of symptomatic recurrent VTE as follows: the number of subjects with events for the primary efficacy outcome within the intended treatment duration was estimated for various numbers of subjects to be randomized, using interim overall incidence rates and interim overall durations of

observation by intended treatment duration. Then, a number of subjects to be randomized was selected that was expected to lead to approximately 88 events.

Randomisation

Randomisation was performed centrally by an interactive voice response system (IVRS) stratified by country and by intended treatment duration.

Allocation was stratified by 1) country and 2) intended treatment duration.

Blinding (masking)

An open label design was chosen taking the complexity of a double blind design in this setting into account.

The design gave the opportunity to use the local VKA agent and it allowed subjects in the comparator group who present with sub-therapeutic INRs to be adjusted back into the therapeutic range while being protected for brief periods with a short-acting anticoagulant such as s.c. LMWH. The clinical evaluation of subjects with suspected outcome events frequently entails un-blinding. Subjects presenting to the hospital in an emergency situation, either with bleeding or a suspected thrombotic event, will often have the INR measured, which would potentially reveal study treatment allocation.

Statistical methods

The observation time relevant for the primary efficacy analysis was given by the pre-assigned intended treatment duration, i.e. 3, 6, or 12 months, based on the decision of the investigator prior to randomization. Thus, only those VTE events which occurred during the pre-assigned intended treatment duration were taken into account.

Subjects who, within the intended treatment duration,

•did not have a VTE event

•were lost to follow-up

•died because of reasons other than DVT/PE, or

•withdrew informed consent and who did not have a primary efficacy outcome

were censored at the last day the subject had a complete assessment for study outcomes.

A dose confirmation analysis was performed for the initial 400 PE subjects, investigating the combination of symptomatic recurrent VTE and asymptomatic deterioration at repeat lung imaging at 3 weeks after start of treatment. The incidence rate of this combined outcome was compared among rivaroxaban and comparator subjects who had a 3 week lung imaging test or who had a symptomatic recurrent VTE before the planned repeat lung imaging test at 3 weeks. he one sided 95% interval of the absolute difference between observed incidence rates was calculated using exact methods. Study 11702 PE was to be continued as planned if the one-sided 95% CI of the difference of the observed incidence rates between rivaroxaban and comparator in the initial 400 subjects did not exceed 8.0%. This margin had been chosen as it was considered clinically important. The analysis was conducted by the independent Dose Confirmation Committee.

There were 5 amendments to the study protocol covering both the EINSTEIN DVT Study and the EINSTEIN PE Study. The amendments are considered not affecting the integrity of the study.

All patients were to have a 30 day observational period after cessation of study treatment. At the end of this observational period a contact was to be taken to record:

- SAEs. including suspected bleeding and vascular events, suspected recurrent PE/DVT
- Anticoagulant medication and any medication given in case of a suspected VTE or bleeding event.

In those patients who discontinued study medication prematurely the same observation period applied.

CHMP comments:

The diagnostic criteria and inclusion/exclusion criteria are considered appropriate. The recommendations for treatment duration provided in the guidance to the investigators are in line with international guidelines.

The diagnostic criteria for recurrent VTE are considered to be appropriate. The interpretation of "Net clinical benefit" should be done with caution as combining major efficacy and safety end-points of different clinical weight may not reflect the benefit risk balance in an optimal way.

An open label design with central blinded adjudication of the end-points may not be ideal but can be accepted in this setting with the arguments provided by the Sponsor.

A CHMP scientific advice meeting was held at EMA in 2006 where the MAH presented a clinical development program for the "treatment and secondary prevention of VTE". Two open-label non-inferiority studies in DVT (11702 DVT) and PE (11702 PE), as well as a double blind placebo controlled extension study (11899) were discussed.

The CHMP expressed preference to the conduct of a double blind design for the pivotal study, however, difficulties in the conduct of a blinded study were acknowledged. The MAH considered an open label design for the study most appropriate. In line with the discussion at that meeting, the MAH implemented measures to compensate for the advantages a blinded study would have provided. These included a central sponsor independent electronic randomization system, a blinded CIAC (Central Independent Adjudication Committee) that assessed efficacy outcomes and key safety outcomes according to pre-defined objective criteria.

The following topics were also discussed at that meeting and were implemented into the study :

- intended duration of treatment before randomization,
- exclusive use of enoxaparin followed by either warfarin or acenocoumarol as comparators,
- duration of treatment,
- definitions of the primary and secondary efficacy outcomes,
- statistical plan,
- safety outcomes,
- liver monitoring, and
- choice of dose.

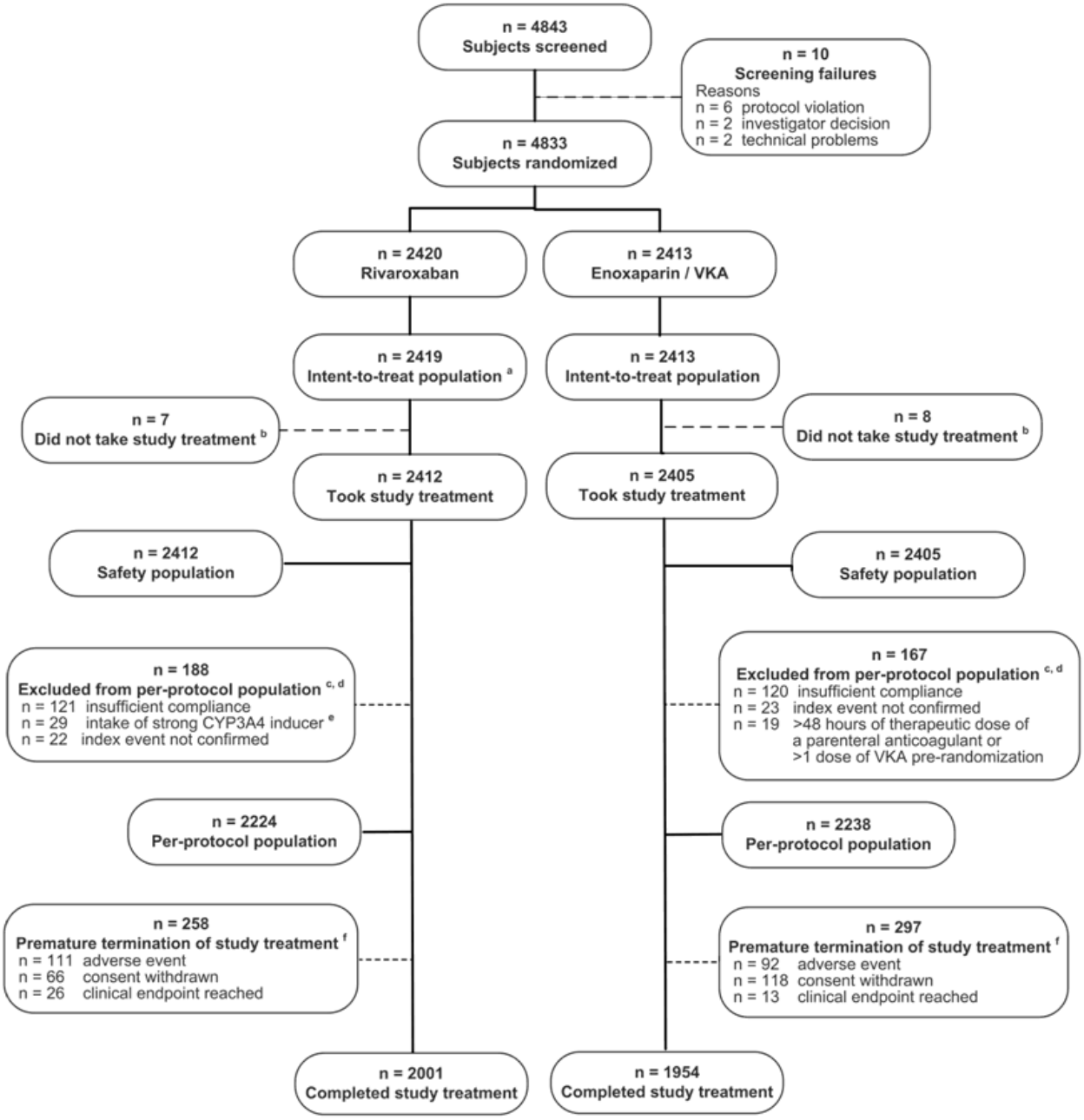
Finally, the choice for a non-inferiority margin of 1.75 for the pooled 11702 DVT and 11702 PE studies was discussed, including the requirement for a non-inferiority margin of 2.0 for each of the 11702 DVT and 11702 PE studies.

A NI margin of 2.0 appears liberal as a doubled incidence of recurrent VTE in comparison with traditional treatment could hardly be accepted. However, the DVT study, which was initiated together with the PE study, could to some extent support an estimation of the efficacy.

In conclusion, the study programme is essentially in agreement with the recommendations given in the CHMP advice.

1.2.2.2. Results

- **Participant flow**



Conduct of the study

The vast majority of subjects (96.9% in the rivaroxaban group and 96.1% in the enoxaparin/VKA group;) either completed the intended treatment period, had a primary efficacy outcome, died, or participated in the study until recruitment was terminated by the sponsor when the required number of primary efficacy outcome events was expected to be reached with the subjects already in the study. The vast majority of the included patients completed the study as intended.

Baseline data

Table 6 : Risk factors Risk factors for thromboembolism by intended treatment duration - study 11702 PE

(ITT population, only rates of at least 4% in any treatment group)

	Rivaroxaban	Enox/VKA
3 months intended treatment duration	(n = 127)	(n = 122)
Recent surgery or trauma	55 (43.3%)	58 (47.5%)
Idiopathic DVT / PE	43 (33.9%)	33 (27.0%)
Immobilization	30 (23.6%)	37 (30.3%)
Use of estrogen-containing drugs	12 (9.4%)	14 (11.5%)
Active cancer	7 (5.5%)	6 (4.9%)
Previous episode(s) of DVT / PE	8 (6.3%)	3 (2.5%)
6 months intended treatment duration	(n = 1387)	(n = 1387)
Recent surgery or trauma	272 (19.6%)	259 (18.7%)
Idiopathic DVT / PE	684 (49.3%)	699 (50.4%)
Immobilization	254 (18.3%)	266 (19.2%)
Use of estrogen-containing drugs	151 (10.9%)	152 (11.0%)
Active cancer	68 (4.9%)	62 (4.5%)
Previous episode(s) of DVT / PE	142 (10.2%)	147 (10.6%)
Known thrombophilic condition [a]	65 (4.7%)	47 (3.4%)
12 months intended treatment duration	(n = 905)	(n = 904)
Recent surgery or trauma	88 (9.7%)	81 (9.0%)
Idiopathic DVT / PE	469 (51.8%)	454 (50.2%)
Immobilization	100 (11.0%)	77 (8.5%)
Use of estrogen-containing drugs	44 (4.9%)	57 (6.3%)
Active cancer	39 (4.3%)	41 (4.5%)
Previous episode(s) of DVT / PE	305 (33.7%)	339 (37.5%)
Known thrombophilic condition [a]	72 (8.0%)	71 (7.9%)
Obesity	42 (4.6%)	46 (5.1%)

[a] types of thrombophilia were not evaluated separately for each cohort

Notes: A subject could have more than one risk factor, and more than one type of thrombophilia. Numbers may not add up. The classification 'idiopathic DVT/PE' was by assessment of the investigator. Enox = enoxaparin, ITT = intention to treat, VKA = vitamin K antagonist

Numbers analysed

Efficacy outcomes were primarily analyzed for the ITT population 4832 subjects overall, with 2419 subjects in the rivaroxaban and 2413 subjects in the enoxaparin / VKA group), with supportive analyses performed for the PP population (4462 subjects overall, with 2224 subjects in the rivaroxaban and 2238 subjects in the enoxaparin / VKA group).

Outcomes and estimation

Results of the Dose-Confirmation Analysis

After inclusion of the initial 400 subjects in study 11702 PE (rivaroxaban group: 205; enoxaparin group: 195), a dose confirmation analysis was performed. This analysis was based on the composite of asymptomatic deterioration on ventilation/perfusion lung scan or sCT and the primary efficacy outcome at 3 weeks. Altogether, 379 subjects had a baseline and a repeat lung scan at 3 weeks. Of these subjects, 18 had a change in anticoagulant medication within 2 weeks after the date of the repeat lung scan (4 subjects treated with rivaroxaban and 14 subjects treated with enoxaparin/VKA).

