



Australian Government

Department of Health

Therapeutic Goods Administration

AusPAR Attachment 2

Extract from the Clinical Evaluation Report for Rivaroxaban

Proprietary Product Name: Xarelto

Sponsor: Bayer Australia Ltd

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About the Extract from the Clinical Evaluation Report

- This document provides a more detailed evaluation of the clinical findings, extracted from the Clinical Evaluation Report (CER) prepared by the TGA. This extract does not include sections from the CER regarding product documentation or post market activities.
- The words [Information redacted], where they appear in this document, indicate that confidential information has been deleted.
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Contents

List of abbreviations	5
1. Introduction	8
2. Clinical rationale	8
3. Contents of the clinical dossier	8
3.1. Scope of the clinical dossier	8
3.2. Paediatric data	10
3.3. Good clinical practice	11
4. Pharmacokinetics	11
4.1. Studies providing pharmacokinetic data	11
4.2. Summary of pharmacokinetics	12
5. Pharmacodynamics	12
6. Dosage selection for the pivotal studies	13
7. Clinical efficacy	13
7.1. For the proposed indication for treatment of PE	13
8. Clinical safety	36
8.1. Studies providing evaluable safety data	36
8.2. Patient exposure	40
8.3. Adverse events	42
8.4. Laboratory tests	46
8.5. Post-marketing experience	47
8.6. Other safety issues	47
8.7. Evaluator's overall conclusions on clinical safety	53
9. First round benefit-risk assessment	56
9.1. First round assessment of benefits	56
9.2. First round assessment of risks	57
9.3. First round assessment of benefit-risk balance	58
10. First round recommendation regarding authorisation	58
11. Clinical questions	58
11.1. Pharmacokinetics	58
11.2. Efficacy	59
12. Second round evaluation of clinical data submitted in response to questions	59
13. Second round benefit-risk assessment	62
13.1. Second round assessment of benefits	62

13.2.	Second round assessment of risks _____	62
13.3.	Second round assessment of benefit-risk balance _____	62
14.	Second round recommendation regarding authorisation ____	62
15.	References _____	62

List of abbreviations

Abbreviation	Meaning
AE	Adverse Event
aPTT	Activated partial thromboplastin time
AUC	Area under the plasma concentration versus time curve from zero to infinity after single (first) dose
AUCnorm	Area under the curve divided by dose per kg body weight
AUC(0-tlast)	AUC from time 0 to the last data point
AUC(tlast-∞)	AUC from the last data point to infinity
AUC(0-24)ss	AUC from time 0 to 24 hours at steady state
b.i.d.	Bis in die, 2 times daily
CI	Confidence interval
CIAC	Central independent adjudication committee
CMI	Consumer Medicines Information
Cmax	Maximum drug concentration in plasma after single dose administration
Cmax,norm	Maximum drug concentration in plasma after single dose administration divided by dose (mg) per kg body weight
Cmax,ss	Maximum drug concentration in plasma at steady state
Cmin,ss	Minimum drug concentration in plasma at steady state
CSR	Clinical Study Report
CYP 3A4	Cytochrome P450 3A4
DVT	Deep vein thrombosis
e.g.	Exempli gratia; for example
EMA	European Medicines Agency
EU	European Union

Abbreviation	Meaning
FDA	the United States Food and Drug Administration
FXa	Activated Factor X
GCP	Good Clinical Practice
i.e.	Id est; that is
INR	International normalised ratio
Kg	Kilogram
L	Litre
LMWH	Low molecular weight heparin
mg	Milligram
mL	Millilitre
Mm	Millimetre
mM	Millimolar
od	Omne in die, once daily
PE	Pulmonary embolism
PI	Product Information
PT	Prothrombin Time
q.d	Quaque die, once daily
SAE	Serious adverse event
SD	Standard Deviation
t _{1/2}	Half-life associated with the terminal slope
TEAE	Treatment emergent adverse event
TESAE	Treatment emergent serious adverse event
TGA	Therapeutic Goods Administration
t _{max}	Time to reach maximum drug concentration in plasma after single (first) dose; time of maximum effect

Abbreviation	Meaning
US	United States of America
VKA	Vitamin K antagonist
VTE	Venous thromboembolism
≥	at or greater than
≤	at or less than
>	greater than
<	less than

1. Introduction

This is a submission to extend the indications of Xarelto.

Rivaroxaban is a highly selective, competitive, direct inhibitor of Factor Xa (FXa). FXa catalyses the conversion of prothrombin to thrombin. Inhibition of FXa blocks the generation of thrombin, and thus reduces thrombin-mediated activation of coagulation and platelets.

The currently approved indications for rivaroxaban in Australia are:

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

The submission is an application to extend the indications of rivaroxaban to include the treatment of pulmonary embolism, with the following proposed indications (proposed addition in bold font):

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

2. Clinical rationale

Standard treatment for acute DVT or PE usually involves initial use of parenteral anticoagulants such as low molecular weight heparin (LMWH; e.g. enoxaparin), unfractionated heparin (UFH) or fondaparinux. Per oral administration of vitamin K antagonists (VKA) such as warfarin is then started in overlap with the parenteral anticoagulants. Parenteral anticoagulants may be discontinued when the international normalised ratio (INR) is equal or above 2.0 for two or more measurements. Treatment with VKAs requires ongoing coagulation laboratory monitoring and dose adjustments to keep the INR in the optimal therapeutic window of 2.0 to 3.0.

The sponsor had stated that rivaroxaban was developed as an alternative anticoagulant to the parenteral anticoagulant/VKA treatment regimen, as it is an oral, direct-acting antithrombotic agent with a predictable dose-response relationship, and can be administered without the need for laboratory monitoring of its anti-coagulant effect and subsequent dose-adjustments.

3. Contents of the clinical dossier

3.1. Scope of the clinical dossier

The clinical dossier contains the clinical study report (CSR) of a pivotal study relating to the proposed extension of indications, 12 meta-analysis study reports, 1 technical report, as well as

several study reports unrelated to the proposed extension of indication (1 biopharmaceutics food effect study, 3 population pharmacokinetic/pharmacodynamic [PK/PD] studies).

The submission contains the following clinical information:

Module 5

- 1 biopharmaceutics study (Study 15921)
- 3 population PK/PD analyses (Studies 13812 and 15539 submitted in Module 5.3.3 “Human PK study reports”; Study 13238 submitted in Module 5.3.5 “Human efficacy/safety study reports”)
- 1 pivotal efficacy/safety study (study Einstein-PE)
- 12 meta-analysis study reports and 1 technical report

The biopharmaceutics study evaluates the effect of a Japanese diet on the bioavailability of rivaroxaban in healthy Japanese male subjects. The population PK/PD studies were conducted to characterise the PK and evaluate the PK/PD relationship in patients co-medicated with strong CYP3A4 inducers, and to provide PK simulations for patients with severe renal impairment or are co-medicated with strong CYP3A4 inhibitors or inducers. One pivotal efficacy/safety study, study Einstein-PE, was submitted to support the application for extension of indication. The 13 meta-analysis and technical reports (submitted in Module 5.3.5 under the heading of efficacy and safety study reports) evaluated parameters as shown below:

Studies involved	Safety only		Efficacy only	Safety and efficacy		PK/PD
Phase I	PH36686 Pooled analysis of safety of rivaroxaban in subjects included in Phase I clinical trials					PH36685 Pooled PK/PD analysis of rivaroxaban in subjects included in Phase I clinical trials
^Einstein-PE only	PH36709 Additional safety report for study Einstein-PE	PH36707 Analysis of multiple bleeding events in study Einstein-PE		PH36705 Analysis of the effect of rivaroxaban on bleedings and efficacy with selected co-medication categories in study Einstein-PE	PH36706* Exploratory analysis of prothrombin time (PT) in subjects treated with rivaroxaban in Einstein-PE (relationship of PT with efficacy and safety outcomes)	

Studies involved	Safety only	Efficacy only	Safety and efficacy	PK/PD	
^Einstein-PE and Einstein-DVT	PH36710 Additional safety report for the pool of studies Einstein-DVT and Einstein-PE	PH36708 Analysis of multiple bleeding events in pool of studies Einstein-DVT and Einstein-PE	PH36749 Satisfaction-with-treatment Questionnaire analysis of the Einstein-DVT and Einstein-PE studies	PH36718 Analysis of the effect of rivaroxaban on bleedings and efficacy with selected co-medication categories in pool of studies Einstein-DVT and Einstein-PE	
				PH36711 Exploratory analysis of prothrombin time (PT) in subjects treated with rivaroxaban in pool of studies Einstein-DVT and Einstein-PE (relationship of PT with efficacy and safety outcomes)	
			PH 36746 Meta-Analysis of the Einstein-DVT and Einstein-PE studies		
^Einstein-Extension	PH36715 Integrated analysis of the safety profile of the rollover subjects from Einstein-DVT or PE to Extension				
Location of evaluation in this evaluation report	Studies PH36686, PH36709, PH36710, PH36707, PH36708 and PH36715 will be evaluated in the Safety Section of this evaluation report.		Study PH36749 will be evaluated in the Efficacy Section of this evaluation report.	Studies PH36705, PH36718, PH36706, PH36711 and PH 36746 will be evaluated in both the Efficacy and Safety Sections respectively of this evaluation report.	Study PH36685 will be evaluated in the PK Section of this evaluation report.

* labelled as "technical report" in Module 5.2 (tabular listing of studies in Module 5)

^ The rivaroxaban Phase III clinical development program consisted of 3 studies: the Einstein-DVT Study and Einstein-PE Study, which evaluated the treatment and prevention of DVT and of PE, respectively, and the Einstein Extension Study, which evaluated the benefit of continued treatment in subjects who had reached "equipoise" (i.e. a state of clinical uncertainty) about the need for continued anticoagulation after the completion of initial anticoagulation treatment.

Module 1

- Application letter, application form, draft Australian PI and CMI

Module 2

- Clinical Overview, Summary of Clinical Efficacy, Summary of Clinical Safety and literature references.

3.2. Paediatric data

The submission does not include paediatric data.

The sponsor had stated that a paediatric development program for rivaroxaban had been agreed with EMA for the conditions "Prevention of thromboembolic events" and "treatment of thromboembolic events", and comprises the development of an oral suspension formulation as well as of a number of non-clinical and clinical studies. These are aimed to support the use of

rivaroxaban in the indication "treatment (secondary prevention) of venous thromboembolism" in children under the age of 18. The sponsor had stated that as the use of rivaroxaban in paediatric population (children under the age of 18) is not the subject of this application, full details of the paediatric development program are not provided in this submission.

3.3. Good clinical practice

The clinical studies reviewed in this evaluation were in compliance with CPMP/ICH/135/95 Note for Guidance on Good Clinical Practice.

4. Pharmacokinetics

4.1. Studies providing pharmacokinetic data

One biopharmaceutics study (Study 15921) and 3 population PK/PD studies (Studies 13238, 13812 and 15539) were submitted. These studies do not provide any data relevant to the evaluation of this submission for the extension of indication for rivaroxaban. The sponsor is not proposing to make any changes to the recommended dosing regimen in patients with severe renal impairment or who are co-medicated with strong CYP3A4 inhibitors or inducers. The sponsor is also not proposing to include any of the results from these studies in the proposed PI, or make any changes to the PK and PD sections of the currently-approved PI.

In addition, a study report PH 36685 was submitted in Module 5.3.5 under the heading of efficacy and safety study reports, but was an exploratory pooled PK/PD analysis of subjects in 64 Phase I studies with no efficacy or safety endpoints. This report consists of a listing of tables and figures, and the sponsor has not summarised or interpreted the results. The sponsor had stated that this study analysis was exploratory, that no PK and PD conclusions were intended to be drawn or presented in this report, and that after medical review of the data provided in this report, rivaroxaban PK and PD results and conclusions drawn from these results will be reported in a separate report. The sponsor is also not proposing to make any changes to the PK and PD sections of the currently-approved PI based on this study report.

Table 1. Submitted pharmacokinetic studies.

PK topic	Subtopic	Study ID	Primary aim of study
PK in healthy adults	Food effect	15921	To investigate the effect of a Japanese meal on the bioavailability of rivaroxaban 15mg tablets in healthy Japanese male subjects
Population PK analyses	Target population	13238 (Einstein-CYP cohort study)	To characterise the population PK/PD of an adapted rivaroxaban dosing regimen in subjects with acute proximal DVT or acute PE and concomitant use of a strong CYP3A4 inducer
		13812	To define structural PK and PK/PD models for rivaroxaban in the Einstein-CYP cohort study by using rivaroxaban plasma concentrations and prothrombin time

PK topic	Subtopic	Study ID	Primary aim of study
	Other	15539	Simulations to describe the expected exposure of various modified dosing regimens in special populations: <ul style="list-style-type: none"> · severe renal impairment (CrCl 15-30 mL/min) · concomitant medication with a strong inhibitor of both CYP3A4 and P-gp (such as ketoconazole) · concomitant medication with a strong CYP3A4/P-gp inducer (such as rifampicin)
	Healthy Subjects	PH36685	Pooled analysis of PK and PD of rivaroxaban in subjects in Phase I clinical trials

DVT: Deep vein thrombosis; PE: Pulmonary embolism; CrCl: creatinine clearance

4.2. Summary of pharmacokinetics

4.2.1. Influence of food

Study 15921 which evaluated the effect of Japanese meal on safety, tolerability and PK of 15 mg rivaroxaban given orally to Japanese healthy male subjects showed that the AUC and C_{max} of rivaroxaban after single administration of 15mg rivaroxaban were similar in the fasted state and the fed state. However, t_{max} for rivaroxaban administered with the Japanese meal was prolonged by 1.5 hours in comparison to t_{max} in the fasted state (4.0 hours compared to 2.5 hours). The elimination of rivaroxaban from plasma was similar between the fasted state and the fed state.