The incidence rate of the combination of symptomatic recurrent VTE and asymptomatic deterioration at repeat lung imaging at 3 weeks was 3/179 subjects (1.7%) in the rivaroxaban group and 1/175 (0.6%) in the enoxaparin/VKA group. The upper 1-sided 95% CI of the absolute difference between

incidence rates, as calculated using the exact methods, was 3.6% and thus did not exceed the pre-specified value of 8.0%.

In addition, the response to treatment was assessed based on the repeated perfusion lung scan results and confirmed symptomatic VTE events up to Day 26. In this assessment, 154/179 rivaroxaban subjects (86.0%) and 150/175 enoxaparin/VKA subjects (85.7%) were considered as having improved; 22/179 rivaroxaban subjects (12.3%) and 24/175 enoxaparin/VKA subjects (13.7%) were considered as unchanged; and 3/179 rivaroxaban subjects (1.7%) and 1/175 enoxaparin/VKA subjects (0.6%) were considered as deteriorated.

The CHMP considered that the dose confirmation analyses supported continuation of the study.

The treatment duration is given in the table 7 below:

		Rivaroxaban n = 2419 (100%)	Enox / VKA n = 2413 (100%)
Overall actual treatment duration (categorized)	No study medication intake	7 (0.3%)	8 (0.3%)
	<1 week	51 (2.1%)	30 (1.2%)
	≥1 week - <1 month	74 (3.1%)	87 (3.6%)
	≥1 month - <3 months	49 (2.0%)	75 (3.1%)
	≥3 months - <6 months	459 (19.0%)	531 (22.0%)
	≥6 months - <9 months	1075 (44.4%)	993 (41.2%)
	≥9 months - <12 months	704 (29.1%)	689 (28.6%)
Overall actual treatment duration (days)	Missing	7	8
	Median (IQR)	183 (179 - 352)	182 (178 - 351)
	Mean ± SD	216.1 ± 98.7	214.2 ± 98.9
	Range	1 - 359	1 - 359

Note: Treatment duration (days) was calculated as the date of last dose of study treatment minus the date of first dose plus 1 if these dates were given. 30 days were taken as 1 month. If the date of last dose of study treatment was missing, imputation was performed as specified in the supplemental SAP (see section 7.7.2). Percentages were calculated including missing values.
Enox = enoxaparin; IQR = interquartile range; ITT = intent to treat; SD = standard deviation; VKA = vitamin K antagonist

For rivaroxaban, compliance with the intended dose schedule was calculated based on the actual number of tablets taken divided by the expected number of tablet intake for the duration of observation from first dispense of study treatment up to the last intake of study treatment (even if it was discontinued prematurely).

Overall compliance in the rivaroxaban group (Table 8)

		ITT n = 2419 (100%)	PP n = 2224 (100%)
Overall compliance	No study treatment taken	7 (0.3%)	0 (0.0%)
	Missing	24 (1.0%)	0 (0.0%)
	<50%	31 (1.3%)	4 (0.2%)
	50 to <80%	78 (3.2%)	8 (0.4%)
	≥80%	2279 (94.2%)	2212 (99.5%)

The CHMP agreed that treatment compliance appeared to be reasonably good in this population.

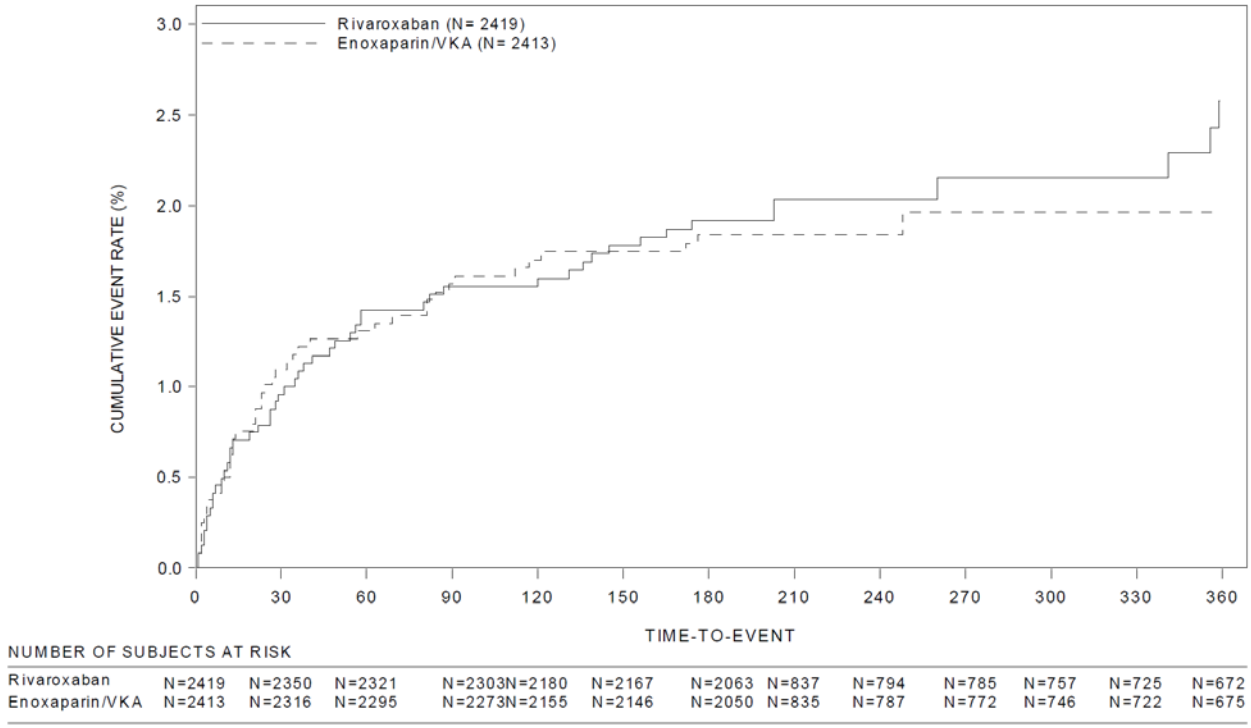
Primary efficacy results

Table 9 Summary of results for primary efficacy outcome - study 11702 PE

Population	ITT	ITT on treatment	PP on treatment
Incidence rate of primary efficacy outcome until intended end of treatment			
Rivaroxaban group	50/2419 (2.1%)	44/2412 (1.8%)	38/2224 (1.7%)
Enox/VKA group	44/2413 (1.8%)	39/2405 (1.6%)	36/2238 (1.6%)
Cox's proportional hazard model for rivaroxaban vs. enox/VKA			
Hazard ratio	1.123	1.115	1.045
Confidence interval	0.749-1.684	0.725-1.717	0.662-1.648
p-value for non-inferiority	0.0026	0.0040	0.0026
p-value for superiority	0.5737	0.6194	0.8504

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.
Enox = enoxaparin, ITT = intention to treat, PP = per protocol, VKA = vitamin K antagonist

A Kaplan-Meyer analysis of the primary efficacy outcome is given below :



Secondary end-points

Table 10 : Incidence rates of efficacy events until intended end of treatment (all events per subject) - ITT population - study 11702 PE

Outcome/ components	Rivaroxaban N=2419 (100%)	Enox/VKA N=2413 (100%)	Cox's model [a] hazard ratio riva vs. enox/VKA	95% confidence interval (CI)
Primary efficacy outcome (pre-specified)	50 (2.1%)	44 (1.8%)	1.123 (p=0.0026) [b] (p=0.5737) [c]	0.749-1.684
Death (PE)	3 (0.1%)	1 (<0.1%)		
Death (PE cannot be excluded)	8 (0.3%)	6 (0.2%)		
Symptomatic PE and DVT	0	2 (<0.1%)		
Symptomatic recurrent PE only	23 (1.0%)	20 (0.8%)		
Symptomatic recurrent DVT only	18 (0.7%)	17 (0.7%)		
Primary efficacy outcome without events confirmed by change in antithrombotic treatment only (pre-specified)	46 (1.9%)	41 (1.7%)	1.108 (p=0.0030) [b] (p=0.6321) [c]	0.728-1.688
Death (PE)	3 (0.1%)	1 (<0.1%)		
Death (PE cannot be excluded)	8 (0.3%)	6 (0.2%)		
Symptomatic PE and DVT	0	2 (<0.1%)		
Symptomatic recurrent PE only	18 (0.7%)	17 (0.7%)		
Symptomatic recurrent DVT only	18 (0.7%)	17 (0.7%)		
Secondary efficacy outcome (pre-specified)	97 (4.0%)	82 (3.4%)	1.156 (p=0.3333) [c]	0.862-1.552
Death (PE)	3 (0.1%)	1 (<0.1%)		
Death (PE cannot be excluded)	8 (0.3%)	6 (0.2%)		
Death (bleeding)	5 (0.2%)	4 (0.2%)		
Death (cardiovascular)	10 (0.4%)	3 (0.1%)		
Death (other)	32 (1.3%)	36 (1.5%)		
Symptomatic PE and DVT	0	2 (<0.1%)		
Symptomatic recurrent PE only	23 (1.0%)	20 (0.8%)		
Symptomatic recurrent DVT only	18 (0.7%)	17 (0.7%)		
Net clinical benefit 1 (pre-specified)	83 (3.4%)	96 (4.0%)	0.849 (p=0.2752) [c]	0.633-1.139
Death (PE)	3 (0.1%)	1 (<0.1%)		
Death (PE cannot be excluded)	8 (0.3%)	6 (0.2%)		
Symptomatic PE and DVT	0	2 (<0.1%)		
Symptomatic recurrent PE only	23 (1.0%)	20 (0.8%)		
Symptomatic recurrent DVT only	18 (0.7%)	17 (0.7%)		
Major bleeding	33 (1.4%)	57 (2.4%)		
Net clinical benefit 2 (post-hoc)	110 (4.5%)	115 (4.8%)	0.940 (p=0.6430) [c]	0.724-1.221
Death (PE)	3 (0.1%)	1 (<0.1%)		
Death (PE cannot be excluded)	8 (0.3%)	6 (0.2%)		
Death (cardiovascular)	10 (0.4%)	3 (0.1%)		
Symptomatic PE and DVT	0	2 (<0.1%)		
Symptomatic recurrent PE only	23 (1.0%)	20 (0.8%)		
Symptomatic recurrent DVT only	18 (0.7%)	17 (0.7%)		
Major bleeding	33 (1.4%)	57 (2.4%)		
STEMI	5 (0.2%)	2 (<0.1%)		
NSTEMI	2 (<0.1%)	11 (0.5%)		
Ischemic Stroke	11 (0.5%)	7 (0.3%)		
Non CNS systemic embolism	6 (0.2%)	3 (0.1%)		

In the above table, incidence rates are given in numbers of subjects reporting the event after randomization up to end of intended treatment time, divided by number of subjects in reference population. If the same subject had several events, the subject was counted for several components so that numbers for the components may not add up to those for the composite outcome

During the 30-day observational period in the ITT population, the incidence rates of the primary efficacy outcome were 0.9% (20 / 2211) in the rivaroxaban group and 0.7% (15 / 2201) in the enoxaparin / VKA group. During this period (by definition), no subjects in the rivaroxaban group took any rivaroxaban. In the enoxaparin / VKA group, a substantial number of subjects continued VKA treatment as routine anticoagulant therapy. In the rivaroxaban group, a smaller number of subjects as compared to the enoxaparin/VKA group received routine anticoagulation. In addition, routine anticoagulation in the rivaroxaban group was initiated with a delay as compared to the enoxaparin/VKA group. The 0.9% vs. 0.7% incidence rates compare favorably with the recurrent VTE incidence rate in subjects with PE and / or DVT randomized to placebo in the EINSTEIN Extension Study 11899 (1.7% per month).

- **Ancillary analyses**

Achievement of Target INR Range of 2.0-3.0

The mean percentage of time subjects' INR was inside or outside the target interval of 2.0-3.0 during the VKA treatment period, which was defined as the period after initiation of VKA and discontinuation of initial low molecular weight heparin, is summarized below. The results are given for unadjusted time in therapeutic range (TTR) and adjusted TTR. The adjusted time excludes

- days where VKA was intentionally interrupted (as determined by the adjudication committee), and the corresponding period of 8 days after re-start of VKA
- days where any additional anticoagulant was used (including heparins, fondaparinux, other VKA), and
- days after primary efficacy outcome or major bleeding event was reported.

Adjusted time was selected because this methodology was used in contemporary studies using double blind study medication and sham INRs.

Table 11 : percentage of time in therapeutic range by intended treatment duration - study 11702 PE
(only subjects in enoxaparin/VKA group; ITT on treatment population)

VKA period	3 months intended treatment duration		6 months intended treatment duration		12 months intended treatment duration	
	unadjusted n=121 [a]	adjusted n=121 [a]	unadjusted n=1374 [a]	adjusted n=1374 [a]	unadjusted n=899 [a]	adjusted n=899 [a]
Week 1	58.5%	59.9%	55.1%	57.1%	55.2%	57.7%
Week 2	60.1%	61.3%	52.2%	53.2%	50.9%	52.5%
Week 3	57.1%	60.0%	55.6%	57.1%	57.1%	58.5%
Week 4	57.8%	58.9%	58.2%	59.3%	57.2%	59.1%
Month 1	57.3%	60.1%	54.6%	56.6%	54.4%	56.0%
Month 2	53.5%	55.2%	59.8%	60.6%	61.2%	63.0%
Month 3	48.7%	52.7%	61.8%	62.6%	63.4%	64.8%
Month 4			64.2%	64.6%	69.3%	70.7%
Month 5			63.9%	65.0%	69.5%	70.3%
Month 6			62.1%	68.5%	66.9%	68.1%
Month 7					65.8%	67.1%
Month 8					66.3%	67.3%
Month 9					68.1%	68.8%
Month 10					68.0%	69.0%
Month 11					69.5%	70.6%
Month 12					67.3%	68.8%
Overall VKA period	52.2%	56.8%	58.8%	61.7%	62.6%	65.0%

[a] Given is the number of subjects with any results; not all subjects had results available for all periods
Given is the mean time in INR target interval (2.0-3.0) based on observed and imputed INR (i.e. using linear interpolation) during the VKA period, which was defined as the period after initiation of VKA and discontinuation of initial low molecular weight heparin. Adjusted values exclude days where VKA was intentionally interrupted (as determined by the adjudication committee) and the corresponding period of 8 days after re-start of VKA, days where any additional anticoagulant was used (including heparins, fondaparinux, other VKA), and days after an event for primary efficacy outcome or a major bleeding event was reported. VKA = vitamin K antagonist

Table 12: Incidences of primary efficacy outcome and mean percentage of adjusted time spent within therapeutic INR range by region - study 11702 PE

(adjusted time in INR target interval for overall VKA period)

	Incidence rate of primary efficacy outcome (ITT population)		Mean TTR (enoxaparin/VKA group; ITT on treatment population)
	Rivaroxaban	Enoxaparin / VKA	
Overall	50/2419 (2.1%)	44/2413 (1.8%)	62.7% (n=2328)
Western Europe	24/1309 (1.8%)	16/1311 (1.2%)	63.1% (n=1269)
North America	5/ 244 (2.0%)	7/ 242 (2.9%)	61.1% (n= 233)
Australia & New Zealand	4/ 306 (1.3%)	10/ 307 (3.3%)	71.4% (n= 297)
South America	0/ 8 (0.0%)	0/ 10 (0.0%)	44.6% (n= 10)
Eastern Europe	3/ 208 (1.4%)	4/ 209 (1.9%)	61.7% (n= 205)
Israel	3/ 78 (3.8%)	1/ 75 (1.3%)	59.8% (n= 70)
South Africa	5/ 121 (4.1%)	3/ 117 (2.6%)	53.3% (n= 111)
Asia	6/ 145 (4.1%)	3/ 142 (2.1%)	54.1% (n= 133)

Notes: Time in therapeutic INR range (TTR) is based on observed and imputed INR (i.e. linear interpolation). TTR data are shown for overall VKA period, which was defined as the period after initiation of VKA and discontinuation of initial low molecular weight heparin. VKA = vitamin K antagonist.

The outcome center TTR tertiles is given below:

Text Table 9-28: Incidence rate of efficacy outcome center time in target INR range of 2.0 to 3.0 (center TTR) (ITT population)

Center TTR	Incidence rate		Rivaroxaban vs. Enox / VKA	p-value for interaction
	Rivaroxaban	Enox / VKA	Hazard ratio (95% CI)	
<58.7%	17/793 (2.14%)	19/802 (2.37%)	0.903 (0.470 - 1.738)	0.082
58.7% - 67.7%	23/808 (2.85%)	11/800 (1.38%)	2.081 (1.014 - 4.270)	
>67.7%	9/790 (1.14%)	14/807 (1.73%)	0.642 (0.277 - 1.484)	
Subjects without center TTR	1/28 (3.57%)	0/4 (0.00%)		

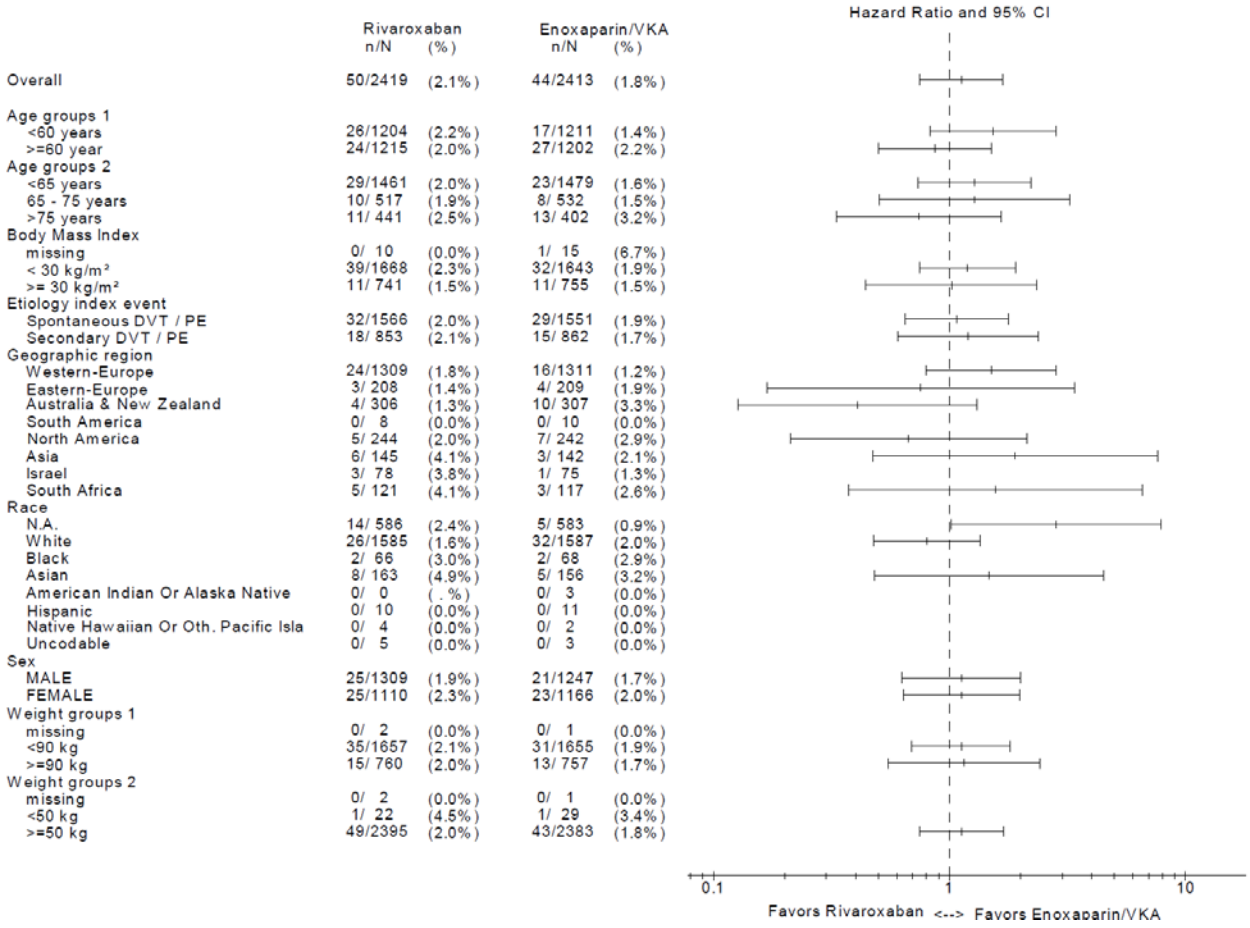
Notes: TTR = time in target INR range of 2-3. Center TTR (cTTR) was calculated by averaging all individual subjects' adjusted TTR (iTTR) within a center. Center(s) with no INR from the comparator group were excluded. Centers were categorized into three subgroups with approximately equal numbers of patients using the overall cTTR tertiles. A stratified Cox-Regression was only done if at least 5 events per category existed, with strata based on intended treatment duration, and active cancer (yes/no) at baseline included in each model as covariate. The p-value for interaction was calculated using the model including covariates treatment group, subgroup, treatment group*subgroup, and active cancer at baseline. The p-values for interaction were calculated excluding subjects without cTTR.

CHMP discussion:

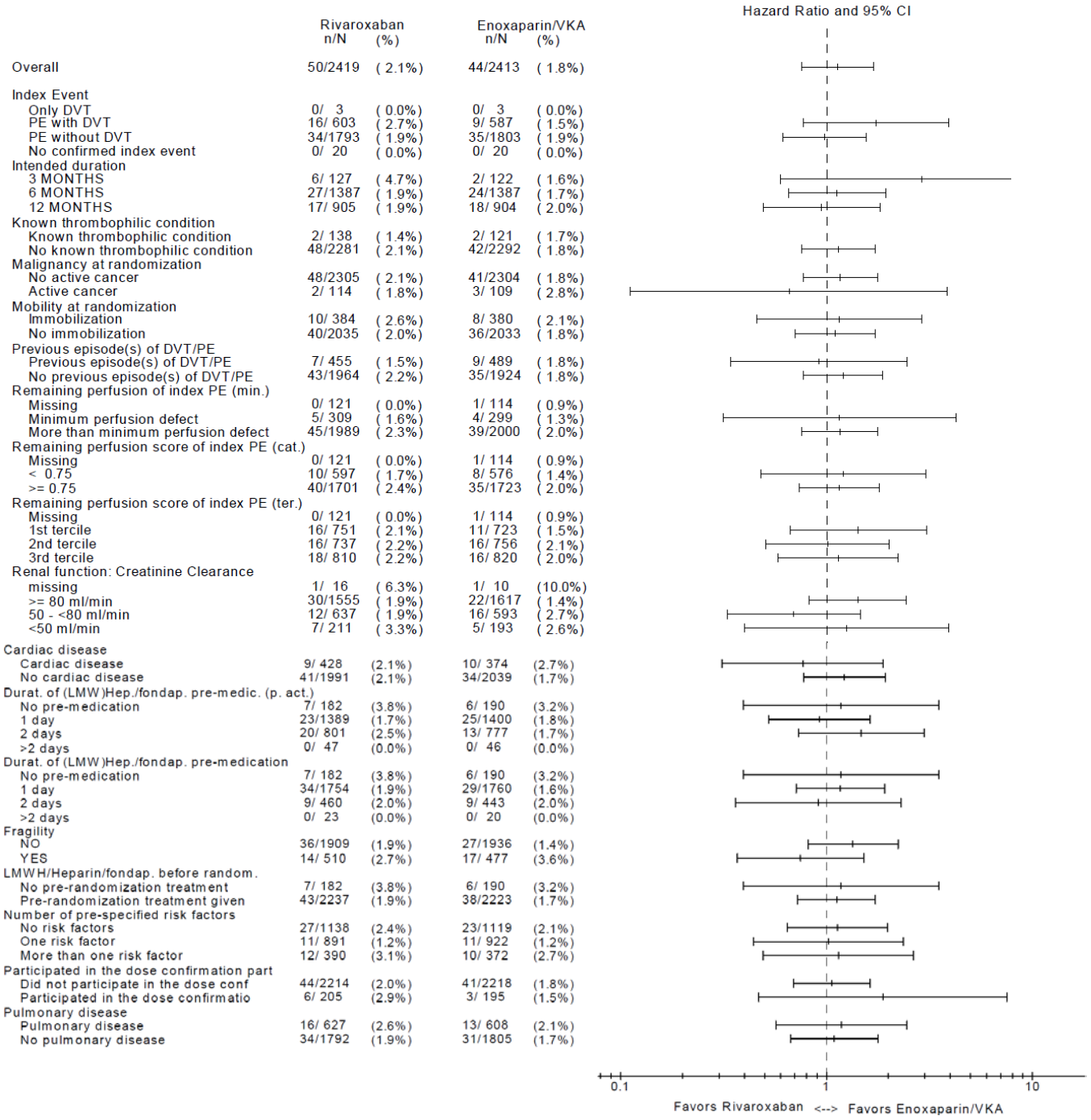
The achieved INR levels are representative for a pan European perspective and the management of the VKA treatment could be considered acceptable although a better performance can be expected in some centres and in some countries.