4.2.2. Pharmacokinetic interactions

Study 13238 (Study Einstein-CYP) was conducted to characterise the population PK/PD of an adapted rivaroxaban dosing regimen (rivaroxaban 30 mg b.i.d. for 3 weeks followed by 20 mg b.i.d.) in subjects with acute proximal DVT or acute PE and concomitant use of a strong CYP3A4 inducer, compared to the usual dose regimen of 15mg b.i.d. for 3 weeks followed by 20mg o.d. for subjects without concomitant use of a strong CYP3A4 inducer. Results showed that during initial treatment (30mg b.i.d.), the median rivaroxaban AUC(0-24)_{ss} in this study was approximately 36% lower than that of the pooled study results from subjects of the Phase II studies treated with the usual 15 mg b.i.d. / 20 mg o.d. dosing regimen. During extended treatment (20mg b.i.d.), the median rivaroxaban AUC(0-24)_{ss} in this study was approximately 15% lower than that of the pooled results from the Phase II studies. The median C_{max,ss} was also lower in this study (approximately 27% and 35% lower during initial and extended treatments, respectively).

5. Pharmacodynamics

Not applicable.

6. Dosage selection for the pivotal studies

The rivaroxaban dose regimen used in the pivotal study (Einstein-PE) is the same as the currently registered dose regimen of rivaroxaban for the treatment of DVT and the prevention of recurrent DVT and PE. The sponsor had stated in the CSR of study Einstein-PE that previous phase II studies (studies 11223 and 11528, performed in subjects with acute symptomatic DVT for a treatment duration of 3 months) showed that 20 mg rivaroxaban total daily dose had been the lowest effective dose associated with a safety profile at least as good as a treatment regimen starting with LMWH followed by VKA. The sponsor stated that the combined analyses of both dose-finding studies had indicated that the optimal regimen consists of administration of rivaroxaban 15mg twice daily (b.i.d.) for an initial 3-week treatment phase followed by 20 mg once daily (o.d.) for the subsequent treatment period.

7. Clinical efficacy

7.1. For the proposed indication for treatment of PE

In this evaluation, the pivotal efficacy study to be evaluated is study Einstein-PE. Study PH36746, which is a pooled analysis of studies Einstein-PE and Einstein-DVT will be evaluated with regards to whether the results were consistent with those in study Einstein-PE. The other efficacy studies (PH36749, PH36705, PH36718, PH36706 and PH36711) were exploratory studies, and will be briefly summarised and evaluated with regards to whether the results are pertinent to the evaluator's recommendations for this submission.

7.1.1. Pivotal efficacy study

7.1.1.1. Study Einstein-PE (Study 11702-PE)

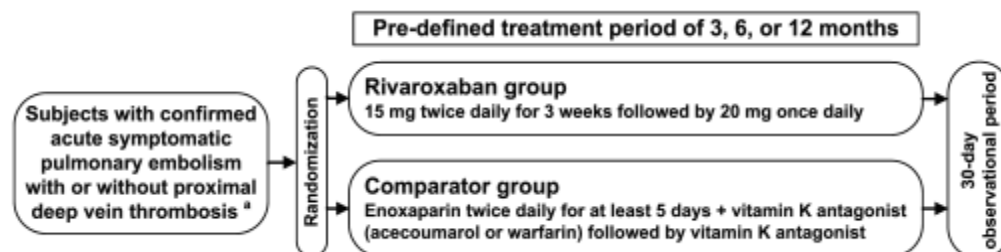
The rivaroxaban Phase III clinical development program consisted of 3 studies: the Einstein-DVT study and Einstein-PE study, which evaluated the treatment and prevention of DVT and of PE, respectively, and the Einstein Extension study, which evaluated the benefit of continued treatment in subjects who had reached "equipose" (i.e. a state of clinical uncertainty) about the need for continued anticoagulation after the completion of initial anticoagulation treatment. The Einstein-DVT study evaluated subjects with confirmed acute proximal symptomatic DVT without symptomatic PE, while the Einstein-PE study evaluated subjects with confirmed acute symptomatic PE with or without symptomatic DVT. The sponsor had stated that both Einstein-DVT and Einstein-PE studies were integrated into a single study protocol, as the subject groups were complementary and were recruited at the same centres, the essential study design features were identical, and both evaluations were supervised and guided by the same study committees. Due to differences in recruitment rates for the target populations, the Einstein-DVT study was completed earlier than the Einstein-PE study, and had been used in a previous submission to include new indication of rivaroxaban 15 mg and 20 mg for the treatment of DVT and for the prevention of recurrent DVT and PE, and this had been approved in April 2012. The current submission presents the Einstein-PE clinical study results to support the additional indication for treatment of PE.

7.1.1.1.1. Study design, objectives, locations and dates

The primary efficacy objective for the Einstein-PE study was to evaluate whether rivaroxaban is at least as effective as enoxaparin/vitamin K antagonist (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 events. The principal safety objective was the evaluation of major and clinically relevant non-major bleeding events.

This was a multi-centre¹, randomised, open-label, parallel-group, active-controlled, event-driven non-inferiority study with a treatment duration of 3, 6, or 12 months. The study start date was 29 March 2007 (first subject, first visit) and the study end date was 01 Dec 2011 (last subject, last visit).

Figure 1. Einstein-PE: Overview of study design.



A dose confirmation analysis was performed in the initial 400 subjects based on the combination of symptomatic recurrent VTE and asymptomatic deterioration at repeat lung imaging at 3 weeks. This will be described in greater detail under *Statistical methods*, below.

7.1.1.1.2. Inclusion and exclusion criteria

Study inclusion and exclusion criteria are presented in the dossier. Subjects in the study were male or female adults above country-specific legal age limit, who had confirmed acute symptomatic PE with or without symptomatic DVT². Subjects with creatinine clearance <30 mL/min, significant liver disease or alanine transaminase >3 times the upper limit of normal, life expectancy <3 months, or on concomitant use of strong CYP3A4 inhibitors (e.g. HIV protease inhibitors, systemic ketoconazole) or strong CYP3A4 inducers (e.g. rifampicin) were excluded. Subjects who had treatment with therapeutic dosages of LMWH/fondaparinux for more than 48 hours pre-randomisation, or more than a single dose of VKA prior to randomisation, were also excluded.

Comments: The inclusion and exclusion criteria aimed to recruit a study population of adult patients with confirmed acute symptomatic PE with or without symptomatic DVT. The selection of study population is consistent with the TGA-adopted EMA guidelines on the clinical investigation of medicinal products for the treatment of venous thromboembolic disease³, and is in keeping with the proposed indication.

The exclusion of concomitant use of strong CYP3A4 inhibitors and inducers is consistent with the known pharmacokinetics and drug interactions profile of rivaroxaban as described in the currently-approved Australian PI which states that the concomitant use of rivaroxaban with substances that strongly inhibit both CYP3A4 and P-gp (e.g. HIV protease inhibitor, ketoconazole) may lead to

¹ There were 263 centres in 38 countries: Andorra (1), Australia (23), Austria (6), Belgium (12), Brazil (2), Canada (4), China (15), Czech Republic (7), Denmark (1), Estonia (1), Finland (2), France (34), Germany (25), Hong Kong (2), Hungary (10), India (1), Indonesia (1), Ireland (1), Israel (10), Italy (13), Lithuania (2), Latvia (1), Malaysia (1), Netherlands (6), New Zealand (5), Norway (3), Philippines (1), Poland (7), Singapore (1), South Africa (10), South Korea (4), Spain (8), Sweden (5), Switzerland (6), Taiwan (3), Thailand (3), United Kingdom (3), United States (23)

² Subjects were potentially eligible if the diagnosis of PE was based on one of the following criteria: (i) A (new) intraluminal filling defect in segmental or more proximal branches on spiral computed tomography (sCT) scan (ii) A (new) intraluminal filling defect or an extension of an existing defect or a new sudden cut-off of vessels more than 2.5 mm in diameter on the pulmonary angiogram (iii) 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) (iv) Inconclusive sCT, pulmonary angiography, or lung scintigraphy with demonstration of DVT in the lower extremities by compression ultrasound (CUS) or venography

³ European Agency for the Evaluation of Medicinal Products. Notes for guidance on clinical investigation of medicinal products for treatment of venous thromboembolic disease. 1999.

reduced hepatic and renal clearance and hence may increase rivaroxaban plasma concentrations and possibly leading to an increased bleeding risk, while the concomitant use of rivaroxaban with strong CYP3A4 inducers may lead to reduced rivaroxaban plasma concentrations, and hence reduced efficacy.

The exclusion of subjects with creatinine clearance (CrCl) <30 mL/min is also consistent with the prescribing information in the currently-approved PI, where it is stated that rivaroxaban plasma levels may be significantly increased in patients with severe renal impairment (CrCl < 30 mL/min), which may lead to an increased bleeding risk, and that rivaroxaban 15 mg and 20 mg should not be used in patients with CrCl < 30 mL/min.

The diagnostic criteria for PE are in line with the TGA-adopted EMA guidelines on the clinical investigation of medicinal products for the treatment of venous thromboembolic disease, which recommends that diagnosis of PE by pulmonary angiography, spiral computed tomography scan, "high-probability" findings on ventilation/perfusion lung scan or symptoms indicative of PE with demonstrated DVT are considered acceptable.

7.1.1.1.3. Study treatments

Subjects were randomised to receive either rivaroxaban or enoxaparin/VKA. Subjects allocated to the rivaroxaban group received rivaroxaban per oral 15 mg twice daily (b.i.d.) for 3 weeks followed by rivaroxaban 20 mg once daily (o.d.) for a total treatment duration of 3, 6, or 12 months. Subjects allocated to the enoxaparin/VKA group received 1 mg/kg enoxaparin b.i.d. subcutaneously for at least 5 days in combination with VKA (warfarin or acenocoumarol; overlap 4 - 5 days), administered orally at individually titrated doses to achieve a target INR of 2.5 (range:2.0 - 3.0) for a total treatment duration of 3, 6, or 12 months. Subjects were continued with VKA only after the INR had been 2.0 for 2 consecutive measurements at least 24 hours apart. The 5-day minimum treatment period with enoxaparin could include the period up to 48 hours before randomisation if enoxaparin b.i.d. was used, and warfarin or acenocoumarol were to be started not later than 48 hours after randomisation.

The decision to treat a subject for 3, 6, or 12 months was at the investigator's discretion, based on his/her assessment of the period during which anticoagulant treatment was expected to have a potentially favourable risk-benefit ratio. This intended treatment duration had to be specified at randomisation, and subjects were stratified accordingly.

Comments: The rivaroxaban dose regimen used is the same as the currently registered dose regimen of rivaroxaban for the treatment of DVT and the prevention of recurrent DVT and PE and is appropriate. The comparator active control drug combination and regimen used is the currently accepted drug combination and dose regimen used in the clinical management of PE⁴.

7.1.1.1.4. Efficacy variables and outcomes

The primary efficacy outcome was symptomatic recurrent VTE (i.e. the composite of recurrent DVT or non-fatal or fatal PE). The secondary efficacy outcomes assessed in this study are outlined in Table 2 below.

⁴ Kearon C, Kahn SR, Agnelli G, *et al.* Antithrombotic therapy for venous thromboembolic disease: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines, 8th edn. *Chest* 2008;133:454–545S.

Table 2. Secondary efficacy outcomes and their components, Study Einstein-PE

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

A blinded central independent adjudication committee (CIAC) evaluated and adjudicated all suspected recurrent VTE, deaths, and all episodes of suspected bleeding and vascular events. The CIAC applied the definitions presented in Table 3 below to confirm a suspected episode of symptomatic recurrent DVT or PE. In the absence of objective testing⁵, 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. A major bleeding event was defined as overt bleeding which was associated with a fall in haemoglobin of 2 g/dL or more, led to a transfusion of 2 or more units of packed red blood cells or whole blood, occurred in a critical site (intracranial, intraspinal, intraocular, pericardial, intra-articular, intramuscular with compartment syndrome, retroperitoneal), or contributed to death.

Table 3. Definitions used by CIAC to confirm a suspected episode of symptomatic recurrent DVT or PE, Study Einstein-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 extremities by CUS or venography

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)

CUS: compression ultrasound; sCT: spiral computed tomography; VPLS: ventilation / perfusion lung scintigraphy

Comments: The TGA-adopted EMA guidelines on the clinical investigation of medicinal products for the treatment of venous thromboembolic disease recommended

⁵ Objective testing was defined as: (i) Laboratory test (D-dimer) in combination with a specific test for diagnosis of DVT or PE (ii) Ultrasound or venography for diagnosis of DVT (iii) Spiral CT, perfusion lung scan, ventilation lung scan, chest X-ray, pulmonary angiography and / or echocardiography for diagnosis of PE

that Phase III trials should primarily address clinical outcome in the form of recurrent, symptomatic VTE (non-fatal DVT and/or non-fatal PE), deaths and bleeding episodes. These guidelines recommend that the primary efficacy endpoint should be a composite of recurrent symptomatic non-fatal DVT/PE and mortality, and that 2 analyses should be performed: the combined incidence of recurrent DVT/PE and all deaths (considered most important in trials aiming to show superiority of the medicinal product under consideration), and the combined incidence of recurrent DVT/PE and deaths related to VTE (considered most important in trials aiming to document non-inferiority). The primary and secondary endpoints of this non-inferiority study are appropriate and consistent with these recommendations, as are the definitions of the endpoints used by the CIAC.

The use of a blinded CIAC to evaluate and adjudicate all suspected recurrent VTE, deaths, and all episodes of suspected bleeding and vascular events is also in line with the recommendations of the guidelines that all major endpoints should be adjudicated by a blinded clinical events committee.

7.1.1.1.5. *Randomisation and blinding methods*

Randomisation was done via an interactive voice response system (IVRS). Randomisation was stratified by country and intended treatment duration (3, 6, or 12 months). Study treatments were not blinded, but the CIAC that adjudicated the suspected clinical outcomes was blinded to treatment allocation.

7.1.1.1.6. *Analysis populations*

The statistical analysis plan defined 4 analysis populations. The intent-to-treat (ITT) population consisted of all randomised subjects and were analysed according to the randomised treatment groups. The ITT on treatment population also consisted of all randomised subjects who were analysed according to the randomised treatment groups, but was restricted to subjects who had received at least one dose of study treatment after randomisation. The valid-for-safety analysis population consisted of all randomised subjects who had received at least one dose of study treatment after randomisation, and were analysed according to the treatment they actually received. The per protocol (PP) population consisted of all randomised subjects without any major deviations from the protocol. These deviations included subjects in whom the presence of PE at baseline could not be confirmed by the CIAC, subjects who did not receive the appropriate treatment as allocated by IVRS or received no treatment at all, and subjects not treated adequately with the study treatment.⁶

All efficacy analyses were performed on the ITT population. Additional supportive analysis of the primary efficacy outcome was carried out based on the PP population.