There is no clear relationship between the quality of the VKA treatment and the relative efficacy of rivaroxaban as compared to VKA treatment even if such a relationship could theoretically be expected.

The primary efficacy results by baseline patients characteristics are given in the figure below:



The subgroup analyses by baseline characteristics are given below:



1.2.2.3. Discussion

The patients included in the 11702 study are considered to be reasonably representative for a European PE population with regards to demographic and risk factor characteristics. Approximately 60 % of the patients were recruited within Europe.

The number of patients lost for follow up are not high and are considered to not be of concern.

A numerically higher incidence of the primary efficacy events were recorded in the rivaroxaban group with a point estimate of 1.12 and a 95% CI up to 1.68. This has been discussed in relation to the MAH

responses to the List of Questions. The uncertainty introduced by the numerical differences observed disfavouring rivaroxaban has been satisfactorily resolved. It is acknowledged that important additional data for the efficacy of rivaroxaban is gained from the Einstein DVT study and the pooling of the results of these two studies which supports the conclusion that rivaroxaban therapy is sufficiently effective in DVT and PE treatment. However, DVT and PE are to be regarded as different clinical manifestations of the same disease.

Additionally, it has to be taken into account that in both studies 11702 PE and study 11702 DVT, the incidence rate of the primary efficacy outcome was the same (2.1%) for rivaroxaban, but the incidence rate of the primary efficacy outcome in the enoxaparin/VKA group was significantly lower in study 11702 PE (1.8%) than in study 11702 DVT (3.0%). The relative low event rate in the Enoxaparin/VKA arm in this event driven study might have also contributed to the numerical differences in this event-driven study."

Considering that a higher number of patients in the rivaroxaban arm were left untreated for a period of time and with the well-known high risk for recurrences in a VTE population it may not be surprising that more patients had a recurrence in the rivaroxaban group. The issue of a possible rebound phenomenon has been extensively discussed in relation to previous applications and at present, there is no convincing evidence for such phenomenon to be present.

1.2.3. Analysis performed across trials (pooled analyses AND meta-analysis)

The study in DVT (11702 DVT) had a similar design as the pivotal study supporting this application (11702 PE). The primary efficacy outcome was the same in both studies, i.e. symptomatic recurrent VTE, defined as the composite of recurrent DVT, non-fatal or fatal PE, including unexplained death for which PE could not be ruled out. Furthermore, DVT and PE are closely related and could be seen as different clinical manifestations of the same disease.

Table 13 : Summary of results for efficacy outcomes across studies 11702 PE, 11702 DVT and pooled analysis

Category Study	Incidence rate (no. of subjects reporting the event after randomization up to end of intended treatment time / no. of subjects in ITT population)		Cox's model [a] hazard ratio riva vs. enox/VKA	95% confidence interval (CI)
	Rivaroxaban	**Enoxaparin/VKA**		
Primary efficacy outcome (pre-specified)				
Study 11702 PE	50/2419 (2.1%)	44/2413 (1.8%)	1.123 (p=0.0026) [b] (p=0.5737) [c]	0.749-1.684
Study 11702 DVT	36/1731 (2.1%)	51/1718 (3.0%)	0.680 (p<0.0001) [b] (p=0.076) [c]	0.443-1.042
Pooled analysis	86/4150 (2.1%)	95/4131 (2.3%)	0.886 (p<0.0001) [b] (p=0.4143) [c]	0.661-1.186
Primary efficacy outcome - only events with objective test available [d]				
Study 11702 PE	46/2419 (1.9%)	41/2413 (1.7%)	1.108 (p=0.0030) [b] (p=0.6321) [c]	0.728-1.688
Study 11702 DVT	*same as primary efficacy outcome (all events confirmed by objective tests)*			
Pooled analysis	82/4150 (2.0%)	92/4131 (2.2%)	0.871 (p<0.0001) [b] (p=0.3628) [c]	0.647-1.173

[a] stratified for intended treatment duration and adjusted for baseline malignancy; up to the end of the intended treatment period; [b] p-value for non-inferiority (one-sided); [c] p-value for superiority (two-sided); [d] primary efficacy outcome without events confirmed by change in antithrombotic treatment

CHMP discussion:

In the DVT study a numerically better outcome with borderline significance was noted in the rivaroxaban group. The enoxaparin/VKA treatment appears to have been handled with similar quality in the two studies. The numerical increase in recurrences in the rivaroxaban has been discussed above and were considered satisfactorily solved in the answer to the LoQ.

The outcome 'net clinical benefit 1' was the composite of the primary efficacy outcome and major bleeding events. In the rivaroxaban group, the incidence rate of net clinical benefit 1 was numerically slightly higher in study 11702 PE (3.4%) than in study 11702 DVT (2.9%); in the pooled analysis it was 3.2%. In the enoxaparin/VKA group, incidence rates were similar between study 11702 PE (4.0%) and study 11702 DVT (4.2%). Hazard ratios for rivaroxaban vs. enoxaparin/VKA were numerically in favor of rivaroxaban (11702 PE: 0.849; 95% CI: 0.633-1.139; p = 0.2752); for study 11702 DVT (0.667; 95% CI: 0.466 0.954; p = 0.027) and for the pooled analysis (0.771; 95% CI: 0.614 0.967; p = 0.0244).

The outcome 'net clinical benefit 2', which was a post-hoc analysis, was the composite of the primary efficacy outcome, major bleeding events, cardiovascular deaths, myocardial infarctions, strokes, and non-CNS systemic embolisms. In the rivaroxaban group, the incidence rate of net clinical benefit 2 was numerically higher in study 11702 PE (4.5%) than in study 11702 DVT (3.6%); in the pooled analysis it was 4.1%. In the enoxaparin/VKA group, incidence rates were similar between study 11702 PE (4.8%) and study 11702 DVT (4.7%). Hazard ratios for rivaroxaban vs. enoxaparin/VKA were numerically in favor of rivaroxaban (11702 PE: 0.940, 95% CI: 0.724-1.221; 11702 DVT: 0.727, 95% CI: 0.522 1.013; pooled analysis: 0.853, 95% CI: 0.695-1.047).

CHMP discussion:

The CHMP agreed that the pooled analyses of "net clinical outcome" are in favour of rivaroxaban as compared to enoxaparin/VKA treatment.

1.2.4. Supportive study (study 11899)

Study 11899 which was conducted to provide evidence for the benefit of continued treatment with rivaroxaban vs. placebo in patients who had completed anticoagulant therapy and for whom clinical equipoise had been reached. Subjects who completed 6 or 12 months of treatment in either study 11702 DVT or 11702 PE or from outside of these two studies were recruited to study 11899.

The results of study 11899, which has previously been assessed by the CHMP (refer to procedure EMEA/H/C/000944/X10) demonstrated a high rate of recurrent VTE in the placebo group, a statistical significant and clinically relevant risk reduction of recurrent VTE in favour of rivaroxaban . The comparison of rivaroxaban vs. placebo treatment yielded a hazard ratio of 0.185 (95% CI 0.087-0.393, $p < 0.0001$) or a 81% relative risk reduction The study provides additional support for the efficacy of rivaroxaban in secondary prevention of PE.

1.2.5. CHMP overall conclusions on clinical efficacy

The pivotal non-inferiority study in treatment and secondary prophylaxis of PE included patients considered to be representative for a European PE population.

The open label design is not ideal but can be accepted taking the central blinded evaluation of the end-points into account. The study was considered well performed with an acceptable quality of the enoxaparin/VKA treatment in the comparator group with an adjusted mean TTR of 63%. The number of patients lost for follow-up was small.

The incidence rate of the primary efficacy outcome (ITT population) until the end of intended treatment was 2.1% (50/2419) in the rivaroxaban group and 1.8% (44/2413) in the enoxaparin/VKA group yielding a hazard ratio of 1.123 (95% CI: 0.749-1.684) in the ITT population. The study met its primary objective as the upper limit of the confidence interval was below the pre defined non-inferiority margin of 2.0. Similar results were obtained in the PP population. The results were consistent in different relevant subgroups.

The predefined delta of <2.0 for the NI appeared liberal in this disease where VTE recurrences can be life-threatening and otherwise may have major clinical consequences for the patents with a need for long-term anticoagulant treatment and risks for post-thrombotic syndromes and chronic pulmonary hypertension. It should however be remembered that the absolute recurrence rates were low in the study and that enoxaparin/warfarin treatment is very effective in this setting. Few prospective randomised studies of this size have been performed in PE. The provided pivotal study is one of the largest prospective comparative studies in PE ever performed.

Numerically, a higher incidence of the primary efficacy end-point was noted in the rivaroxaban group and the 95% CI indicated that an increased relative risk for recurrences of approximately 70% could be at hand comparing with conventional treatment. It could, however, be argued that the claimed non-inferiority in the pivotal PE study is supported by the more favourable results of the DVT study. It can be said that DVT and PE are different clinical manifestations of the same underlying disease and traditionally they are treated in the same way if anticoagulants are used.

Further support for the efficacy of rivaroxaban in the prevention of PE is provided in study 11899 which was a double-blind and placebo-controlled trial performed in a population that had VTE but was not considered to necessarily be in need of prolonged anticoagulant treatment.

In conclusion, the CHMP considered that the study 11702 PE, together with the additional supportive data and analysis provided sufficient evidence for efficacy for the treatment of PE and secondary prevention of PE in adult patients.

1.3. Clinical Safety aspects

1.3.1. Methods – analysis of data submitted

The results of the pooled 11702 PE and 11702 DVT studies are presented to enable a comparison of the data and to demonstrate their consistency especially for the clinically meaningful bleeding events (primary and secondary safety outcomes). This is considered acceptable by the CHMP and is justified by the fact that subject characteristics were similar with similar incidence rates of adverse events. As DVT and PE are considered to be manifestations of the same disease, albeit of different severity, and are treated in the same way, it was considered medically appropriate to pool results from studies 11702 DVT and PE in several analyses.

1.3.2. Results

1.3.2.1. Patient exposure

Table 14 : Total number of subjects valid for safety in study 11702 PE and the pooled analysis (11702 DVT and PE)

Study / Drug and Dosage	N	Total for safety population
Study 11702 PE		4817
Rivaroxaban 15 mg b.i.d. for 3 weeks followed by rivaroxaban 20 mg o.d.	2412	
Enoxaparin overlapping with and followed by VKA	2405	
Pooled analysis		8246
Rivaroxaban 15 mg b.i.d. for 3 weeks followed by rivaroxaban 20 mg o.d.	4130	
Enoxaparin overlapping with and followed by VKA	4116	

Abbreviations: b.i.d. =twice daily; o.d. = once daily; VKA = vitamin K antagonist

Table 15: Duration of study treatment in the pooled analysis

	Rivaroxaban	Enoxaparin/VKA
Total treatment duration categories		
n	4130 (100.0%)	4116 (100.0%)
<1 week	73 (1.8%)	52 (1.3%)
>= 1 week -<1 month	123 (3.0%)	171 (4.2%)
>= 1 month -<3 months	100 (2.4%)	143 (3.5%)
>= 3 months -<6 months	871 (21.1%)	985 (23.9%)
>= 6 months -<9 months	1934 (46.8%)	1763 (42.8%)
>= 9 months -<12 months	885 (21.4%)	878 (21.3%)

1.3.2.2. Adverse events

The presentation of safety data refered to treatment-emergent adverse events unless otherwise stated.

Bleeding events are presented as bleeding events confirmed by the CIAC (Central Independent Adjudication Committee) unless otherwise stated. The treatment-emergent period for bleeding events was defined as the period starting after randomization and ending 2 days after stop of medication.

The principal safety outcome was the composite of major or clinically relevant non-major bleeding events.

The secondary safety outcome was major bleeding events.

Table 16 Summary of adverse events - safety population of study 11702 PE

Incidence of	Rivaroxaban 20 mg o.d. [a] N=2412 (100%)	Enox/VKA N=2405 (100%)
Any adverse event	1959 (81.2%)	1928 (80.2%)
Any serious adverse event	504 (20.9%)	497 (20.7%)
Any death	63 (2.6%)	51 (2.1%)
Any TEAE	1937 (80.3%)	1901 (79.0%)
Any drug-related TEAE	776 (32.2%)	784 (32.6%)
Any TESAE	471 (19.5%)	463 (19.3%)
Any drug-related TESAE	112 (4.6%)	118 (4.9%)
Any AE resulting in permanent discontinuation of study drug	123 (5.1%)	99 (4.1%)
Any AE leading to (prolonged) hospitalization	425 (17.6%)	430 (17.9%)
Any AE starting >2 days after stop of study drug	332 (13.8%)	332 (13.8%)
Any drug-related AE starting >2 days after stop of study drug	33 (1.4%)	40 (1.7%)
Any SAE starting >2 days after stop of study drug	67 (2.8%)	75 (3.1%)
Any drug-related SAE starting >2 days after stop of study drug	1 (<0.1%)	6 (0.2%)

20mg o.d. is used to abbreviate both the 15mg b.i.d. followed by 20mg o.d. regismen

The term "treatment-emergent" as used in this document refers to the period from randomization until 2 days after the last dose of study drug.

The incidence rates of all adverse events were higher in study 11702 PE (about 80%) than in study 11702 DVT (about 64%), which may be explained by the sicker study population in the PE study (as indicated by the different prevalence rates of co-morbidities) and the longer treatment duration. The incidence rates were comparable between the treatment groups for the PE and DVT studies. Therefore, the incidence rates were similar (about 74%) for both treatment groups in the pooled analysis.

Table 17 Pooled analysis of adverse events

Adverse event summary	Rivaroxaban N=4130 (100%)	Enoxaparin/VKA N=4116 (100%)
Any adverse event	3062 (74.1%)	3035 (73.7%)
Any adverse event starting >2 days after stop of study drug	484 (11.7%)	491 (11.9%)
Any drug-related adverse event	1184 (28.7%)	1208 (29.3%)
Any drug-related adverse event starting >2 days after stop of study drug	44 (1.1%)	56 (1.4%)
Any serious adverse event	726 (17.6%)	751 (18.2%)
Any serious adverse event starting >2 days after stop of study drug	98 (2.4%)	120 (2.9%)
Any drug-related serious adverse event	157 (3.8%)	175 (4.3%)
Any drug-related serious adverse event starting >2 days after stop of study drug	2 (<0.1%)	9 (0.2%)
Any bleeding adverse event (investigator reported)*	1274 (30.8%)	1267 (30.8%)
Any death	104 (2.5%)	103 (2.5%)
Any treatment emergent death (time window: 2 days)	45 (1.1%)	39 (0.9%)
Any treatment emergent death (time window: 7 days)	56 (1.4%)	51 (1.2%)
Any treatment-emergent adverse event (time window: 2 days)	3015 (73.0%)	2981 (72.4%)
Any treatment-emergent adverse event (time window: 7 days)	3022 (73.2%)	2989 (72.6%)
Any treatment-emergent adverse event, excluding bleeding adverse events (investigator reported, time windows: 2 days) *	2841 (68.8%)	2819 (68.5%)
Any treatment-emergent adverse event, excluding bleeding adverse events (investigator reported, time windows: 7 days) *	2852 (69.1%)	2830 (68.8%)
Any treatment-emergent bleeding adverse event (investigator reported, time window: 2 days) *	1235 (29.9%)	1206 (29.3%)
Any treatment-emergent bleeding event (adjudicated) time window: 2 days	1169 (28.3%)	1153 (28.0%)
Any drug-related treatment-emergent adverse event (time windows: 2 days)	1177 (28.5%)	1178 (28.6%)
Any drug-related treatment-emergent adverse event (time windows: 7 days)	1178 (28.5%)	1185 (28.8%)
Any drug-related treatment-emergent adverse event, excluding bleeding adverse events (investigator reported, time windows: 2 days) *	487 (11.8%)	481 (11.7%)
Any drug-related treatment-emergent adverse event, excluding bleeding adverse events (investigator reported, time windows: 7 days) *	488 (11.8%)	483 (11.7%)
Any drug-related treatment-emergent bleeding adverse event (windows: 2 days) *	882 (21.4%)	875 (21.3%)
Any treatment-emergent serious adverse event (windows: 2 days)	678 (16.4%)	696 (16.9%)
Any treatment-emergent serious adverse event (windows: 7 days)	684 (16.6%)	710 (17.2%)
Any treatment-emergent serious adverse event, excluding bleeding adverse events (investigator reported, time windows: 2 days) *	592 (14.3%)	613 (14.9%)
Any treatment-emergent serious adverse event, excluding bleeding adverse events (investigator reported, time windows: 7 days) *	601 (14.6%)	627 (15.2%)
Any treatment-emergent bleeding serious adverse event (time windows: 2 days) *	141 (3.4%)	158 (3.8%)

Table 18 Summary of treatment-emergent adverse events (at least 5% in any treatment group) by MedDRA system organ class/preferred term (subjects valid for safety analysis in studies 11702 PE)

MedDRA SOC Preferred term (primary term)	Study 11702 PE Rivaroxaban 20 mg o.d.[a] (N=2412)	Enox/VKA (N=2405)
ANY EVENT	1937 (80.3%)	1901 (79.0%)
Gastrointestinal disorders		
Constipation	139 (5.8%)	131 (5.4%)
Diarrhoea	125 (5.2%)	124 (5.2%)
Nausea	106 (4.4%)	122 (5.1%)
General disorders and administration site conditions		
Chest pain	183 (7.6%)	185 (7.7%)
Infections and infestations		
Nasopharyngitis	181 (7.5%)	189 (7.9%)
Injury, poisoning and procedural complications		
Contusion	92 (3.8%)	129 (5.4%)
Musculoskeletal and connective tissue disorders		
Back pain	88 (3.6%)	131 (5.4%)
Pain in extremity	154 (6.4%)	154 (6.4%)
Nervous system disorders		
Headache	193 (8.0%)	174 (7.2%)
Respiratory, thoracic and mediastinal disorders		
Cough	155 (6.4%)	169 (7.0%)
Dyspnoea	161 (6.7%)	136 (5.7%)
Epistaxis	218 (9.0%)	197 (8.2%)

No apparent differences between the treatment groups with respect to treatment-emergent adverse events (about 73%) were seen in the pooled analysis of the DVT and PE studies.

Table 19 Summary of the most common treatment-emergent drug-related adverse events (at least 1% in any treatment group) by preferred term - safety population of study 11702 PE

MedDRA system organ class Preferred term (primary term)	Rivaroxaban 20 mg o.d.[a] N=2412 (100%)	Enox/VKA N=2405 (100%)
ANY EVENT	776 (32.2%)	784 (32.6%)
Eye disorders		
Conjunctival hemorrhage	20 (0.8%)	25 (1.0%)
Gastrointestinal disorders		
Gingival bleeding	46 (1.9%)	64 (2.7%)
Rectal haemorrhage	41 (1.7%)	32 (1.3%)
Injury, poisoning and procedural complications		
Contusion	53 (2.2%)	86 (3.6%)
Subcutaneous hematoma	21 (0.9%)	32 (1.3%)
Investigations		
ALT increased	26 (1.1%)	33 (1.4%)
INR increased	4 (0.2%)	76 (3.2%)
Nervous system disorders		
Headache	35 (1.5%)	11 (0.5%)
Renal and urinary disorders		
Haematuria	49 (2.0%)	52 (2.2%)
Reproductive system and breast disorders		
Menorrhagia	61 (2.5%)	34 (1.4%)
Respiratory, thoracic and mediastinal disorders		
Epistaxis	173 (7.2%)	159 (6.6%)
Haemoptysis	62 (2.6%)	45 (1.9%)
Vascular disorders		

Table 19 Summary of the most common treatment-emergent drug-related adverse events (at least 1% in any treatment group) by preferred term - safety population of study 11702 PE

MedDRA system organ class Preferred term (primary term)	Rivaroxaban 20 mg o.d.[a] N=2412 (100%)	Enox/VKA N=2405 (100%)
Haematoma	37 (1.5%)	68 (2.8%)

1.3.2.3. Serious adverse events and deaths

Table 20 Summary of the most frequent serious treatment-emergent adverse events (at least 0.5% in any treatment group) by preferred term - (safety population of study 11702 PE)

MedDRA system organ class Preferred term (primary term)	Rivaroxaban 20 mg o.d.[a] N=2412 (100%)	Enox/VKA N=2405 (100%)
ANY EVENT	471 (19.5%)	463 (19.3%)
Blood and lymphatic system disorders		
Anemia	12 (0.5%)	5 (0.2%)
General disorders		
Chest pain	20 (0.8%)	27 (1.1%)
Infections and infestations		
Pneumonia	19 (0.8%)	19 (0.8%)
Nervous system disorders		
Ischemic stroke [b]	11 (0.5%)	4 (0.2%)
Renal and urinary disorders		
Haematuria	8 (0.3%)	11 (0.5%)
Respiratory, thoracic and mediastinal disorders		
Dyspnoea	16 (0.7%)	13 (0.5%)
Pleural effusion	8 (0.3%)	11 (0.5%)

No apparent differences with respect to serious TEAEs (16.4% [678/4130] rivaroxaban vs. 16.9% [696/4116] enoxaparin/VKA) as well as to serious drug-related TEAEs (3.7% [154/4130] rivaroxaban vs. 4.1% [169/4116] enoxaparin/VKA) were seen in the pooled analysis compared to the individual studies.

Deaths

The incidence rate of death within the study period was numerically higher in the rivaroxaban group (2.6% [63/2412]) than in the enoxaparin/VKA group (2.1% [51/2405]). In both treatment groups, the 3 most frequently reported primary causes for death were: cancer (0.9% [22/2412] rivaroxaban vs. 1.0% [23/2405] enoxaparin/VKA), infectious disease (0.4% [9/2412] rivaroxaban vs. 0.2% [6/2405] enoxaparin/VKA), and unexplained death for which PE could not be ruled out (0.3% [8/2412] rivaroxaban vs. 0.2% [6/2405] enoxaparin/VKA).

In the safety population of the 11702 PE and the 11702 DVT studies, the number of subjects who died after randomization was balanced between the rivaroxaban and the enoxaparin/VKA groups across both studies (2.6% [63/2412] rivaroxaban vs. 2.1% [51/2405] enoxaparin/VKA in 11702 PE study; 2.4% [41/1718] rivaroxaban vs. 3.0% [52/1711] enoxaparin/VKA in 11702 DVT study). The primary causes of deaths were similar in both 11702 PE and 11702 DVT.

Adverse Events of Interest (Bleeding)

The definition of major bleeding events used in the EINSTEIN study program is consistent with the definition of the International Society on Thrombosis and Hemostasis.

The CIAC (central Independent Adjudication committee) categorized the bleeding events as major, clinically relevant non-major or trivial.

A major bleeding event was defined as overt bleeding

- associated with a fall in hemoglobin of 2 g/dL or more or
- leading to a transfusion of 2 or more units of packed red blood cells or whole blood or
- that occurred in a critical site: intracranial, intraspinal, intraocular, pericardial, intra articular, intramuscular with compartment syndrome, retroperitoneal or
- contributing to death.

Clinically relevant non-major bleeding events were defined as overt bleeding not meeting the criteria for major bleeding event but associated with

- medical intervention or
- unscheduled contact (visit or telephone call) with a physician or
- (temporary) cessation of study treatment or
- discomfort for the subject such as pain or
- impairment of activities of daily life.

Examples of such clinically relevant non-major bleeding events were:

- epistaxis if it lasted for more than 5 minutes, if it was repetitive (i.e. 2 or more episodes of true bleeding, i.e. not spots on a handkerchief, within 24 hours), or led to an intervention (e.g. packing, electrocoagulation), or
- gingival bleeding if it occurred spontaneously (i.e. unrelated to tooth brushing or eating), or if it lasted for more than 5 minutes, or
- hematuria if it was macroscopic, and either spontaneous or lasted for more than 24 hours after instrumentation (e.g. catheter placement or surgery) of the urogenital tract, or
- macroscopic gastro-intestinal hemorrhage: at least one episode of melena/hematemesis, if clinically apparent, or
- rectal blood loss, if more than a few spots, or
- hemoptysis, if more than a few speckles in the sputum, or
- intramuscular hematoma, or
- subcutaneous hematoma if the size was larger than 25 cm2, or larger than 100 cm2 if provoked, or
- multiple source bleeding.

All other overt bleeding episodes not meeting the criteria for clinically relevant bleeding were classified as trivial bleeding events.

The principal safety outcome in study 11702 PE was the composite of treatment-emergent major bleeding events and other clinically relevant non-major bleeding events.