Comments: The definitions of the analysis populations are in keeping with the TGA-adopted ICH E 9 Statistical Principles for Clinical Trials. Analysis of primary efficacy endpoints in both the ITT and PP analysis populations is appropriate. As this is a non-inferiority study, it needs to be considered that since subjects who have low compliance may be due to a lack of response to study treatment, using the ITT analysis population may bias towards demonstrating non-inferiority⁷. Hence additional analyses on the PP population set are appropriate.

⁶ A subject on rivaroxaban was to be considered valid for per protocol analysis if compliance in the 15mg b.i.d. part and in the 20mg o.d. part were each not less than 80%. A subject on enoxaparin/VKA was to be considered valid for per protocol analysis if compliance in the enoxaparin part and in the VKA part were each not less than 80%.

⁷ European Medicines Agency. ICH Topic E 9 Statistical Principles for Clinical Trials. September 1998.

7.1.1.1.7. Sample size

This was an event-driven study. The sponsor assumed equal efficacy between treatment groups, and calculated that a total of 88 confirmed symptomatic recurrent VTE events was needed 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 $\alpha=0.05$). The sponsor assumed an overall incidence rate for the primary efficacy outcome of 3% for both treatment groups, and at least 1465 subjects per group were determined to be needed. This number of subjects to be recruited was to be adjusted based on the observed overall incidence rate of symptomatic recurrent VTE. The decision to stop recruitment when the required number of events was reached was taken by the executive committee and was based on the observed overall incidence rate of confirmed events.

A dose confirmation analysis was planned in the first 400 subjects⁸ based on the composite endpoint of symptomatic recurrent VTE (i.e. primary efficacy outcome) and asymptomatic deterioration at repeat lung imaging⁹ at 3 weeks. The incidence rate of this combined outcome was to be compared between the control and rivaroxaban subjects. The 1-sided 95% confidence interval (CI) of the absolute difference between observed incidence rates was to be calculated. If the 1-sided 95% CI of the difference of the observed incidence rates did not exceed 8.0%, the study was to be continued as planned.

The sponsor had stated that the subsequent results of the dose confirmation analysis resulted in a protocol amendment, which allowed inclusion of the subjects participating in the dose confirmation analysis into the primary analysis, and not recruiting an additional 400 subjects at the end of the study. It had been initially hypothesised that the performance of a mandatory repeat lung imaging test at 3 weeks in the subjects participating in the dose confirmation part had the potential to introduce a 'treatment adaptation bias' in subjects in whom the repeat lung imaging showed an asymptomatic deterioration of the PE, or no or little improvement, such as resulting in additional use of anticoagulant drugs. However, the sponsor stated that an analysis of the subjects enrolled in the dose confirmation part did not indicate that the early repeat lung imaging performed after 3 weeks of treatment had an impact on further treatment, but indicated that any change of anticoagulant therapy was based on medical reasons (treatment of adverse events or sub-therapeutic INRs), and not linked to the lung imaging investigation results. For that reason, the sponsor considered that it was justified to include the subjects who were part of the dose confirmation and not recruit an additional 400 subjects at the end of the study.

7.1.1.1.8. Statistical methods

For the primary efficacy analysis, the time to the first event of the composite primary efficacy outcome was analysed using a stratified Cox proportional hazards model with intended treatment duration (3, 6, or 12 months) as stratum and adjusted for the baseline presence of cancer. The rivaroxaban-to-comparator hazard ratio was computed with 2-sided 95% CI. Based on this model, rivaroxaban was to be considered non-inferior to the comparator if the upper limit of the CI was less than 2.0 (non-inferiority margin). If non-inferiority for the primary efficacy outcome was demonstrated, superiority for the primary efficacy outcome was to be tested utilising the 2-sided 95% CI interval for the hazard ratio.

⁸ Approximately 200 subjects in each treatment group was estimated to be necessary, based on an assumed incidence rate of 4% (i.e. 2% symptomatic recurrent VTE plus 2% asymptomatic deterioration at repeat lung imaging at 3 weeks), a 1-sided type I error of 0.05 and a power of 0.90.

⁹ In the dose confirmation phase, the initial consecutive 400 subjects had repeat lung imaging [ventilation / perfusion lung scan (VPLS) or spiral computed tomography (sCT)], depending on the test used for confirmation of the index event] at 3 weeks (Day 21). The paired sets of lung imaging tests were assessed for deterioration of thrombotic burden (i.e. extension of perfusion defect for VPLS or new intraluminal filling defect for sCT).

For the primary efficacy analysis, all confirmed events were considered up to the end of the intended duration of treatment (3, 6, or 12 months) irrespective of the actual treatment duration. Events occurring after the pre-planned study period were only documented and not included in the analysis. For the ITT analysis, subjects who did not experience a VTE event during the time of the pre-defined treatment duration, who were lost to follow-up, who died because of other reasons than DVT/PE, or who withdrew informed consent before the end of the predefined treatment duration and did not have a primary efficacy outcome, were censored at the last day the subject had a complete assessment for study outcomes within the intended treatment duration.

The secondary efficacy outcomes were analysed and summarised similarly to the primary efficacy outcome, including the calculation of hazard ratio and corresponding 95% CI of the treatment effect. In addition, subgroup analyses¹⁰ were done on the primary efficacy outcome by calculating the hazard ratios and corresponding 95% CIs of the treatment effect.

Comments: The statistical methods are appropriate for a non-inferiority study. The rationale and justification for the inferiority margin of 2.0 was presented by the sponsor in an appendix to the CSR, and are in line with the recommendations of the ICH E 9 Statistical Principles for Clinical Trials as well as of the EMA Guidelines on the choice of the non-inferiority margin, which involved identifying the maximally acceptable loss of control assessed as the difference between the currently recommended and approved standard of care, and placebo or no-treatment. This quantification of the effect of active control relative to placebo is to be derived from historical studies. In this study, the sponsor identified 14 studies from 1960 to 1997 that compared the treatment regimen of initial LMWH followed by VKA for 3 - 12 months with placebo treatment, no treatment or less effective treatment. From the data in these studies, the overall estimated difference between 'more effective' therapy in comparison to 'less effective' therapy was calculated using the random effect model on log odds ratio and resulted in an overall odds ratio of 0.18 (95 % CI: 0.14 to 0.25). The sponsor considered the upper limit of the 95 % confidence interval (minimal effect) of this historical difference between 'more effective' and 'less effective' treatment (i.e. 0.25), and considered retaining approximately 66% of the treatment effect as acceptable, and thus calculated the non-inferiority margin as: $1 + (1 - 0.666) \left(\frac{1}{0.25} - 1 \right) = 2.0$

The subgroup analyses allowed evaluation of the impact of baseline characteristics (e.g. age, gender, weight), characteristics of index PE event (e.g. aetiology, severity in terms of perfusion score, with or without DVT), risk factors (e.g. presence of malignancy at randomisation, thrombophilic conditions,

¹⁰ The subgroups were: Sex (male vs. female); Age (<60 vs. ≥60 years; <60 vs. ≥60 to 75 years vs. >75 years); Weight (<90 vs. ≥90 kg; <50 vs. ≥50 kg; ≤70 vs. >70 to 90 vs. >90 kg); Body Mass Index (< 30 kg/m² vs. ≥ 30 kg/m²); Geographic regions; Race; Aetiology of the index event (spontaneous DVT/PE vs. secondary DVT/PE); Index Event (Only DVT vs. PE with DVT vs. PE without DVT vs. no confirmed index event); Perfusion score of the index PE (<0.75 vs. ≥0.75; terciles; minimal perfusion defect vs. more than minimal defect); Known thrombophilic condition (yes vs. no); Malignancy at randomisation (yes vs. no); Mobility at randomisation (immobilisation vs. no immobilisation); Number of pre-specified risk factors by the investigator (no risk factor vs. 1 vs. > 1 risk factors); Previous episode(s) of DVT /PE (yes vs. no); Renal function (creatinine clearance [CL_{CR}; estimated using the Cockcroft/Gault formula] <50 mL/min vs. 50 ≤ CL_{CR} >80 mL/min vs. CL_{CR} ≥80 mL/min); Pulmonary disease (concomitant respiratory, thoracic, and mediastinal disorders vs. no such concomitant disease); Cardiac disease (concomitant cardiac disorders vs. no such concomitant disease); Fragility (yes vs. no) (Subjects were regarded being fragile when they were either >75 years of age, or their body weight was ≤50 kg or their creatinine clearance was <50 mL/min); Low molecular weight heparin (LMWH) / heparin / fondaparinux treatment before randomisation (yes vs. no); Duration of LMWH/ heparin / fondaparinux pre-medication (categorical) up to randomisation (no pre-medication vs. 1 say vs. 2 days vs. > 2 days); Duration of LMWH/ heparin / fondaparinux pre-medication (categorical) up to randomisation corrected for pharmacological activity (no pre-medication vs. 1 say vs. 2 days vs. > 2 days); Participation in the dose confirmation part (yes vs. no); Intended treatment duration (3 months vs. 6 months vs. 12 months)

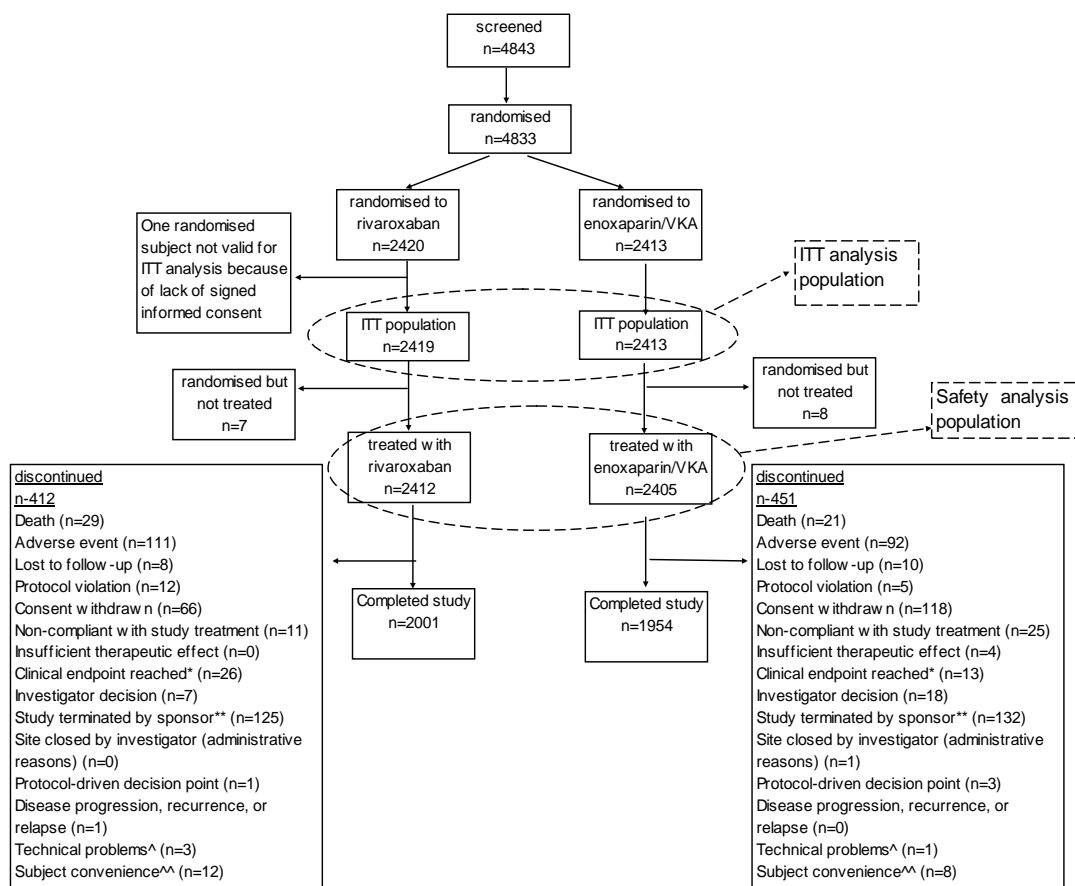
mobility), premorbid status (e.g. concomitant renal impairment, pulmonary or cardiac disease) and study treatment characteristics (e.g. whether there was pre-randomisation coagulation, intended treatment duration) on the primary efficacy outcome.

7.1.1.1.9. Participant flow

An initial 400 randomised subjects participated in the dose confirmation part of this study (205 and 195 in the rivaroxaban and enoxaparin/VKA groups, respectively). Altogether, 379 subjects had a baseline and a repeat lung scan at 3 weeks. The incidence rate of the combination of symptomatic recurrent VTE and asymptomatic deterioration at repeat lung imaging at 3 weeks was 1.7% (3/177 subjects) in the rivaroxaban group and 0.6% (1/174) in the enoxaparin / VKA group. The upper limit of the 1-sided 95% CI of the absolute difference between observed incidence rates was 3.7%. As this did not exceed the pre-specified value of 8.0%, the Dose Confirmation Committee recommended continuing the study as planned without the need to change the study conditions.

In the overall study, a total of 4843 subjects were screened, and 4833 subjects were randomised: 2420 to rivaroxaban and 2413 to enoxaparin/VKA (see flow chart below).

Figure 2. Study 11702-PE. Participant flow.



*After reaching a clinical endpoint, it was at the investigator's discretion whether to continue or to stop study treatment. This included only cases where investigators decided to stop study treatment.

**After the planned number of events had been reached (pre-specified in the study protocol)

^ Technical problems were "difficulty to access veins for blood sampling", "no more study treatment", and "institutional review board discontinued" for the 3 subjects randomised to rivaroxaban as well as "not all local laboratory results obtained at screening" for the subject randomised to enoxaparin / VKA.

^^ The end-of-study visit was performed earlier than planned per protocol due to relocation of subjects or conflicting appointments of the subject (including 2 subjects who were incarcerated).

Overall, 5.2% of the randomised subjects had an intended treatment duration of 3 months, 57.4% had an intended treatment duration of 6 months, and 37.4% had an intended treatment

duration of 12 months. A summary of the analysis population datasets and the primary reasons for exclusion from analysis sets is presented in the CSR.