The incidences of the primary safety end-point and major bleedings in the PE and DVT studies and in the pooled analyses are given in the tables below

Table 4-17 Incidence rate of treatment-emergent bleeding events and results from the Cox proportional hazard model as assessed by the Central Adjudication Committee safety population of studies 11702 PE, 11702 DVT, or the pooled analysis 11702 DVT and PE

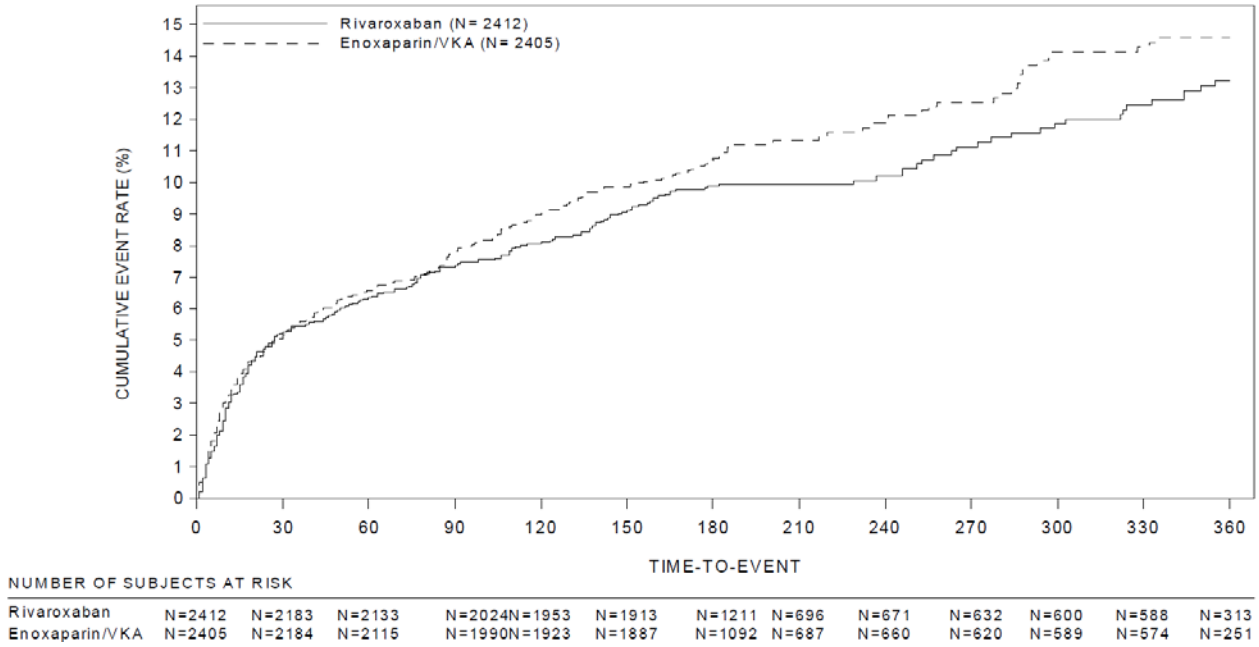
Outcome	Rivaroxaban 20 mg o.d.	Enox/VKA	Hazard Ratio	95% CI	p value for superiority
Study 11702 PE	**N=2412 (100%)**	**N=2405 (100%)**			
Principal safety outcome (major or clinically relevant non-major bleeding event)	249 (10.3%)	274 (11.4%)	0.900	0.758 - 1.069	0.2305
Major bleeding event	26 (1.1%)	52 (2.2%)	0.493	0.308 - 0.789	0.0032
All confirmed bleeding events	757 (31.4%)	774 (32.2%)			
Study 11702 DVT	**N=1718 (100%)**	**N=1711 (100%)**			
Principal safety outcome (major or clinically relevant non-major bleeding event)	139 (8.1%)	138 (8.1%)	0.966	0.763 - 1.222	0.7709
Major bleeding event	14 (0.8%)	20 (1.2%)	0.646	0.326 - 1.282	0.2117
All confirmed bleeding events	412 (24.0%)	379 (22.2%)			
Pooled analysis	**N=4130 (100%)**	**N=4116 (100%)**			
Principal safety outcome (major or clinically relevant non-major bleeding event)	388 (9.4%)	412 (10.0%)	0.925	0.805 - 1.063	0.2721
Major bleeding event	40 (1.0%)	72 (1.7%)	0.539	0.366 - 0.794	0.0018
All confirmed bleeding events	1169 (28.3%)	1153 (28.0%)			

Table 4-15 All confirmed treatment-emergent major bleeding events reported by at least >2 subjects[a] in any pooled treatment group - safety population of studies 11702 PE, 11702 DVT, or the pooled analysis 11702 DVT and PE)

	11702 PE		11702 DVT		Pooled analysis	
Bleeding event	Rivaroxaban N=2412 (100%)	Enox/VKA N=2405 (100%)	Rivaroxaban N=1718 (100%)	Enox/VKA N=1711 (100%)	Rivaroxaban N=4130 (100%)	Enox/VKA N=4116 (100%)
Major bleeding event	**26 (1.1%)**	**52 (2.2%)**	**14 (0.8%)**	**20 (1.2%)**	**40 (1.0%)**	**72 (1.7%)**
Fatal bleeding	***2 (<0.1%)***	***3 (0.1%)***	***1 (<0.1%)***	***5 (0.3%)***	***3 (<0.1%)***	***8 (0.2%)***
Intracranial	2 (<0.1%)	2 (<0.1%)	0	2 (0.1%)	2 (<0.1%)	4 (<0.1%)
Retroperitoneal	0	1 (<0.1%)	0	0	0	1 (<0.1%)
Non-fatal critical organ bleed	***7 (0.3%)***	***26 (1.1%)***	***3 (0.2%)***	***3 (0.2%)***	***10 (0.2%)***	***29 (0.7%)***
Intracranial	1 (<0.1%)	10 (0.4%)	2 (0.1%)	0	3 (<0.1%)	10 (0.2%)
Retroperitoneal	1 (<0.1%)	7 (0.3%)	0	1 (<0.1%)	1 (<0.1%)	8 (0.2%)
Intraocular	2 (<0.1%)	2 (<0.1%)	1 (<0.1%)	0	3 (<0.1%)	2 (<0.1%)
Intra-articular	0	3 (0.1%)	0	1 (<0.1%)	0	4 (<0.1%)
Non-fatal non-critical organ bleeding (fall in Hb ≥ 2 g/dl and/or transfusions ≥ 2 units)	***17 (0.7%)***	***25 (1.0%)***	***10 (0.6%)***	***12 (0.7%)***	***27 (0.7%)***	***37 (0.9%)***
Surgical site	0	3 (0.1%)	0	0	0	3 (<0.1%)
Skin (other than injection site)	1 (<0.1%)	2 (<0.1%)	0	2 (0.1%)	1 (<0.1%)	4 (<0.1%)
Urogenital	1 (<0.1%)	1 (<0.1%)	1 (<0.1%)	3 (0.2%)	2 (<0.1%)	4 (<0.1%)
Gastrointestinal	9 (0.4%)	16 (0.7%)	3 (0.2%)	4 (0.2%)	12 (0.3%)	20 (0.5%)
Rectal	1 (<0.1%)	0	1 (<0.1%)	3 (0.2%)	2 (<0.1%)	3 (<0.1%)
Uterus	3 (0.1%)	0	5 (0.3%)	0	8 (0.2%)	0

Note: Incidence rates 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 randomization and up to 2 days after the last dose of study drug.

The time event pattern for the principal safety outcome is given in the figure below



Adverse Events by Subgroups (selected), PE study

Age: incidence rate for principal safety outcome for subjects of

- age < 65 years: 9.1% (132/1458) rivaroxaban vs. 9.2% (136/1472) enoxaparin/VKA,
- age 65 to 75 years: 11.5% (59/514) rivaroxaban vs. 13.3% (71/532) enoxaparin/VKA, and
- age > 75 years: 13.2% (58/440) rivaroxaban vs. 16.7% (67/401) enoxaparin/VKA.

Creatinine clearance: incidence rate for principal safety outcome for subjects with a creatinine clearance

≥ 80 mL/min: 9.6% (149/1553) rivaroxaban vs. 9.9% (159/1610) enoxaparin/VKA and

50 to < 80 mL/min: 11.5% (73/634) rivaroxaban vs. 13.7% (81/593) enoxaparin/VKA,

And < 50 mL/min: 12.4% (26/209) rivaroxaban vs. 17.7% (34/192) enoxaparin/VKA

Fragile subjects: Fragile subjects were defined as having an age >75 years or body weight ≤ 50 kg or calculated creatinine clearance < 50 mL/min.

The incidence rate for the principal safety outcome for subjects with status:

fragile: 12.6% (64/508) rivaroxaban vs. 16.8% (80/476) enoxaparin/VKA and

non-fragile: 9.7% (185/1904) rivaroxaban vs. 10.1% (194/1929) enoxaparin/VKA

A total of 33.3% (802/2412) subjects in the rivaroxaban treatment group and in 33.6% (807/2405) subjects in the enoxaparin/VKA treatment group had investigator-assessed, treatment-emergent bleeding events; most of them were assessed by the investigators as drug-related.

Investigator reported serious treatment-emergent bleeding AEs occurred in 3.9% (94/2412) rivaroxaban treated subjects vs. 4.6% (111/2405) enoxaparin/VKA treated subjects.

Hepatic events

The incidence rates of post-baseline ALT >3 x ULN were lower with rivaroxaban treatment (1.9% [45/2351]) than with enoxaparin/VKA treatment (3.0% [70/2324]).

The data using both central and local laboratory determined values for combined concurrent cases of ALT >3 x ULN and total bilirubin >2 x ULN also show no differences between the rivaroxaban and enoxaparin/VKA treatment groups, see table below

Table 21 Incidence rates of combined concurrent ALT >3 x ULN and total bilirubin >2 x ULN (central and local laboratory) - safety population of study 11702 PE

Time of occurrence	Rivaroxaban Num [a] / Den [b]	Enox / VKA Num [a] / Den [b]
At any time [c]	5/2404 (0.2%)	4/2399 (0.2%)
Baseline [d]	0/2197 (0.0%)	0/2200 (0.0%)
Post-baseline [e]	5/2355 (0.2%)	4/2327 (0.2%)
Treatment emergent [f]	4/2126 (0.2%)	2/2112 (0.1%)

When looking at the incidence rates of AEs identified using SMQ for hepatic disorders with an incidence rate of at least 0.5%, overall, 8.3% (199/2412) of the subjects in the rivaroxaban treatment group had hepatic disorder events compared with 12.4% (299/2405) subjects in the enoxaparin/VKA treatment group. The majority of hepatic disorder AEs were laboratory abnormalities, which occurred in 5.3% (128/2412) of the subjects in the rivaroxaban treatment group compared with 9.2% (222/2405) subjects in the enoxaparin/VKA treatment group.

Overall, 1.0% (23/2412) of the subjects in the rivaroxaban treatment group experienced hepatic serious TEAEs compared with 1.5% (36/2405) subjects in the enoxaparin/VKA treatment group.

The Hepatic Event Assessment Committee were sent 36 cases in study 11702 PE for review with the number of cases balanced between the 2 treatment groups overall (19 rivaroxaban, 17 enoxaparin/VKA). No cases were given a definite causality assessment by any reviewer.

The case narratives have been provided. The CHMP agreed with the MAH that the reported data do not indicate a clear signal for hepatic toxicity.

Cardiovascular events

The incidence rates of cardiovascular events were equally distributed between the treatment group,see table below where the pooled data are presented:

Table 22 Incidence rates of cardiovascular events based on central adjudication - safety population of pooled analysis 11702 DVT and PE

Outcome / components	Rivaroxaban N=4130 n (100%)	Enoxaparin/VKA N=4116 n (100%)
On-treatment events		
All cardiovascular events	47 (1.1%)	51 (1.2%)
All fatal and non-fatal and TIAs	16 (0.4%)	23 (0.6%)
All fatal and non-fatal and UAs	21 (0.5%)	23 (0.6%)
Death (cardiovascular)	9 (0.2%)	4 (<0.1%)
Myocardial infarction	2 (<0.1%)	1 (<0.1%)
Ischemic stroke	3 (<0.1%)	2 (<0.1%)
Heart failure	2 (<0.1%)	0
Other vascular event	2 (<0.1%)	0
Other cardiac death	0	1 (<0.1%)
STEMI [a]	5 (0.1%)	2 (<0.1%)
NSTEMI	6 (<0.1%)	11 (0.3%)
UA	10 (0.2%)	10 (0.2%)
TIA	3 (<0.1%)	11 (0.3%)
Ischemic stroke [b]	13 (0.3%)	11 (0.3%)
Non-CNS systemic embolism	7 (0.2%)	5 (0.1%)

Other adverse events of interest

Acute pancreatitis was reported as TEAE with an incidence rate of none for subjects in the rivaroxaban treatment group and <0.1% (1/2405) for subjects in the enoxaparin/VKA treatment group in the PE study.