7.1.1.1.10. Major protocol violations/deviations

The sponsor had stated in the CSR that, among all randomised subjects, 12 subjects (0.5%; 12/2420) and 5 subjects (0.2%; 5/2413) in the rivaroxaban group and the enoxaparin/VKA group, respectively, had protocol violations. No further details were given on the nature of the protocol violations, although a listing of all protocol deviations, and protocol deviations that were reasons for exclusions from analysis sets were provided (Table 4). This will be raised as a clinical question.

Table 4. Analysis populations and primary reasons for exclusion from analysis (randomised subjects), Study Einstein-PE

	Rivaroxaban	Enox / VKA
Subjects randomized	2420 / 2420 (100.0%)	2413 / 2413 (100.0%)
Subjects valid for intent-to-treat analysis	2419 / 2420 (>99.9%)	2413 / 2413 (100.0%)
Subjects valid for safety analysis	2412 / 2420 (99.7%)	2405 / 2413 (99.7%)
Subjects valid for per-protocol analysis	2224 / 2420 (91.9%)	2238 / 2413 (92.7%)
Excluded from intent-to-treat analysis	1 / 2420 (<0.1%)	0 / 2413 (0.0%)
Invalid informed consent	1 / 2420 (<0.1%)	0 / 2413 (0.0%)
Excluded from safety analysis	7 / 2420 (0.3%)	8 / 2413 (0.3%)
Did not take study treatment	7 / 2420 (0.3%)	8 / 2413 (0.3%)
Excluded from per-protocol analysis ^a	188 / 2420 (7.8%)	167 / 2413 (6.9%)
Insufficient compliance	121 / 2420 (5.0%)	120 / 2413 (5.0%)
Wrong intake of study treatment ^b	0 / 2420 (0.0%)	10 / 2413 (0.4%)
Index event was not confirmed	22 / 2420 (0.9%)	23 / 2413 (1.0%)
Intake of a strong CYP3A4 inhibitor / P-gp inhibitor during treatment period	1 / 2420 (<0.1%)	0 / 2413 (0.0%)
Intake of a strong CYP3A4 inducer for >2 days during treatment period	29 / 2420 (1.2%)	0 / 2413 (0.0%)
Use of other antithrombotic medication for >1 week during treatment period unless there was a medical need for an anticoagulant	8 / 2420 (0.3%)	0 / 2413 (0.0%)
>48 hours of therapeutic dose of a parenteral anticoagulant or >1 dose of VKA pre-randomization	13 / 2420 (0.5%)	19/2413 (0.8%)
Thrombolytics to treat the index event	1 / 2420 (<0.1%)	0 / 2413 (0.0%)

a. Subjects who were excluded from the safety analysis were excluded from the per-protocol analysis as well

b. Wrong intake of study treatment: under-dosing of initial enoxaparin study treatment

Note: Subjects may have multiple reasons for exclusion from an analysis set.

Enox = enoxaparin; VKA = vitamin K antagonist

7.1.1.1.11. Baseline data

The baseline demographic characteristics were comparable between treatment groups in the ITT analysis population and the PP analysis population. In the ITT analysis population, the majority of subjects in each treatment group were male (54.1% [1309/2419] and 51.7% [1247/2413] in the rivaroxaban and enoxaparin/VKA groups, respectively), and White¹¹ (65.5% [1585/2419] and 65.8% [1587/2413], respectively). The mean (Standard Deviation [SD]) age was 57.9 (17.3) and 57.5 (17.2) years in the rivaroxaban group and the enoxaparin/VKA group, respectively. The age range was 18 to 97 years in each of the treatment groups.

The baseline disease characteristics were also comparable between treatment groups in the ITT and PP analysis populations. The baseline risk factors for thromboembolism were comparable between treatment groups, and the most commonly reported risk factor was idiopathic DVT/PE (ITT dataset: 49.4% [1196/2419] and 49.2% [1186/2413] in the rivaroxaban and

¹¹ For 24.2% of subjects in each treatment group, race was not collected, in accordance with local laws which prohibit documentation of subject race.

enoxaparin/VKA groups, respectively; PP dataset: 49.4% [1099/2224] and 49.3% [1103/2238], respectively). The majority of subjects in each treatment group had no suspected coexisting DVT at baseline: 71.4% (1728/2419) in the rivaroxaban group and 71.6% (1728/2413) in the enoxaparin/VKA group in the ITT population; 71.4% (1587/2224) and 71.0% (1589/2238), respectively in the PP population. The severity of the index PE (extent of the perfusion defect) was documented using perfusion score¹², and was similar in the 2 treatment groups in both the ITT population and the PP population. The mean (SD) perfusion score was 0.81 (0.12) in both treatment groups for both ITT and PP analysis sets, and the majority of subjects in each treatment group had a perfusion score of ≥ 0.75 (ITT population: 70.3% [1701/2419] and 71.4% [1723/2413] in the rivaroxaban and enoxaparin/VKA groups, respectively; PP population: 70.7% [1573/2224] and 72.3% [1618/2238], respectively). The majority of the index PE was reported as spontaneous PE¹³ (ITT: 64.7% [1566/2419] and 64.3% [1551/2413], respectively; PP: 64.6% [1436/2224] and 64.3% [1438/2238], respectively), and the causes of secondary PE were similar between treatment groups in both the ITT population and the PP population.. Baseline co-existing medical conditions were also comparable between treatment groups in both ITT and PP datasets.

Comments: Overall, the baseline demographic and disease characteristics were comparable between treatment groups. The median age was not presented, but it is noted that in the ITT analysis population, 39.6% and 38.7% of subjects in the rivaroxaban and enoxaparin/VKA groups, respectively, were aged ³ 65 years, and 18.2% and 16.7% of subjects, respectively, were aged > 75 years. Similar age distribution was seen in the PP population. The study population profile of the aetiology of the index PE event and the risk factors for VTE are consistent with those in the target patient population.

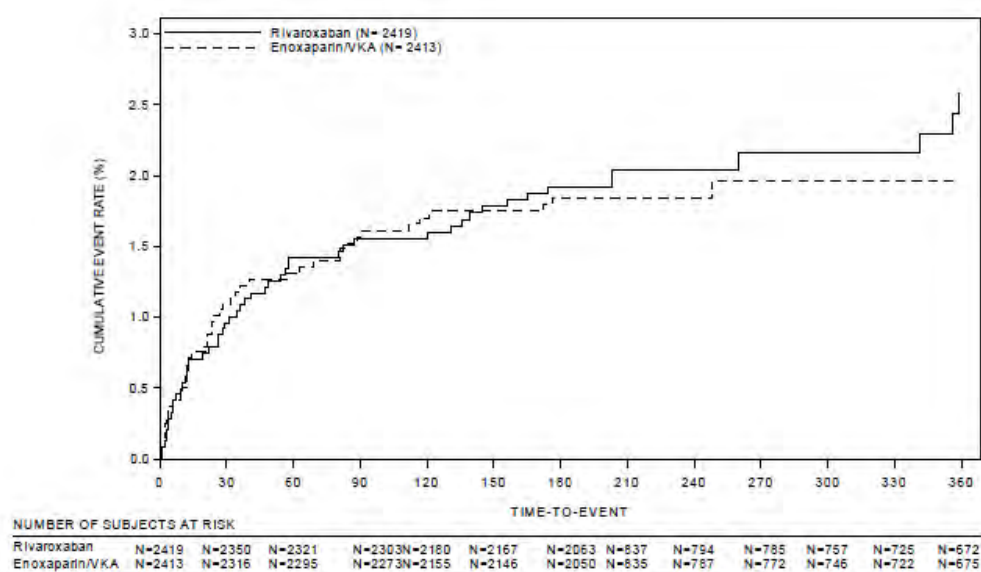
7.1.1.1.12. Results for the primary efficacy outcome

In the ITT population, the percentage of subjects with events for the primary efficacy outcome until the end of intended treatment duration was 2.1% (50/2419) in the rivaroxaban group and 1.8% (44/2413) in the enoxaparin/VKA group. In the Cox's proportional hazard model, the comparison of rivaroxaban with enoxaparin/VKA treatment yielded a hazard ratio of 1.123 (95% CI of 0.749-1.684). The upper limit of the confidence interval was below the pre-defined non-inferiority margin of 2.0, showing non-inferiority of rivaroxaban over enoxaparin/VKA for the primary efficacy outcome. The test for superiority of rivaroxaban versus enoxaparin/VKA was not statistically significant ($p_{\text{superiority}} = 0.5737$). The Kaplan-Meier cumulative incidence rate plot in the ITT population is presented in Figure 3. Analyses of the primary efficacy endpoint in the ITT on treatment population and the PP population yielded similar results.

¹² perfusion score = 0 means perfusion defect in all lung lobes, perfusion score = 0.75 means no perfusion defect in 75% of the large vessels, and perfusion score = 1 means no perfusion defect at all.

¹³ The index PE at baseline was categorised as secondary PE if at least one of the following risk factors was specified by the investigator: recent surgery or trauma, immobilisation, use of estrogen-containing drugs, active cancer, or puerperium. Otherwise, the index PE was considered as spontaneous PE.

Figure 3. Kaplan-Meier cumulative incidence rate of primary efficacy outcome until the intended end of study treatment (time point: event or censoring up to the intended treatment duration) (ITT population), Study Einstein-PE



7.1.1.1.13. Results for other efficacy outcomes

Analyses on the individual components of the primary efficacy outcome yielded incidence rates which were comparable between treatment groups. The table also presents the results of an analysis of primary efficacy endpoint that excluded events confirmed by a change in antithrombotic treatment only¹⁴, and showed results comparable to the primary efficacy outcome analysis (incidence rates of 1.9% (46/2419) in the rivaroxaban group and 1.7% (41/2413) in the enoxaparin/VKA group; hazard ratio of 1.108 with 95% CI of 0.728-1.688).

The analyses on the secondary efficacy outcomes and their individual components are also presented. The main secondary efficacy outcome was a composite of recurrent DVT, non-fatal PE and all-cause mortality. The incidence rates of this main secondary efficacy outcome until the end of intended treatment duration were 4.0% (97/2419) in the rivaroxaban group and 3.4% (82/2413) in the enoxaparin/VKA group. In the Cox's proportional hazard model, the comparison of rivaroxaban with enoxaparin/VKA treatment yielded a hazard ratio of 1.156 (95% CI of 0.862-1.552). The upper limit of the confidence interval was below the pre-defined non-inferiority margin of 2.0, showing non-inferiority of rivaroxaban over enoxaparin/VKA for the main secondary efficacy outcome. The test for superiority of rivaroxaban versus enoxaparin/VKA was not statistically significant ($p_{\text{superiority}} = 0.3333$).

The secondary efficacy outcome of 'net clinical benefit 1' was the composite of the primary efficacy outcome and major bleeding events. The incidence rates of 'net clinical benefit 1' until the end of intended treatment duration were 3.4% (83/2419) in the rivaroxaban group and 4.0% (96/2413) in the enoxaparin/VKA group. The comparison of rivaroxaban with enoxaparin/VKA treatment with the Cox's proportional hazard model yielded a hazard ratio of 0.849 (95% CI of 0.633-1.139; $p_{\text{superiority}} = 0.2752$).

The secondary efficacy outcome of 'net clinical benefit 2' was the composite of the primary efficacy outcome, major bleeding events, and cardiovascular events/deaths (cardiovascular deaths, myocardial infarctions, strokes, and non-CNS systemic embolisms). The incidence rates

¹⁴ For the primary efficacy outcome, the study protocol had specified that objective testing was to be done for all subjects with suspected recurrent DVT / PE to assess the recurrent episode, but that 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.

of 'net clinical benefit 2' until the end of intended treatment duration were 4.5% (110/2419) and 4.8% (115/2413) in the rivaroxaban and the enoxaparin/VKA groups, respectively. In the Cox's proportional hazard model, the comparison of rivaroxaban with enoxaparin/VKA treatment yielded a hazard ratio of 0.940 (95% CI of 0.724-1.221; $p_{\text{superiority}} = 0.6430$).

Results of analyses of the incidences of the components of the efficacy outcomes in terms of deaths, recurrent PE and recurrent DVT in the ITT population are presented. The incidence rates of all deaths until the end of intended treatment duration were 2.4% (58/2419) and 2.1% (50/2413) in the rivaroxaban and the enoxaparin/VKA groups, respectively. Those of recurrent PE were 1.4% (33/2419) and 1.2% (28/2413), respectively, and of recurrent DVT were 0.7% (18/2419) and 0.8% (19/2413), respectively.

Subgroup analyses for the primary efficacy outcome are shown. There was no evidence for heterogeneity of hazard ratios across the different subgroups, i.e. no test for interaction of any baseline or demographic factor resulted in a p-value < 0.05 ¹⁵. Subgroup analyses on secondary outcome of "net clinical benefit 1" are also presented. The p-values for the interaction tests were all ≥ 0.05 , except for the subgroup analyses by fragility (yes vs. no) and for both sets of age groups (< 60 years vs. ≥ 60 years and < 65 vs. 65 to 75 years vs. > 75 years), where the p-values for interaction were < 0.05 .

Comments on results of efficacy outcomes:

The efficacy results of the primary efficacy endpoint, the secondary efficacy endpoints, and the main components of the efficacy endpoints are summarised in Table 5, below.

Table 5. Efficacy results of the primary efficacy endpoint, the secondary efficacy endpoints, and the main components of the efficacy endpoints, ITT population unless otherwise specified, Study Einstein-PE

	Incidence in rivaroxaban group % (n/N)	Incidence in enoxaparin/VKA group % (n/N)	Hazard ratio (rivaroxaban to enoxaparin/VKA)	95% confidence interval of hazard ratio	p-value for superiority
Primary efficacy endpoint	2.1% (50/2419)	1.8% (44/2413)	1.123	0.749-1.684	0.5737
Primary efficacy endpoint (PP population)	1.7% (38/2224)	1.6% (36/2238)	1.066	0.697 - 1.632	0.8504
Main secondary endpoint	4.0% (97/2419)	3.4% (82/2413)	1.156	0.862-1.552	0.3333
Net clinical benefit 1	3.4% (83/2419)	4.0% (96/2413)	0.849	0.633-1.139	0.2752
Net clinical benefit 2	4.5% (110/2419)	4.8% (115/2413)	0.940	0.724-1.221	0.6430

¹⁵ No interaction p-value was calculated for the subgroups of geographic regions, race, index event and duration of pre-medication with LMWH/Heparin/fondaparinux. The sponsor had stated that this was because in at least one category of these subgroup, no event occurred within a treatment group

	Incidence in rivaroxaban group % (n/N)	Incidence in enoxaparin/VKA group % (n/N)	Hazard ratio (rivaroxaban to enoxaparin /VKA)	95% confidence interval of hazard ratio	p-value for superiority
Main components of the efficacy endpoints					
Recurrent PE	1.4% (33/2419)	1.2% (28/2413)	N.A.	N.A.	N.A.
Recurrent DVT	0.7% (18/2419)	0.8% (19/2413)	N.A.	N.A.	N.A.
All deaths	2.4% (58/2419)	2.1% (50/2413)	N.A.	N.A.	N.A.
Major bleeding events	1.4% (33/2419)	2.4% (57/2413)	N.A.	N.A.	N.A.