Renal failure was reported as TEAE with an incidence rate of <0.1% (2/2412) in the rivaroxaban treatment group compared to 0.1% (3/2405) in the enoxaparin/VKA treatment group in the Einstein PE trial.

Overall, anaphylactic reactions/severe cutaneous reactions were reported as TEAE with an incidence rate of 0.12% (5/4130) for subjects in the rivaroxaban treatment group and 0.15% (6/4116) for subjects in the enoxaparin/VKA treatment group in the DVT and pool analysis.

1.3.2.4. Laboratory findings

Thrombocytopenia was reported as TEAE with an incidence rate of 0.1% (3/2412) in the rivaroxaban treatment group compared to 0.3% (7/2405) in the enoxaparin/VKA treatment group in the Einstein PE trial.

1.3.2.5. Immunological events

Overall, anaphylactic reactions/severe cutaneous reactions were reported as TEAE with an incidence rate of 0.12% (5/4130) for subjects in the rivaroxaban treatment group and 0.15% (6/4116) for subjects in the enoxaparin/VKA treatment group

1.3.2.6. Safety related to drug-drug interactions and other interactions

Examples of performed exploratory analyses of co-medication are given below :

Treatment with statins at baseline: 2.1% (8/380) rivaroxaban vs. 3.3% (12/362) enoxaparin/VKA in subjects treated with statins, and 0.9% (18/2032) rivaroxaban vs. 2.0% (40/2043) enoxaparin/VKA in subjects not treated with statins had a major bleeding event.

Treatment with ASA at baseline: 1.2% (3/253) rivaroxaban vs. 5.1% (12/235) enoxaparin/VKA in subjects treated with ASA, and 1.1% (23/2159) rivaroxaban vs. 1.8% (40/2170) enoxaparin/VKA not treated with ASA had a major bleeding event.

Treatment with NSAIDs at baseline: 1.7% (4/240) rivaroxaban vs. 3.5% (8/230) enoxaparin/VKA in subjects treated with NSAIDs and 1.0% (22/2172) rivaroxaban vs. 2.0% (44/2175) enoxaparin/VKA in subjects not treated with NSAIDs had a major bleeding event.

Treatment with CYP3A4 inhibitors at baseline: 1.3% (2/153) rivaroxaban vs. 4.8% (8/165) enoxaparin/VKA in subjects treated with CYP3A4 inhibitors and 1.1% (24/2259) rivaroxaban vs. 2.0% (44/2240) enoxaparin/VKA in subjects not treated with CYP3A4 inhibitors had a major bleeding event.

Thus, major bleeding events were consistently lower in these groups on treatment with rivaroxaban than on treatment with enoxaparin/VKA, however given the limited number of subjects in each co–medication group no final interpretation of the data can be drawn from this exploratory analyses.

In summary, for the following co-medications, no firm conclusions can be drawn due to the low number of subjects having received the respective co-medication at baseline: clopidogrel/ ticlopidine (31 subjects in the rivaroxaban treatment group and 34 in the enoxaparin/VKA treatment group); strong CYP3A4 inhibitors: 25 subjects in the rivaroxaban treatment group and 29 in the enoxaparin/VKA treatment group), and P-gp inhibitors (62 subjects in the rivaroxaban treatment group and 59 in the enoxaparin/VKA treatment group).

The CHMP agreed with the MAH that there are no indications that the combination of these medicines with rivaroxaban would increase bleeding rates to a larger extent than the combination with enoxa/VKA.

1.3.2.7. Discontinuation due to AES

Adverse events leading to discontinuation of study drug

The incidence rate of AEs resulting in permanent discontinuation of study drug was higher in the rivaroxaban group (5.1% in the rivaroxaban treatment group and 4.1% in the enoxaparin/VKA treatment group)

Table 23 Summary of the most frequent adverse events resulting in permanent discontinuation of study drug (at least 0.5% in a SOC in any treatment group) by preferred term - safety population of study 11702 PE

MedDRA system organ class Preferred term (primary term)	Rivaroxaban 20 mg o.d. [a] N=2412 (100%)	Enox/VKA N=2405 (100%)
ANY EVENT	123 (5.1%)	99 (4.1%)
Blood and lymphatic system disorders		
Anemia	6 (0.2%)	2 (<0.1%)
Gastrointestinal disorders		
Rectal hemorrhage	4 (0.2%)	2 (<0.1%)
Nervous system disorders		
Ischaemic stroke [b]	6 (0.2%)	0
Respiratory, thoracic and mediastinal disorders		
Pleural effusion	0	4 (0.2%)
Skin and subcutaneous tissue disorders		
Rash	4 (0.2%)	1 (0.1%)

The incidence of AEs leading to hospitalization or prolonged hospitalization was in the range of 17% in both treatment groups (17.6% on rivaroxaban vs. 17.9% on enoxaparin/VKA).

1.3.2.8. Post marketing experience

The results of an interim analysis of the XAMOS study 13802 were assessed in relation to the application for DVT treatment. As of data base lock of this submission on 31 Dec 2011, no new data were available.

The experience with rivaroxaban from spontaneous reporting is generally consistent with the experience from clinical studies. No new specific safety concerns are judged to be derived from these data.

1.3.3. Discussion

When the DVT and PE studies are pooled, the incidences of adverse events are similar between the treatment groups.

The number of patients are considered sufficient by the CHMP for assessment of the safety profile taking also the experience from other indications into account.

With regards to serious adverse events, referring to previous studies in DVT and atrial fibrillation, there is a tendency for more mucosal bleedings in the rivaroxaban group (anaemia, rectal bleeding, uterine bleeding, epistaxis). For rivaroxaban-treated women aged < 55 years, a higher rate of uterine bleeding events (predominantly menstrual bleeding) was observed when compared to enoxaparin/VKA treatment. The majority of these events occurred during the initial treatment phase (i.e., in the first 30 days) and generally the subjects continued their treatment. In summary, the current information in the SmPC is adequate and remains unchanged.

The numerically slightly higher mortality in the rivaroxaban arm in the PE study was noted. However, there was no indication that this slight imbalance is related to the different anticoagulant regimens when looking at the narratives and the reported causes for death. Further discussion within this procedure, the CHMP considered this not to be of concern for the proposed indication.

A higher incidence of withdrawals due to adverse events was noted in the rivaroxaban group, but there are no clear differences in the patterns of reasons for these withdrawals between the study groups. Therefore, it was not considered to be of concern by the CHMP.

With regards to bleeding, the bleeding rates by subgroups were consistently lower in the rivaroxaban group. The lower overall incidences of major bleedings and of intracranial and retroperitoneal bleedings in the rivaroxaban groups may represent an important clinical advantage.

1.3.4. Conclusions on clinical safety

The safety database for acute treatment and secondary prophylaxis of VTE contains over 4000 patients included in the phase II and III studies. Thus the experience should be sufficient to capture common adverse events and to characterise bleeding risks in the target population. The reported incidence of major or clinically relevant bleedings was not increased as compared to enoxaparin/VKA treatment. As noted earlier the bleeding pattern seems to differ from what was seen during VKA treatment with a higher incidence of uterine and GI bleedings but with a lower incidence of intracranial bleedings. This has been extensively discussed in previous applications and may be related to the different mechanisms of action.

There are no indications that treatment with rivaroxaban would be associated with severe hepatic adverse events thrombocytopenia or pancreatic adverse reactions in the proposed new indication. The post-marketing experience from the approved indications has so far not revealed any safety concerns resulting in regulatory actions.

1.4. PSUR cycle

This new indication does not require a need to change the PSUR cycle.

1.5. Risk management plan

The MAH submitted an updated Risk Management Plan within this variation procedure.

The update of the EU-RMP has been performed to support the submission for the new proposed indication: treatment of pulmonary embolism (PE) and prevention of recurrent deep vein thrombosis (DVT) and PE in adults. The RMP was subsequently updated during the procedure upon CHMP request.

The data presented didn't reveal any new important safety issues that require an update of the Safety Specifications.

The already proposed drug utilisation studies have been amended to include the PE indication, which is agreed. However, it seems acceptable to also include PE treatment in the modified PEM (prescription event monitoring) and SCEM (specialist cohort event monitoring) epidemiological studies, to provide further safety information in this indication as proposed by the MAH.

No new risk minimisation activities in addition to those already being performed were requested by the CHMP. However, the CHMP requested the MAH to insert the Patient Alert Card into the labelling to better ensure that appropriate information is provided to all patients treated with Xarelto.

The prescriber guide (assessed in earlier RMPs) has been updated, to include PE treatment, which is acceptable.

Table 24 Summary of the risk management plan

Safety concern	Agreed pharmacovigilance activities (routine and additional)	Agreed risk minimization activities (routine and additional)
Important identified risks		

Haemorrhage	Routine pharmacovigilance activities Additional information from clinical trials Drug utilization and specific outcome studies Modified Prescription Event Monitoring Study Specialist Cohort Event Monitoring Study Post-marketing non-interventional cohort studies (XAMOS /13802, XALIA/15915, XANTUS/15914) Prescriber/patient surveys will be performed in order to measure effectiveness of additional risk minimization activities	Contraindication in SmPC section 4.3 "*Contraindication*" Warning in SmPC section 4.4 "*Special warnings and precautions for use*" Warning in SmPC section 4.5 "*Interaction with other medicinal products and other forms of interactions*" Cyp 3A4 and P-gp inhibitors Anticoagulants NSAIDS/platelet aggregation inhibitor Warfarin Haemorrhage is listed in SmPC section 4.8 "*Undesirable effect*" Additional Risk Minimisation Activities for DVT-T, PE-T, SPAF and ACS Prescriber Guide Patient Alert Card
Important potential risks		
Embryo-fetal toxicity	Routine pharmacovigilance activities Drug utilization database studies Drug utilization and specific outcome studies Modified Prescription Event Monitoring Study Specialist Cohort Event Monitoring Study Post-marketing non-interventional cohort studies (XALIA/15915, XANTUS/15914)	SmPC section 4.3 "*Contraindication*" SmPC section 4.6 "*Fertility, pregnancy, and breast feeding*"
Important missing information		
Patients undergoing major orthopaedic surgery other than elective hip or knee replacement surgery	Routine pharmacovigilance activities Drug utilization database studies	SmPC (10 mg) section 4.1 "*Therapeutic indications*" and section 4.4. "*Special warnings and precautions for use*"
Patients with severe renal impairment (CrCl < 30 mL/min	Routine pharmacovigilance activities Drug utilization and specific outcome studies Modified Prescription Event Monitoring Study Specialist Cohort Event Monitoring Study Post-marketing non-interventional cohort studies (XAMOS/13802, XALIA/15915, XANTUS/15914)	SmPC section 4.2 "*Posology and method of administration*" (Renal impairment) and section 4.4 "*Special warnings and precaution for use*" (Renal impairment)
Remedial procoagulant therapy for excessive haemorrhage	Routine pharmacovigilance activities Additional information from clinical trials Post-marketing non-interventional cohort studies (XAMOS/13802, XALIA/15915, XANTUS/15914)	SmPC section 4.9 "*Overdose*"
Patients receiving systemic treatment with Cyp3A4 and P-gp inhibitors other than azole antimycotics (e.g. ketoconazole) and HOV-protease inhibitors (e.g. ritonavir)	Routine pharmacovigilance activities Drug utilization database studies Drug utilization and specific outcome studies Modified Prescription Event Monitoring Study Specialist Cohort Event Monitoring Study Post-marketing non-interventional cohort studies (XAMOS /13802, XALIA/15915, XANTUS/15914)	SmPC section 4.5 "*Interaction with other medicinal products and other forms of interaction*"
Pregnant or breast-feeding women	Routine pharmacovigilance activities Drug utilization database studies Drug utilization and specific outcome studies Modified Prescription Event Monitoring Study Specialist Cohort Event Monitoring Study Post-marketing non-interventional cohort studies (XALIA/15915, XANTUS/15914)	SmPC section 4.3 "*Contraindication*" SmPC section 4.6 "*Fertility, pregnancy and breast feeding*"
Patients with AF and prosthetic valve	Routine pharmacovigilance activities	SmPC (15/20 mg) section 4.4 "Special warnings and precaution for use" (Patients

		with prosthetic valves)
Long-term therapy for treatment of DVT, PE and SPAF in real-life setting	Routine pharmacovigilance activities Drug utilization and specific outcome studies Modified Prescription Event Monitoring Study Specialist Cohort Event Monitoring Study For DVT-T and SPAF: Post-marketing non-interventional cohort studies (XALIA/15915, XANTUS/15914)	All safety concerns mentioned in this chapter which may occur during long-term therapy in a real-life setting for treatment of DVT, PE and SPAF indications are addressed in the SmPC in the relevant sections
Patients with significant liver diseases (severe hepatic impairment/Child Pugh C)	Routine pharmacovigilance activities Drug utilization and specific outcome studies Modified Prescription Event Monitoring Study Specialist Cohort Event Monitoring Study For DVT-T and SPAF: Post-marketing non-interventional cohort studies (XALIA/15915, XANTUS/15914)	Section 4.2 Posology and method of administration "Hepatic impairment" Section 4.3 "*Contraindication*"
Patients < 18 years	Routine pharmacovigilance activities Additional information from clinical trials (For 'Treatment of thromboembolic events': PIP EMEA-000430-PIP01-08-M03) Drug utilization and specific outcome studies Modified Prescription Event Monitoring Study Specialist Cohort Event Monitoring Study	SmPC section 4.2 "*Posology and method of administration*" (Paediatric population)

The CHMP, having considered the data submitted, was of the opinion that no new pharmacovigilance activities in addition to those already being performed were needed to monitor the safety of the product.