N.A. = not available

Efficacy results showed that rivaroxaban was non-inferior to enoxaparin/VKA for the primary efficacy outcome of symptomatic recurrent VTE in both the ITT and PP populations. These results of non-inferiority of rivaroxaban treatment regimen compared to the enoxaparin /VKA treatment regimen was maintained through the secondary efficacy outcomes. The test for superiority of rivaroxaban over enoxaparin/VKA yielded p-values which were not statistically significant in all primary and secondary efficacy outcomes. However, this study had been designed as and powered for a non-inferiority study and not superiority study. The point estimate of the hazard ratio for the primary efficacy outcome was > 1 , while that for net clinical benefit 1 was < 1 (i.e. in favour for rivaroxaban). As the efficacy outcome of net clinical benefit 1 was the composite of the primary efficacy outcome and major bleeding, this suggested that the difference in the results for the hazard ratio between the primary efficacy outcome and the efficacy outcome of net clinical benefit 1 was driven by a lower incidence of major bleeding in the rivaroxaban group compared to the enoxaparin/VKA group. This was supported by the analyses on the individual components of the efficacy outcomes, which showed that while the incidence rates of recurrent PE, recurrent DVT and all-cause deaths were comparable between treatment groups, the incidence rate of major bleeding event was lower in the rivaroxaban group compared to the enoxaparin/VKA group (Table 5 above). This will be discussed in greater detail in the safety section (Section 8) of this evaluation.

In the subgroup analyses on the primary efficacy endpoint and the secondary efficacy outcome of net clinical benefit 1, the low event rates and/or small sample sizes in some subgroups make interpretation difficult. Subgroups where the upper limits of the 95% CI of the hazard ratios were ≥ 2.0 had associated wide 95% CIs. In the subgroup analyses on the primary efficacy endpoint, the p-values for the interaction tests were all ≥ 0.05 .

However subgroup analyses on the secondary efficacy outcome of net clinical benefit 1 yielded p-values for interaction tests of < 0.05 for the subgroup of fragility (yes vs. no) and for both sets of age groups (< 60 years vs. ≥ 60 years and < 65 vs. 65 to 75 years vs. > 75 years). The hazard ratios (95% CI) comparing rivaroxaban to enoxaparin/VKA were 1.082 (0.747-1.568) in the subgroup of non-fragile subjects, and 0.526 (0.321-0.863) in the subgroup of fragile subjects, suggesting that rivaroxaban is less effective in non-fragile subjects compared to fragile subjects. However, it is noted that the upper limit of the 95% CI of the hazard ratio for non-fragile subjects was < 2.0 , indicating that for this subgroup of patients, rivaroxaban was still non-

inferior to enoxaparin/VKA. The hazard ratios (95% CI) comparing rivaroxaban to enoxaparin/VKA were 1.337 (0.811-2.202) in the subgroup of subjects aged < 60 years, and 0.654 (0.451-0.948) in the subgroup of subjects aged ≥ 60 years, suggesting that rivaroxaban is less effective in younger subjects aged < 60 years compared to older subjects aged ≥ 60 years. In particular, the upper limit of the 95% CI of the hazard ratio for subjects aged < 60 years was ≥ 2.0, suggesting that for this subgroup of subjects, rivaroxaban was not non-inferior to enoxaparin/VKA, and that there could be a 1.3x higher risk of having a composite outcome of symptomatic recurrent VTE or major bleeding events compared to subjects on enoxaparin/VKA. This result was consistent with the analyses in the age subgroups of subjects aged <65, those aged 65 to 75 years and those aged >75 years, with hazard ratios (95% CI) of 1.094 (0.699-1.711), 1.133 (0.635-2.024) and 0.437 (0.251-0.760), respectively.

It is also noted that in the subgroup analyses on the primary efficacy endpoint, although the p-values for the interactions tests were ≥ 0.05 for the subgroups of subjects by age (< 60 years vs. ≥ 60 years and <65 vs. 65 to 75 years vs. >75 years), the upper limits of the 95% CIs of the hazard ratios for subjects aged < 60 years (hazard ratio [95% CI]: 1.530 [0.830-2.820]), < 65 years (hazard ratio [95% CI]: 1.276 [0.738-2.206]) and 65 to 75 years (hazard ratio [95% CI]: 1.279 [0.504-3.245]) were all ≥ 2.0, suggesting that in these subgroup of younger subjects, rivaroxaban was not non-inferior to enoxaparin/VKA, and there was a 1.3 to 1.5x higher risk of having an outcome of symptomatic recurrent VTE compared to subjects on enoxaparin/VKA. However, these results need to be interpreted with care due to the small sample sizes/event rates, reflected in the wide 95% CIs.

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

7.1.2.1. Study PH36746

Study PH36746 is a meta-analysis of the Einstein-DVT and Einstein-PE studies. The sponsor had stated that both Einstein-DVT and Einstein-PE studies were integrated into a single study protocol, as the subject groups were complementary and were recruited at the same centres, the essential study design features were identical, and both evaluations were supervised and guided by the same study committees. The only difference in study design between the 2 studies was that Einstein-DVT study enrolled subjects with confirmed acute proximal symptomatic DVT without symptomatic PE, while the Einstein-PE study enrolled subjects with confirmed acute symptomatic PE with or without symptomatic DVT.

This pooled analysis of studies Einstein-DVT and Einstein-PE followed the statistical methods and approach previously described for study Einstein-PE, with some exceptions to take into account combining the study populations, and a more conservative non-inferiority margin. Specifically, for the pooled analysis, the time to first event of the primary efficacy outcome was analysed using Cox's proportional hazard model, with stratification by index event (DVT only, or PE with or without DVT) and intended treatment duration and adjustment for baseline malignancy. Based on this model, rivaroxaban was considered non-inferior to enoxaparin/VKA if the upper limit of the two-sided 95% confidence interval for the hazard ratio (rivaroxaban to enoxaparin/VKA) was below the pre-defined non-inferiority margin of 1.75. This more conservative margin was chosen for the pooled analysis as it corresponds to a retention of 75% of the minimal effect in the population of patients with VTE. The pooled analysis result was only to be considered confirmatory if there was no significant interaction between treatment and index event (DVT only vs. PE with or without DVT).

7.1.2.1.1. Results

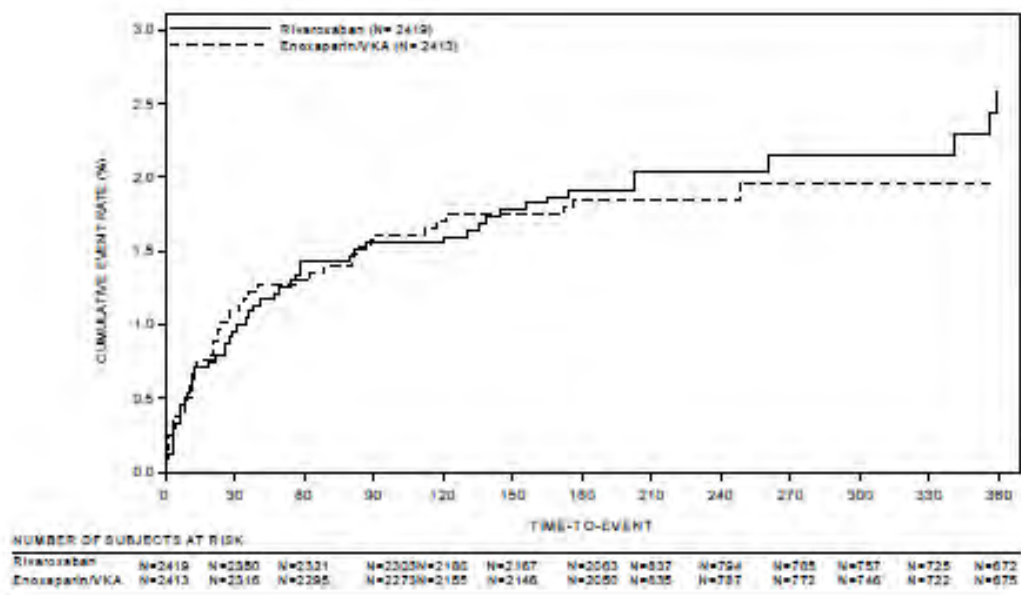
In the pooled studies, there were a total of 8282 randomised subjects: 4151 in the rivaroxaban group and 4131 in the enoxaparin/VKA group. The subject analysis populations are presented in the dossier.

The baseline demographic characteristics were comparable between the pooled treatment groups in the ITT analysis population and the PP analysis population. In the ITT analysis

population, the majority of subjects in each treatment group were male (55.5% [2302/4150] and 53.6% [2214/4131] in the pooled rivaroxaban and enoxaparin/VKA groups, respectively), and white¹⁶ (70.2% [2912/4150] and 70.3% [2906/4131], respectively). The mean (SD) age was 57.0 (17.0) and 57.0 (16.8) in the pooled rivaroxaban group and enoxaparin/VKA groups, respectively. Overall 37.2% of subjects in the pooled rivaroxaban group and 37.3% in the pooled enoxaparin/VKA group were ≥ 65 years old, while 15.8% and 15.2%, respectively, were > 75 years old. The baseline risk factors for thromboembolism were comparable between treatment groups and the most commonly reported risk factor was idiopathic DVT/PE (48.3% [2003/ 4150] and 49.6% [2048/ 4131] in the pooled rivaroxaban and enoxaparin/VKA group, respectively).

The primary efficacy outcome was the same in both studies Einstein-DVT and Einstein-PE (i.e. symptomatic recurrent VTE). In the pooled ITT population, the percentage of subjects with events for the primary efficacy outcome until the end of intended treatment duration was 2.1% (86/4150) in the rivaroxaban group and 2.3% (95/4131) in the enoxaparin/VKA group. The Cox's proportional hazard model of rivaroxaban versus enoxaparin/VKA treatment yielded a hazard ratio of 0.886 (95% CI of 0.661-1.186). The upper limit of the confidence interval was below the pre-defined non-inferiority margin of 1.75, showing non-inferiority of rivaroxaban over enoxaparin/VKA for the primary efficacy outcome in the pooled analysis. The test for superiority of rivaroxaban versus enoxaparin/VKA was not statistically significant ($p_{\text{superiority}} = 0.4143$). The p-value for interaction of treatment effect by index event was not statistically significant at 0.097. The Kaplan-Meier cumulative incidence rate plots in the ITT populations in studies Einstein-DVT and Einstein-PE and the pooled analysis are presented in Figure 4, 5 and 6, respectively. Analyses of the primary efficacy endpoint in the pooled ITT on treatment population and the pooled PP population yielded similar results.

Figure 4. Kaplan-Meier Cumulative Rate plots of the primary efficacy outcome until the intended end of study treatment across study Einstein-DVT, ITT population



¹⁶ For 17.1% of subjects in each pooled treatment group, race was not collected, in accordance with local laws which prohibit documentation of subject race.

Figure 5. Kaplan-Meier Cumulative Rate plots of the primary efficacy outcome until the intended end of study treatment across study Einstein-PE, ITT population

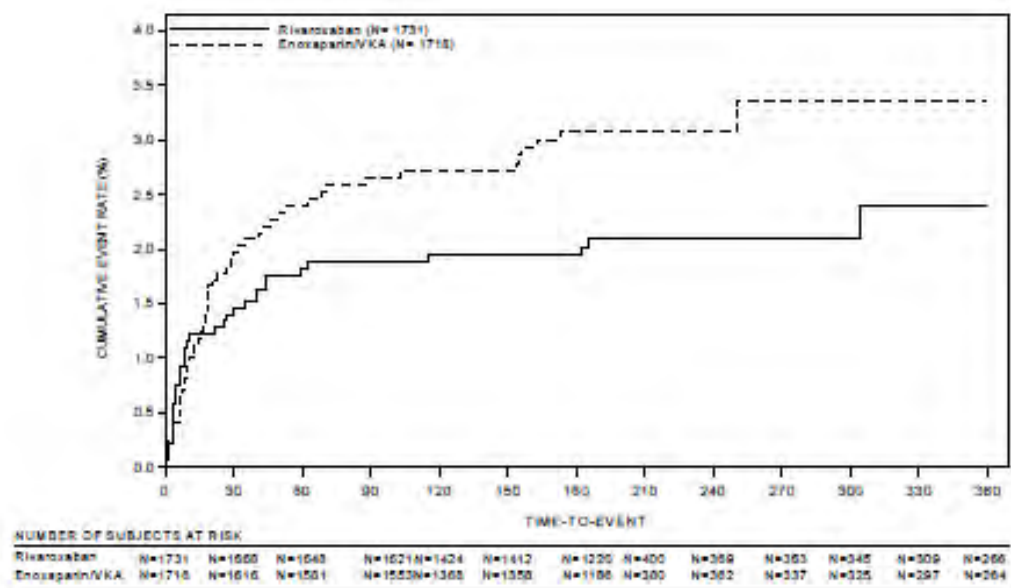
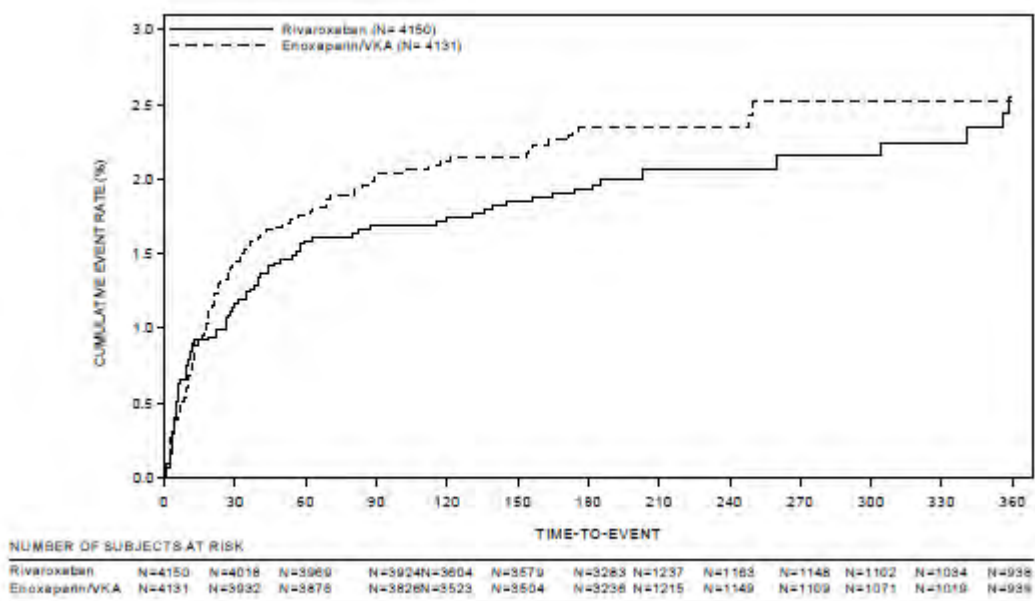


Figure 6. Kaplan-Meier Cumulative Rate plots of the primary efficacy outcome until the intended end of study treatment: pooled analysis, ITT population, Study PH 36746



When the primary efficacy outcome was limited to events confirmed by objective tests only, (i.e. excluding events confirmed solely by a change in antithrombotic medication), results were comparable to the primary efficacy outcome analysis (incidence rates of 2.0% (82/4150) in the pooled rivaroxaban group and 2.2% (92/4131) in the pooled enoxaparin/VKA group; hazard ratio of 0.871 with 95% CI of 0.647-1.173).

The analyses on the secondary efficacy outcomes are presented in the dossier. The main secondary efficacy outcome was a composite of recurrent DVT, non-fatal PE and all-cause mortality. The incidence rates of the main secondary efficacy outcome until the end of intended treatment duration were 4.0% (166/4150) in the pooled rivaroxaban group and 4.1% (169/4131) in the pooled enoxaparin/VKA group. The Cox's proportional hazard model of rivaroxaban versus enoxaparin/VKA treatment yielded a hazard ratio of 0.930 (95% CI of

0.751-1.153). The upper limit of the confidence interval was below the pre-defined non-inferiority margin of 1.75, showing non-inferiority of rivaroxaban over enoxaparin/VKA for the main secondary efficacy outcome. The test for superiority of rivaroxaban vs. enoxaparin/VKA was not statistically significant ($p_{\text{superiority}} = 0.5086$).

The incidence rates of net clinical benefit 1 until the end of intended treatment duration were 3.2% (134/4150) in the pooled rivaroxaban group and 4.1% (169/4131) in the pooled enoxaparin/VKA group. The Cox's proportional hazard model of rivaroxaban versus enoxaparin/VKA treatment yielded a hazard ratio of 0.771 (95% CI of 0.614-0.967), showing non-inferiority of rivaroxaban over enoxaparin/VKA for net clinical benefit 1. The test for superiority of rivaroxaban vs. enoxaparin/VKA was statistically significant ($p_{\text{superiority}} = 0.0244$).

The incidence rates of net clinical benefit 2 until the intended end of treatment were 4.1% (172/4150) in the pooled rivaroxaban group and 4.7% (196/4131) in the pooled enoxaparin/VKA group. In the Cox's proportional hazard model, the comparison of rivaroxaban with enoxaparin/VKA treatment yielded a hazard ratio of 0.853 (95% CI of 0.695-1.047; $p_{\text{superiority}} = 0.1275$).

Analyses of the incidences of the components of the efficacy outcomes in the ITT population in study Einstein-DVT, study Einstein-PE and pooled analysis are summarised and presented in the dossier. The incidences of the components of the efficacy outcomes were comparable between the pooled treatment groups except for that of major bleeding event, which occurred in 1.2% (48/4150) of subjects in the pooled rivaroxaban group and 1.9% (80 /4131) in the pooled enoxaparin/VKA group.

Subgroup analyses for the primary efficacy outcome for the pooled analysis are summarised in the dossier. The p-values for the interaction tests were all ≥ 0.05 , except for the subgroup of previous episode(s) of DVT/PE (yes vs. no), where the interaction tests p-value was 0.032. Subgroup analyses on secondary outcome of "net clinical benefit 1" in the pooled analysis are presented. The p-values for the interaction tests were all ≥ 0.05 , except for the subgroup analyses by fragility (yes vs. no) and for both sets of age groups (< 60 years vs. ≥ 60 years and <65 vs. 65 to 75 years vs. >75 years), where the p-values for interaction were < 0.05.

Comments: Pooled analysis of the Einstein-DVT and Einstein-PE studies is appropriate as both studies have similar designs, including efficacy outcomes and statistical methods, except that Einstein-DVT study enrolled subjects with confirmed acute proximal symptomatic DVT without symptomatic PE, while the Einstein-PE study enrolled subjects with confirmed acute symptomatic PE with or without symptomatic DVT. In addition, both conditions of DVT and PE are considered clinically related.

The baseline demographic characteristics, including age distribution, in the pooled analysis were comparable with those in study Einstein-PE. Results of the pooled analysis with regards to the primary and secondary efficacy outcomes were consistent with those in study Einstein-PE, showing non-inferiority of rivaroxaban compared to enoxaparin/VKA across these efficacy outcomes. In the pooled analysis, the point estimate of hazard ratios of rivaroxaban to enoxaparin/VKA for the primary and secondary efficacy outcomes were all < 1.0 (i.e. in favour of rivaroxaban), compared to the results in study Einstein-PE, where the hazard ratios were all > 1.0. In addition, while the tests for superiority of rivaroxaban over enoxaparin/VKA were all not statistically significant across the efficacy outcomes in study Einstein-PE, in the pooled analysis, the test for superiority of rivaroxaban over enoxaparin/VKA yielded statistically significant result for the outcome of net clinical benefit 1. These better results in the pooled analyses were mainly driven by the results in study Einstein-DVT. For the primary efficacy outcome and the main secondary efficacy outcome, this is

mainly due to a higher event incidence rate in the enoxaparin/VKA group in study Einstein-DVT compared to that in study Einstein-PE, while the event incidence rate in the rivaroxaban groups were comparable between both studies.

In the pooled subgroup analyses, the p-values for the interaction tests were all ≥ 0.05 , except for the subgroup of previous episode(s) of DVT/PE (yes vs. no), where the interaction tests p-value was 0.032. The hazard ratios (95% CI) comparing rivaroxaban to enoxaparin/VKA were 1.044 (0.754-1.446) in the subgroup of subjects without previous episodes of DVT/PE, and 0.445 (0.219-0.905) in the subgroup of subjects with previous episodes of DVT/PE, suggesting rivaroxaban is less effective in subjects without previous episodes of DVT/PE compared to those with such previous episodes. However, it is noted that the upper limit of the 95% CI of the hazard ratio for subjects without previous episode of DVT/PE was < 1.75 , indicating that for the subgroup of patients without previous episodes of DVT/PE, rivaroxaban is still non-inferior to enoxaparin/VKA.

The pooled subgroup analyses on the secondary outcome of “net clinical benefit 1” showed results comparable to those in study Einstein-PE, where the p-values for the interaction tests were all ≥ 0.05 , except for the subgroup analyses by fragility (yes vs. no) and for both sets of age groups (< 60 years vs. ≥ 60 years and < 65 vs. 65 to 75 years vs. > 75 years), where the p-values for interaction were < 0.05 . The hazard ratios of rivaroxaban to enoxaparin/VKA were comparable between study Einstein-PE and the pooled analysis, showing in both analyses that rivaroxaban was less effective in subjects who were non-fragile (compared to those who were), in those who were < 60 years old (compared to those ≥ 60 years old), and in those who were < 65 years old and between 65-75 years old (compared to those > 75 years old) (Table 6, below). However, in the pooled analysis, it is noted that the upper limit of the 95% CI of the hazard ratios for these subgroups were all below the pre-specified non-inferiority margin of 1.75.

Table 6. Hazard ratios of rivaroxaban to enoxaparin/VKA for efficacy outcome of “net clinical benefit 1” in subgroups of fragility and age, ITT population, Study Einstein-PE and pooled analysis of studies Einstein-PE and Einstein-DVT

Subgroups		Study Einstein-PE		Pooled analysis of study Einstein-PE and study Einstein-DVT	
		Hazard ratio (rivaroxaban to enoxaparin/VKA)	95% confidence interval of hazard ratio	Hazard ratio (rivaroxaban to enoxaparin/VKA)	95% confidence interval of hazard ratio
Fragility	yes	0.526	0.321-0.863	0.511	0.340-0.768
	no	1.082	0.747-1.568	0.931	0.706-1.228
Age group 1	< 60 years	1.337	0.811-2.202	1.096	0.771-1.557
	≥ 60 years	0.654	0.451-0.948	0.595	0.440-0.805

Subgroups		Study Einstein-PE		Pooled analysis of study Einstein-PE and study Einstein-DVT	
		Hazard ratio (rivaroxaban to enoxaparin/VKA)	95% confidence interval of hazard ratio	Hazard ratio (rivaroxaban to enoxaparin/VKA)	95% confidence interval of hazard ratio
Age group 2	<65 years	1.094	0.699-1.711	0.969	0.706-1.330
	65-75 years	1.133	0.635-2.024	0.798	0.499-1.276
	>75 years	0.437	0.251-0.760	0.449	0.280-0.719

7.1.2.2. Study PH36749

The objective of this study was to evaluate the treatment effect of rivaroxaban compared to enoxaparin/VKA in studies Einstein-DVT and Einstein-PE on patient-reported treatment satisfaction through analyses on two questionnaire responses: the Anti-Clot Treatment Scale (ACTS) and the Treatment Satisfaction Questionnaire for Medication (TSQM). The principal analysis was on patient responses to the ACTS questionnaire, which is an anti-coagulation specific questionnaire, with supportive analysis using the TSQM, which is a generic treatment satisfaction scale.

Study population was the ITT analysis population in studies Einstein-DVT and Einstein-PE in seven participating countries: United States, United Kingdom, Canada, Germany, France, Italy, and the Netherlands.

The ACTS is a 17-item patient-reported measure of satisfaction with anticoagulant treatment, and consists of 13 items about the burdens of ACT (scored on a 12-60 scale) and 4 items about the benefits of ACT (scored on a 3-15 scale). The ACTS was administered at six study time points (Day 15, and 1, 2, 3, 6 and 12 months.) The TSQM is an 11-item generic measure of treatment satisfaction for medication, consisting of four subscales (Effectiveness, Side Effects, Convenience and Global Satisfaction) and scored on a 0-100 scale. It was administered alongside the ACTS at months 1, 3, 6 and 12 months. The ACTS and TSQM coding techniques were adopted such that a higher score indicated a higher treatment satisfaction.

There were two primary endpoints: analysis on the Burdens subscale of ACTS and analysis on Benefits subscale of ACTS. As the questionnaire responses were multiple measurements on the patient satisfaction of treatment over a period of time, repeated measures analyses were used to analyse the questionnaire data. For each of the subscale analyses, there were two hierarchical tests. The hypothesis to be tested first was that subjects on rivaroxaban had increased benefit or decreased burden compared with subjects on enoxaparin/VKA over time. The statistical model for repeated measures analysis under this hypothesis had terms for treatment, visit, and interaction of treatment by visit, stratified by planned treatment duration. The second hypothesis to be tested was that, averaged across all the visits, subjects on rivaroxaban had increased benefit or decreased burden than patients on enoxaparin/VKA. The statistical model under this hypothesis had terms for treatment, and visit, stratified by planned treatment duration.

7.1.2.2.1. Results

The study population consisted of 1472 subjects (737 in rivaroxaban group and 735 in enoxaparin/VKA group) in the ITT analysis set in study Einstein-DVT and 2397 subjects (1200 in rivaroxaban group and 1197 in enoxaparin/VKA group) in the ITT analysis set in study

Einstein-PE. Baseline demographic and clinical characteristics were comparable between treatment groups.

The p-values of the treatment by visit interaction from the repeated measures models showed that for the ACTS Burdens subscale score, there was a consistent treatment effect for rivaroxaban across all visits, with a non-significant p-value for the test of treatment by visit interaction ($p=0.0585$ for study Einstein-DVT, $p=0.5989$ for study Einstein-PE). However, for the ACTS Benefits subscale score, the treatment effect was not consistent across visits, with a significant p-value for the test of treatment by visit interaction ($p=0.0159$ for study Einstein-DVT, $p=0.0291$ for study Einstein-PE), indicating an effect that is not consistent across visits.

This is reflected by the results of the least-square-means (LSMs) by treatment and visit, from the model including the test of treatment by visit interaction, which showed that for the ACTS Burdens subscale score, the treatment effect was consistent across the visits, but for the ACTS Benefits subscale score, the LSMs by treatment and visit indicated that the rivaroxaban group had increased benefit as compared to enoxaparin/VKA group mainly at the later visits (i.e. Months 2, 3, 6 and 12).

The sponsor also presented the results from the repeated measures model without treatment by visit interaction in order to provide data on the treatment effect averaged across all visits. The results showed a higher treatment satisfaction with rivaroxaban compared to enoxaparin/VKA in both ACTS subscales.

7.1.2.3. Studies PH36705 and PH36718

Both studies were identical in objectives and design except that study PH36705 evaluated data on study Einstein-PE only, while study PH36718 is a meta-analysis of studies Einstein-PE and Einstein-DVT. These studies were analyses of the effect of rivaroxaban on bleedings and efficacy with selected co-medication categories in study Einstein-PE (study PH36705) and in pooled studies Einstein-PE and Einstein-DVT (study PH36718). The main objectives of the analyses in these studies were to investigate the effect of concomitant use of CYP3A4 inducers, statins, Non-Steroidal Anti-Inflammatory Drugs (NSAIDs), acetylsalicylic acid (ASA) and platelet aggregation inhibitors on the primary efficacy outcome (i.e. symptomatic recurrent VTE), and the effect of concomitant use of NSAIDs, ASA, platelet aggregation inhibitor, clopidogrel/ticlopidine, strong CYP3A4 inhibitors, P-gp inhibitors and statins (and steroids for study PH36718 only) on the risk of adjudicated and confirmed treatment-emergent bleeding events.