No additional risk minimisation activities were required beyond those already being performed were requested by the CHMP.

1.6. Changes to the Product Information

During the procedure, the CHMP requested further amendments to the initial PI submitted by the MAH.

Update of sections 4.1, 4.2, 4.3, 4.4, 4.7, 4.8 and 5.1 of the SmPC for the 15 mg and 20 mg strengths are introduced and discussed in the scientific part. The Package Leaflet and Labelling are updated accordingly.

The summary of changes introduced is as follows. For the complete changes introduced please refer to the PI provided in attachment of this report.

The new indication, combined with the existing DVT indication, is the following:

Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults. (See section 4.4 for haemodynamically unstable PE patients.)

The posology section is amended to provide information relative to dosage in PE and amendment for moderate renal impairment is introduced for both PE and DVT treatments.

Upon request of the CHMP, the information related to bleeding was updated in section 4.3 and 4.4 to provide more detailed information and harmonise with other anticoagulants of the same class.

A warning for haemodynamically unstable PE patients or patients who require thrombolysis or pulmonary embolectomy is introduced in section 4.4.

Section 4.8 was updated with the additional safety data from clinical trials and subsequent change in section 4.7 is introduced.

Update of section 5.1 with data provided from the clinical trials previously described.

In addition during the procedure, the CHMP requested the MAH to insert the Patient Alert Card into the labelling to better ensure that appropriate information is provided to all patients treated with Xarelto. The content of the Patient Alert Card was previously agreed and handled at national level.

Following the introduction of the new indication, the annex II has been amended, and reference to the Patient alert Card is introduced as now part of the labelling.

In conclusion, in this variation amendments to the Update of Summary of Product Characteristics, Annex II, Labelling and Package Leaflet have been introduced.

2. Benefit-Risk Balance

Benefits

Beneficial effects

This application is supported by one pivotal open-label non-inferiority study (study 11702), which was well designed and well performed. The study population was considered sufficiently representative of the European target PE population with regards to demographic characteristics, concomitant diseases and VTE risk factors. The endpoints are in line with the CHMP recommendations regarding pulmonary embolism. The methodology used in the pivotal study was considered acceptable. Measures were undertaken to reduce the potential for bias, all predefined efficacy and safety end-points were adjudicated centrally and the patients were followed on regular intervals with instructions to the investigators to evaluate key symptoms of possible outcome events. The incidence rate of the primary efficacy outcome (ITT population) until the end of intended treatment was 2.1% (50/2419) in the rivaroxaban group and 1.8% (44/2413) in the enoxaparin/VKA group yielding a hazard ratio of 1.123 (95% CI: 0.749-1.684) in the ITT population. The results were consistent with per protocol analyses and the secondary efficacy end-points supported the primary outcome. Consistency in the results was also obtained in important subgroups such as different age, gender, risk factors etc.

The claimed non-inferiority as compared to enoxaparin/VKA treatment is supported by favourable results of the DVT study which had an almost identical design and where rivaroxaban was convincingly demonstrated to be non-inferior with a hazard ratio of 0.680 (95% CI: 0.443-1.042). This is acceptable as DVT and PE can be seen as different clinical manifestations of the same underlying disease, managed traditionally in the same way for the use of anticoagulant therapy.

The supportive study (study 11899) comparing rivaroxaban with placebo in secondary VTE prevention in patients that had either rivaroxaban or VKA was designed as a double blind study. It provided convincing evidence in qualitative terms of the efficacy of rivaroxaban in the secondary prevention after acute VTE. The same composite efficacy end-point as in the pivotal study 11702 was used. Superior efficacy of rivaroxaban therapy over placebo was demonstrated with a hazard ratio of 0.185 (95% CI 0.087-0.393, $p < 0.0001$) or a 81% relative risk reduction.

Uncertainty in the knowledge about the beneficial effects

The predefined delta of <2.0 for the NI may appear liberal in this disease where VTE recurrences can be life-threatening otherwise with major clinical consequences with a need for long-term anticoagulant treatment for the patient with subsequent risk for post-thrombotic syndromes and chronic pulmonary hypertension. It should however be highlighted that the absolute recurrence rates were low in the study and that enoxaparin/warfarin treatment is very effective in this setting. Furthermore, it should

be recognised that the statistical considerations resulted in one of the largest prospective controlled PE studies ever performed.

Numerically a higher incidence of the primary efficacy end-point was noted in the rivaroxaban group and the 95% CI indicates an increased relative risk for recurrences of approximately 70% as compared with conventional treatment which would be potentially difficult to accept. This was extensively discussed and it was finally agreed that the absolute numbers of recurrences were low and the results together with external support showed that rivaroxaban is effective in this setting. Much higher rates would be expected if it would be ethically possible to follow a placebo treated group of patients.

Nevertheless, even if the point estimate of the difference in recurrence rate between the study groups was low, with 0.23 % higher rate in the rivaroxaban arm, it can be noted that the upper 95% CI was 1.02 % during median treatment duration of 8.6 months. Such an increase would appear potentially difficult to accept if external support for efficacy was lacking and if no better safety profile were shown. External support was provided by the results in the DVT study and some advantages with regards to safety are further discussed below.

Additionally, it has to be taken into account that, the incidence rate of the primary efficacy outcome was the same (2.1%) for rivaroxaban in both studies (11702 PE and study 11702 DVT), but the incidence rate of the primary efficacy outcome in the enoxaparin/VKA group was significantly lower in study 11702 PE (1.8%) than in study 11702 DVT (3.0%). The relative low event rate in the Enoxaparin/VKA arm in this event driven study might have also contributed to the difficulties in concluding on non-inferiority in this event-driven study.

Uncertainties on efficacy are related to fact that the application is supported on only one pivotal open-labelled non-inferiority study. However, the study was well performed and the results are considered to be sufficiently robust including adequate blinded central adjudication.

PE patients have a somewhat more severe prognosis and it can be assumed that on average the thrombotic burden in symptomatic PE is higher than in DVT. However, the different manifestations of VTE are treated similarly and the results of the DVT study provided important additional information for the current applied indication. From an efficacy perspective the provided data for long-term treatment is judged to be sufficient.

Risks

Unfavourable effects

The most important observed adverse reactions are bleedings. The incidence of major bleedings was numerically lower in the rivaroxaban treated group as compared with the enoxaparin/VKA treated. Importantly, the number of intracranial bleeding was lower than in the enoxaparin/warfarin group. This finding was consistent with what has been observed for rivaroxaban and other new anticoagulants.

The bleeding pattern seemed to differ to some extent from what is seen during VKA treatment with a higher incidence of uterine and GI bleeding. However, this is adequately addressed in the product information.

There are no indications from the clinical studies performed in the proposed new indication that treatment with rivaroxaban would be associated with severe hepatic adverse events or induce thrombocytopenia or pancreatic adverse reactions.

The bleeding risks are judged to be adequately addressed in the SmPC. In addition, harmonisation with other anticoagulants is also introduced with more detailed information introduced in the Product

information. An unfavourable aspect with rivaroxaban treatment is the lack of a specific antidote. The MAH has an on-going development programme for an antidote on which CHMP advice has been given.

Finally, it needs to be clarified that Xarelto should not be used in haemodynamically unstable PE patients or patients who require thrombolysis or pulmonary embolectomy. A clear warning has been implemented and reference is also introduced in the indication section.

Uncertainty in the knowledge about the unfavourable effects

Haemoglobin or haematocrit levels were not monitored in the phase III trial after week 4. However, they were monitored more intensively in the phase II study TIMI-46 and no major differences were seen between the treatment groups.

The overall the safety database from long-term treatment is still limited. Many of the patients treated for secondary prophylaxis of VTE can be expected to be treated for many years. This is adequately addressed in the updated risk management plan in particular with regards to bleeding risks and unexpected adverse events during prolonged treatment.

Benefit risk balance

Importance of favourable and unfavourable effects

One could question whether the open labelled comparative non inferiority study resulting in a numerically slightly higher incidence of recurrences in the rivaroxaban arm and with a CI indicating a possibly 70% relative increase of such events provided sufficient evidence of efficacy. However, the MAH has demonstrated that the difference of the observed absolute risk between study arms was low (0.25%) with an upper 95% CI of 1.02%. There was also important additional data from the DVT study, where a clearly lower incidence of recurrences in comparison with conventional treatment was observed. Furthermore, the potential safety advantages of an oral anticoagulant and the convenience with the proposed regimen are important.

The safety profile of rivaroxaban in this setting compared with VKA treatment indicated a favourable decreased risk for major bleedings, intracranial bleedings and possibly bleedings into critical organs. This outweighs the observed increased bleeding risk for uterine, GI bleedings and anaemia provided that the patients are adequately clinically monitored.

Discussion on the benefit-risk balance

The new indication for treatment of pulmonary embolism and prevention of recurrent pulmonary embolism is based on only one pivotal well designed study showing non-inferiority as compared to enoxaparin/VKA treatment. However, these data were also supported by favourable results of the DVT study with almost identical design and where rivaroxaban was convincingly demonstrated to be non-inferior with a hazard ratio of 0.680 (95% CI: 0.443-1.042). This was considered acceptable as DVT and PE can be seen as different clinical manifestations of the same underlying disease, managed in the same way with regards to the use of anticoagulant therapy.

The only available major alternative for oral long term secondary prophylaxis after PE today is VKA treatment from which experience exists since several decades. VKA treatment requires continuous monitoring and careful consideration of numerous possibilities for interaction with other drugs and food. The quality of VKA treatment is varying between centres. Lower quality has been associated with increased risks for bleeding and VTE recurrences. A simpler and more predictable alternative for oral

use that would not need such intense monitoring is therefore a valuable alternative, especially for patients where VKA treatment is not functioning well.

VKA therapy, if well performed, is very effective in preventing recurrences after an acute PE. From a pragmatic point of view recurrences hardly occur if INR values are kept within the therapeutic range unless there is an underlying malignancy.

The safety profile of rivaroxaban indicated a favourable decreased risk for major bleedings, intracranial bleedings and possibly bleedings into critical organs in comparison with VKA therapy. This outweighs the observed increased bleeding risk for uterine, GI bleedings and anaemia observed provided that the patients are adequately clinically monitored.

In conclusion, the CHMP considered that overall Benefit risk of rivaroxaban is positive for the treatment of pulmonary embolism and prevention of recurrent pulmonary embolism in adult patients.

3. Recommendations

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation(s) to the terms of the Marketing Authorisation, concerning the following changes:

Variation accepted		**Type**
C.I.6.a	Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	II

Update of sections 4.1, 4.2, 4.3, 4.4, 4.7, 4.8 and 5.1 of the SmPC for the 15 mg and 20 mg strengths in order to add a new indication for the treatment of pulmonary embolism (PE) and prevention of recurrent pulmonary embolism in adults.

The Package Leaflet and Labelling are updated accordingly and the Patient Alert Card is inserted now as part of the labelling.

The requested variation proposed amendments to the Update of Summary of Product Characteristics, Annex II, Labelling and Package Leaflet.