The sponsor had stated that these analyses were purely exploratory, and that no statistical tests had been performed and no statistical models had been applied. The sponsor had stated that these 2 reports were purely technical reports serving to describe the definitions and statistical approaches underlying these additional safety analyses, and that results and conclusions will be described in a separate report. These 2 study reports consisted of a description of study methods and a listing of study data. The sponsor is also not proposing to make any changes to the currently-approved PI using data derived from these 2 study reports.

The efficacy analyses in these 2 studies were performed based on the ITT on treatment population. The safety analyses in this report were performed based on the population of subjects valid for safety analysis. The efficacy endpoint in these 2 studies was the primary efficacy outcome of symptomatic recurrent VTE. The safety outcomes were bleeding events (treatment-emergent major bleeding, treatment-emergent major or non-major clinically relevant bleeding [i.e. the principal safety outcome in studies Einstein-DVT and Einstein PE], and any treatment-emergent bleeding).

The number of subjects with each category of co-medication use at baseline was comparable between treatment groups in both study Einstein-PE and in the pooled analysis. Results from the Cox proportional hazard model, for each co-medication class, for a treatment effect on the primary efficacy outcome in specified subpopulations of subjects (subjects with use of co-medication at baseline, subjects without use of co-medication at baseline, subjects without use

of co-medication in the at-risk period, subjects with limited use ($\leq 50\%$ of time) of co-medication in the at-risk period, and subjects with extended use ($> 50\%$ of time) of co-medication in the at-risk period) are presented in the dossier. Safety results will be summarised in Section 8.7.1.2.5 of the evaluation report.

Comments: Although the interaction p-values were all not statistically significant, interpretation of the results is limited by the small event rates in the subpopulations of subjects with co-medication use. The sponsor had not provided any interpretation or conclusion on the results, and had stated that these 2 reports were purely technical reports and that results and conclusions will be described in a separate report. It is not critical that the separate report be provided now in order that a recommendation can be made with regards to this submission. However it will be raised as a question to the sponsor as to when the separate report will be expected.

7.1.2.4. Studies PH36706 and PH36711

Both studies were identical in objectives and design except that study PH36706 evaluated data on study Einstein-PE only, while study PH36711 is a meta-analysis of studies Einstein-PE and Einstein-DVT. The objective of the studies was to evaluate the relationship between the pharmacodynamic marker for rivaroxaban, prothrombin time (PT; measured with Neoplastin reagent), and efficacy and safety outcomes. The efficacy outcome analysed was the incidence of the primary efficacy outcome (i.e. symptomatic recurrent VTE). The safety outcomes were bleeding events (treatment-emergent major bleeding, treatment-emergent major or non-major clinically relevant bleeding [i.e. the principal safety outcome in studies Einstein-DVT and Einstein PE], and any treatment-emergent bleeding).

The sponsor has stated that these analyses were purely exploratory (no statistical tests performed and no statistical models applied) and that these 2 reports were technical reports serving to describe the definitions and statistical approaches underlying the analysis, and that results and conclusions will be described in a separate report. These 2 study reports consisted of a description of study methods and a listing of study data. They do not provide any data relevant to the evaluation of this submission for the extension of indication for rivaroxaban. The sponsor is also not proposing to make any changes to the currently-approved PI with data derived from these 2 study reports. In view of the above, this evaluation will summarise the analysis methods without reference to any results, which were not summarised or interpreted by the sponsor in these 2 study reports. The clinical summary of safety in Module 2.7 of the submission had briefly summarised the distribution of prothrombin time (baseline and peak) by bleeding events. These will be summarised and presented in Section 8.7.1.2.6 of this evaluation report.

The efficacy analysis is performed on the ITT on treatment analysis population who had been randomised to the rivaroxaban group. The safety analysis was performed on the valid-for-safety analysis population who had been randomised to the rivaroxaban group. In both studies Einstein-PE and Einstein-DVT, after randomisation, PT measurements were taken from subjects randomised to the rivaroxaban group according to the schedule in Table 7, below. A total of 2412 subjects treated with rivaroxaban in study Einstein-PE were included for analysis for study PH36706, while a total of 4130 subjects treated with rivaroxaban in studies Einstein-PE and Einstein-DVT were included for analysis for study PH36711. The number of rivaroxaban subjects with primary efficacy outcome and bleeding events in study Einstein-PE and in pooled studies Einstein-PE and Einstein-DVT are presented in Table 8.

Table 7. Scheduled prothombin time measurements by dosing and intended treatment duration, studies PH36706 and PH36711

Intended Treatment Duration			15 mg BID	20 mg OD			
			Day 15	Day 60	Month 3	Month 6	Month 12
3 months	x	Baseline					
		At					
6 months	x	trough	x	x			
		peak	x		x		
12 months	x	trough	x	x		x	
		peak	x		x		x

Table 8. Number of rivaroxaban subjects with primary efficacy outcome and bleeding events, studies PH36706 and PH36711

Population Outcome	ITT on treatment Primary Efficacy outcome	Safety		
		Major bleeding	Clinically relevant bleeding	All confirmed bleedings
11702 DVT	34	14	139	412
11702 PE	44	26	249	757
Pooled	78	40	388	1169

The analyses were to be divided into four parts: PT and bleeding events in the whole study period, PT and bleeding events in the b.i.d. dosing phase, PT and bleeding events in the o.d. dosing phase, and PT relating to the primary efficacy outcome in the whole study period. Analyses in the whole study period and in the o.d. dosing phase were to be done separately for subjects with “3 or 6 months” and “12 months” intended treatment duration, since the measurement scheme differed for different intended treatment duration. Descriptive summary statistics and box-percentile plots for peak and trough measurements of PT were to be given by visit. Summary statistics and box-percentile plots were to be given for the entire population of rivaroxaban subjects, and also for subgroups of subjects with “no bleeding”, subjects with “major bleeding”, subjects with “clinically relevant bleeding”, subjects with “any bleeding”, and subjects with and without primary efficacy outcome. Tables and figures would be prepared for the entire population as well as by subgroups defined by baseline characteristics.

Comments: The sponsor had stated that these 2 reports were purely technical reports and that results and conclusions will be described in a separate report. It is not critical that the separate report be provided now in order that a recommendation can be made with regards to this submission. However it will be raised as a question to the sponsor as to when the separate report will be expected.

7.1.3. Evaluator’s conclusions on clinical efficacy for the proposed additional indication for treatment of pulmonary embolism

Overall, in the pivotal study, study Einstein-PE, the study design and study inclusion and exclusion criteria were appropriate and consistent with the TGA-adopted EMA guidelines on the clinical investigation of medicinal products for the treatment of venous thromboembolic disease. The comparator active control drug combination and regimen of enoxaparin/VKA is a currently accepted drug combination regimen used in the clinical management of PE. The primary and secondary endpoints of this non-inferiority study are appropriate and consistent with these recommendations of the above-mentioned TGA-adopted EMA guidelines. The statistical methods are appropriate for a non-inferiority study. The rationale and justification for the inferiority margin are in line with the recommendations of the ICH E 9 Statistical Principles for Clinical Trials as well as the EMA Guidelines on the choice of the non-inferiority

margin. The baseline demographic and disease characteristics of the study population were comparable between treatment groups, and also consistent with those in the target patient population.

The efficacy results in the pivotal study showed non-inferiority of rivaroxaban compared with enoxaparin/VKA across all primary and secondary efficacy outcomes. Analyses on the individual components of the efficacy outcomes showed that the incidence rates of recurrent PE, recurrent DVT and all-cause deaths were comparable between treatment groups, but the incidence rate of major bleeding event was lower in the rivaroxaban group (1.4%) compared to the enoxaparin/VKA group (2.4%). The p-values for superiority were not statistically significant across all efficacy endpoints. However, this study was designed as a non-inferiority study, and not powered for test of superiority. Efficacy results of the pooled analysis using data from studies Einstein-PE and Einstein-DVT were consistent with those in study Einstein-PE alone, showing non-inferiority of rivaroxaban compared to enoxaparin/VKA across the primary and secondary efficacy outcomes.

Overall, interpretation of subgroup analyses on the primary efficacy endpoint and the secondary efficacy endpoint of net clinical benefit 1 in study Einstein-PE was difficult due to the low event rates and/or small sample sizes in some subgroups, but did not raise significant concerns that rivaroxaban was less effective in certain subgroups. The p-values for interaction tests for the primary efficacy endpoint were ≥ 0.05 for all the subgroups. Subgroup analyses on net clinical benefit 1 initially triggered a more detailed look at the subgroup categories of age groups, but overall, when evaluated together with the subgroup analysis results in the pooled analysis, did not raise significant concerns.

Subgroup analyses in study Einstein-PE of the efficacy outcome of net clinical benefit 1, which is a composite evaluation of symptomatic recurrent VTE and major bleeding events, showed that the upper limit of the 95% CI of the hazard ratio for the subgroup of subjects aged < 60 years was above 2.0, suggesting that in this subgroup of younger subjects, rivaroxaban was not non-inferior to enoxaparin/VKA, and that there was a 1.3 x higher risk of having a composite outcome of symptomatic recurrent VTE or major bleeding events compared to subjects on enoxaparin/VKA. In addition, the p-value for interaction was < 0.05 in this age subgroup category, suggesting that rivaroxaban was less effective in younger subjects < 60 years in terms of net clinical benefit 1, compared to older subjects ≥ 60 years.

When the endpoint of major bleeding events was not factored in (i.e. primary efficacy endpoint of symptomatic recurrent VTE), subgroup analyses in study Einstein-PE again showed that the upper limits of the 95% CIs of the hazard ratios for younger subjects (subjects aged < 60 years, those aged < 65 years and those aged 65 to 75 years) were again above the pre-specified inferiority margin of 2.0, suggesting that in these subgroup of younger subjects, rivaroxaban was not non-inferior to enoxaparin/VKA, and that there was a 1.3 to 1.5x higher risk of having an outcome of symptomatic recurrent VTE compared to subjects on enoxaparin/VKA. However, the p-values for the interactions tests were now ≥ 0.05 for these subgroup categories, suggesting that there was no statistically significant difference between the younger and older age groups for the efficacy endpoint of symptomatic recurrent VTE. Interpretation of these results was confounded by the relatively low event rates in these subgroups.

Subgroup analyses on the efficacy outcome of net clinical benefit 1 in the pooled analysis of studies Einstein-PE and Einstein-DVT, with overall bigger sample sizes and event rates, showed that although p-values for interaction tests were < 0.05 in the age group subgroup categories (suggesting that rivaroxaban was less effective in subjects who were < 60 years old [compared to those ≥ 60 years old], and in those who were < 65 years old or between 65-75 years old [compared to those > 75 years old]), the upper limits of the 95% CI of the hazard ratios for these younger age subgroups were all below the pre-specified non-inferiority margin of 1.75, indicating rivaroxaban was non-inferior compared to enoxaparin/VKA in these younger subjects.

Subgroup analyses on the primary efficacy endpoint of symptomatic recurrent VTE in the pooled analysis of studies Einstein-PE and Einstein-DVT suggested non-inferiority of rivaroxaban compared to enoxaparin/VKA in these subgroups for the primary efficacy endpoint (upper limits of the 95% CIs of the hazard ratios for pooled subjects aged < 60 years, those aged < 65 years and those aged 65 to 75 years were all below the pre-specified inferiority margin of 1.75), and that there was no statistically significant difference between the younger and older age groups for the primary efficacy endpoint (p-values for the interaction of ≥ 0.05).

Overall, using the subgroup analysis results in the pooled studies Einstein-PE and Einstein-DVT in view of the larger sample sizes and event rates, the subgroup analyses suggested that rivaroxaban was non-inferior compared to enoxaparin/VKA across all age groups for the endpoint of symptomatic recurrent VTE, and that there was also no statistically significant difference between the younger and older age groups for this efficacy endpoint. Rivaroxaban was also non-inferior compared to enoxaparin/VKA across all age groups when major bleeding events were factored in (i.e. net clinical benefit 1), but rivaroxaban appeared to be less effective in the younger age groups compared to the older age groups.

8. Clinical safety

Studies providing evaluable safety data are described in Section 8.1. In this evaluation report, the pivotal study to be evaluated is study Einstein-PE. Study PH36746, which is a pooled analysis of studies Einstein-PE and Einstein-DVT will be evaluated with regards to whether the results were consistent with those in study Einstein-PE. The other studies were exploratory studies, and study methods and results will be briefly summarised.

8.1. Studies providing evaluable safety data

The following studies provided evaluable safety data:

8.1.1. Pivotal efficacy study

In the pivotal efficacy study (study Einstein-PE), the following safety data were collected:

- General adverse events (AEs)

The occurrence of AEs was checked at the regular study visits or telephone contacts. All AEs occurring after the subject had signed the informed consent were recorded on the case report form (CRF). Treatment-emergent AEs (TEAEs) were defined in the study protocol as AEs occurring or worsening after randomisation but not more than 7 days after stop of study treatment. However, the sponsor had stated that in order to ensure consistency of the evaluation across the rivaroxaban development program, tabulations of incidence rates of TEAEs starting after randomisation but not more than 2 days after stop of study medication were also presented. In the CSR of Einstein-PE (and hence in this evaluation report), the term "treatment-emergent" refers to the period from randomisation until 2 days after the last dose of study drug, unless otherwise specified. AEs were coded according to the Medical Dictionary for Regulatory Activities (MedDRA).

- AEs of particular interest

The principal safety outcome was clinically relevant bleeding events (i.e. the composite of major bleeding events and other clinically relevant non-major bleeding events). Secondary safety outcomes included all deaths, other cardiovascular events, and laboratory variables.

The CIAC categorised the bleeding events as major, clinically relevant non-major, or trivial. A major bleeding event was defined as overt bleeding which was associated with a fall in haemoglobin of 2 g/dL or more, led to a transfusion of 2 or more units of packed red blood cells or whole blood, occurred in a critical site (intracranial, intraspinal, intraocular, pericardial,

intra-articular, intramuscular with compartment syndrome, or retroperitoneal), or contributed 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, unscheduled contact (visit or telephone call) with a physician, cessation of study treatment, discomfort for the subject such as pain, or impairment of activities of daily life. All other overt bleeding episodes not meeting the above criteria were classified as trivial bleeding events.

- Laboratory tests

The sponsor had stated that special attention was given to liver-related laboratory tests. Liver function tests (bilirubin [total and direct], alanine aminotransferase [ALT], aspartate aminotransferase [AST], alkaline phosphatase [AP]) and amylase were done in the centralised laboratory. Other laboratory tests, including haematology (haemoglobin [only if suspicion of bleeding event] and platelets [only if suspicion of recurrent DVT/PE]), and coagulation tests (activated partial thromboplastin time [aPTT], INR [only if suspicion of recurrent DVT/PE or bleeding event]) were done in local laboratories. Laboratory tests were performed according to a schedule provided.

8.1.2. Non-pivotal efficacy studies/ meta-analyses study reports

The non-pivotal efficacy studies/meta-analyses study reports provided safety data, as follows:

8.1.2.1. Study PH 36746

This was a meta-analysis of studies Einstein-DVT and Einstein-PE. The safety parameters and outcome measures were the same in both studies Einstein-DVT and Einstein-PE. The efficacy results of this pooled analysis has been presented and discussed in Section 7.1.2.1. Safety results will be discussed in this safety section of the evaluation report. The subject analysis populations, including the valid-for-safety analysis population in this pooled analysis, are presented in the dossier.

8.1.2.2. Studies PH36705 and PH36718

Both studies were identical in objectives and design except that study PH36705 evaluated data from study Einstein-PE only, while study PH36718 was a meta-analysis of the respective data from studies Einstein-PE and Einstein-DVT. These studies were analyses of the effect of rivaroxaban on bleedings and efficacy with selected co-medication categories in study Einstein-PE (study PH36705) and in pooled studies Einstein-PE and Einstein-DVT (study PH36718). Study objectives, methods and efficacy results have been summarised in Section 7.1.2.3 of this evaluation report. Safety results are summarised in Section 8.6.1.2.4.

8.1.2.3. Studies PH36706 and PH36711

Both studies were identical in objectives and design except that study PH36706 evaluated data on study Einstein-PE only, while study PH36711 is a meta-analysis of studies Einstein-PE and Einstein-DVT. The objective of the studies was to evaluate the relationship between the pharmacodynamic marker for rivaroxaban, prothrombin time (PT; measured with Neoplastin reagent), and efficacy and safety outcomes. The efficacy outcome analysed was the incidence of symptomatic recurrent VTE. The safety outcomes were bleeding events (treatment-emergent major bleeding, treatment-emergent major or non-major clinically relevant bleeding, and any treatment-emergent bleeding). Study methods have been summarised in Section 7.1.2.4 of this evaluation report. The clinical summary of safety in Module 2.7 of the submission had briefly summarised the distribution of prothrombin time (baseline and peak) by bleeding events. These will be summarised and presented in Section 8.6.1.2.5 of this evaluation report.

8.1.3. Other studies/meta-analyses study reports evaluable for safety only

8.1.3.1. Study PH36715

Study PH 36715 presented the results of an integrated analysis of the safety profile of the rollover subjects from study Einstein-DVT or study Einstein-PE to the Einstein-Extension study. Study Einstein Extension was a multi-centre, randomised, double-blind, placebo-controlled, event-driven, superiority efficacy study with study treatment duration of 6 or 12 months. Subjects with confirmed symptomatic DVT or PE who had completed 6 or 12 months of treatment with rivaroxaban or VKA (acenocoumarol or warfarin) in studies Einstein-DVT or Einstein-PE, or 6 to 14 months of treatment outside studies Einstein-DVT and Einstein-PE were included in this trial.

As the objective of this study PH 36715 was the safety profile of long-term rivaroxaban use as treatment for DVT or PE, the study population analysed was restricted to the rollover subjects (i.e. subjects who participated in studies Einstein-DVT or Einstein-PE and also in study Einstein Extension, and who took rivaroxaban in both parts). The sponsor had stated that the analyses described in this report were purely exploratory. In addition all analyses were purely descriptive, and no statistical tests had been performed and no statistical models had been applied.

Overall, a total of 1196 subjects were randomised in study Einstein Extension (602 and 594 in the rivaroxaban and placebo groups, respectively). Approximately half of these subjects (314 [52%] in the rivaroxaban group and 318 [53%] in the placebo group) had previously taken part in studies Einstein-DVT or Einstein-PE. A total of 598 subjects in study Einstein Extension received rivaroxaban 20 mg once daily for the full study treatment duration, among whom 172 subjects received rivaroxaban in studies Einstein-DVT or Einstein-PE as well as in study Einstein Extension. This integrated safety analysis was focussed on these 172 rollover subjects, and on the safety outcomes of treatment emergent serious adverse events (TESAEs), treatment emergent major bleeding events, and treatment emergent clinically relevant bleeding events (i.e. the principal safety outcome of treatment-emergent major or clinically relevant non-major bleeding events). Results of the safety outcome of TESAEs are summarised in Section 8.3.3.2.2 of this evaluation report, while those of treatment emergent major bleeding events and clinically relevant bleeding events are summarised in Section 8.6.1.2.2.

8.1.3.2. Studies PH36707 and PH36708

Both studies were identical in objectives and design except that study PH36707 evaluated data from study Einstein-PE only, while study PH36708 was a meta-analysis of the respective data from studies Einstein-PE and Einstein-DVT. These studies were analyses of multiple bleeding events in study Einstein-PE (study PH36707) and in pooled studies Einstein-PE and Einstein-DVT (study PH36708). The objective of the analyses in these studies was to investigate the bleeding profile of rivaroxaban in terms of multiple bleeding events that had been confirmed by the CIAC.

The sponsor had stated that the rationale for these analyses was that given the long treatment exposure in the Einstein studies, multiple bleedings occurring longitudinally over time were expected to occur. However, the reporting of bleeding events into the study database was likely to differ between study sites as the study protocols had not specified particular handling of multiple bleedings (e.g. an intermittent nose bleed could have been reported into the CRF as a single event extending over a long duration, or as multiple brief episodes with distinct start days). During adjudication by the CIAC for the main study analyses in studies Einstein-DVT and Einstein-PE, these multiple bleeding episodes were individually adjudicated and not further aggregated. These 2 studies, PH36707 and PH36708, were intended to provide separate analyses of the pattern of multiple bleedings within subjects.

The sponsor had stated that these analyses were purely exploratory (no statistical tests performed and no statistical models applied) and that these 2 reports were purely technical

reports serving to describe the definitions and statistical approaches underlying these additional safety analyses, and that results and conclusions will be described in a separate report. These 2 study reports consisted of a description of study methods and a listing of study data. The sponsor is also not proposing to make any changes to the currently-approved PI using data derived from these 2 study reports.

The analyses in these studies were performed based on the valid-for-safety analysis population. A process was established centrally within the CIAC to assess, in a blinded fashion, all previously-confirmed bleeding events within a subject for multiple bleeding events. All confirmed bleeding events occurring after the first bleeding event were assessed as either a new event or as a “non-new” event which was linked to a previous bleeding, using the following guidelines: bleeding events occurring at other sites (system organ class) were considered separate bleeding events; an escalation of bleeding severity (from trivial to clinically relevant non-major or major; or from clinically relevant non-major to major) was considered a new bleeding event; bleeding events occurring at the same site or circumstances were considered related if they occurred within 4 weeks (e.g. repetitive minor epistaxis).

Multiple bleeding events analyses were performed for the categories of treatment emergent major bleeding events, treatment emergent clinically relevant bleeding events (i.e. the principal safety outcome of treatment-emergent major or clinically relevant non-major bleeding events), and all treatment-emergent bleeding events. The results are summarised in Section 8.6.1.2.3 of this evaluation.

Comments: The sponsor had stated that these 2 reports were purely exploratory and that results and conclusions will be described in a separate report. It is not critical that the separate report be provided now in order that a recommendation can be made with regards to this submission. However it will be raised as a question to the sponsor as to when the separate report will be expected.

8.1.3.3. Study PH36709 and PH36710

Both studies were identical in objectives and design except that study PH36709 evaluated data from study Einstein-PE only, while study PH36710 was a meta-analysis of the respective data from studies Einstein-PE and Einstein-DVT. These studies were additional safety report for study Einstein-PE (study PH36709) and for pooled studies Einstein-PE and Einstein-DVT (study PH36710).

The objectives of the analyses in these studies were to present the investigator-reported AE rates by MedDRA groupings of special interest¹⁷, characterise these reported AEs with respect to the event outcome and severity, present bleeding events in subjects with anemia as well as AEs and medical history profile in subjects with anemia but without overt bleeding events, present AE rates by Medical Labeling Groupings (MLGs; i.e. sponsor-defined groupings of MedDRA preferred terms) to address the MedDRA granularity, and present the time course of liver laboratory parameters in subjects with ALT >8x upper limit normal (ULN).

The analyses in these studies were performed based on the valid-for-safety analysis population. The sponsor had stated that these analyses were purely exploratory, and that no statistical tests

¹⁷ The MedDRA Standardised MedDRA Queries (SMQs) presented in these reports were Haemorrhages; Haemorrhage terms (excl. laboratory terms); Gastrointestinal haemorrhage; Hepatic disorders; Hepatic disorders SMQ excluding the sub-SMQ “Liver related investigations, signs and symptoms”; Hepatic disorders SMQ excluding the sub-SMQ “Liver-Related Coagulation and Bleeding Disturbances”; Hepatic disorders SMQ excluding the sub-SMQs “Liver related investigations, signs and symptoms” and “Liver-Related Coagulation and Bleeding Disturbances”; Acute pancreatitis based on narrow search; Acute renal failure; Anaphylactic / Severe cutaneous reactions identified by searching the narrow terms; Anaphylactic Reaction SMQ and Severe Cutaneous Adverse Reactions. In addition, the following MedDRA groupings of special interest were analysed: Product specific Bayer MedDRA query Thrombocytopenia; Medical Labeling Grouping Anemia; Preferred Terms (PTs) Occult blood and Occult blood positive; Low level terms (LLTs) Haematuria microscopic, Haematuria microscopic, Microscopic haematuria, Microscopic haematuria and Urinary tract bleed microscopic.

had been performed and no statistical models had been applied. The sponsor had stated that these 2 reports were technical reports serving to describe the definitions and statistical approaches underlying these additional safety analyses, and that results and conclusions will be described in a separate report. These 2 study reports consisted of a description of study methods and a listing of study data. The sponsor is also not proposing to make any changes to the currently-approved PI with data derived from these 2 study reports. In view of the above, this evaluation will summarise the analysis methods without reference to any results, which were not summarised or interpreted by the sponsor in these 2 study reports.

Study objectives and SMQ terms used have been described in preceding paragraphs. Detailed statistical analysis methods were not given in these 2 reports except to state that “all analyses in this report are purely descriptive. Incidence rates for adverse events are calculated as the number of subjects with the event of interest relative to the number of subjects in the safety population.”

Comments: The sponsor had stated that these 2 reports were purely exploratory and that results and conclusions will be described in a separate report. It is not critical that the separate report be provided now in order that a recommendation can be made with regards to this submission. However it will be raised as a question to the sponsor as to when the separate report will be expected.

8.1.4. Clinical pharmacology studies

8.1.4.1. Study PH36686

This report presented a pooled safety analysis of rivaroxaban in subjects included in 64 Phase I clinical trials. Overall, the safety data of 1938 subjects were collected in the 64 studies. Of these, 1600 subjects received at least one dose of rivaroxaban or placebo (1419 received rivaroxaban and 181 received placebo) and were valid for the analysis of safety. Safety outcomes analysed were AEs and changes of laboratory data. Data were presented by descriptive statistical methods.

AEs presented in this study report were treatment emergent AEs. AEs were considered to be treatment emergent if they started during treatment with study medication, from intake of the first dose up to 30 days after the last dose. In crossover studies, AEs were attributed to the last dose of study drug administered prior to the start of the AE. Follow up for each period lasted up to the start of the following period. For the last period, follow up lasted for 30 days after the last dose.

The sponsor had stated that no safety conclusions were to be presented in this report, and that after medical review of the data, the rivaroxaban safety results and conclusions drawn from these data will be reported in a separate report. The main baseline demographic characteristics of the valid-for-safety population are presented in the dossier. The safety results are summarised in Sections 8.3.1.2.2, 8.3.2.2.2, 8.3.3.2.3, and 8.4.1.2.2 of this report.

Comments: The sponsor had stated that these 2 reports were purely exploratory and that results and conclusions will be described in a separate report. It is not critical that the separate report be provided now in order that a recommendation can be made with regards to this submission. However it will be raised as a question to the sponsor as to when the separate report will be expected.

8.2. Patient exposure

The summary of drug exposure in the Einstein-PE study is presented in Tables 9 and 10. The median duration of treatment was similar between the 2 treatment groups (183 days and 182 days in the rivaroxaban and enoxaparin /VKA groups, respectively). Overall, 73.7% of the subjects in the rivaroxaban group and 70.0% of the subjects in the enoxaparin/VKA group were treated for ≥ 6 months.

The summary of drug exposure in the pooled analysis of studies Einstein-DVT and Einstein-PE (applicable for studies PH 36746, PH36708, PH36710 and PH36718) is presented in Tables 10 and 11. The pooled median duration of treatment was similar between the 2 treatment groups (183 days and 182 days in the rivaroxaban and enoxaparin /VKA groups, respectively). Overall, 71.7% of the subjects in the pooled rivaroxaban group and 67.1% of the subjects in the pooled enoxaparin/VKA group were treated for ≥ 6 months.

Table 9. Duration of actual study treatment after randomisation (safety population), study Einstein-PE

Total treatment duration categories	Rivaroxaban	Enoxaparin/VKA
n	2412 (100.0%)	2405 (100.0%)
<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 (22.1%)
≥ 6 months <9 months	1075 (44.6%)	993 (41.3%)
≥ 9 months <12 months	609 (25.2%)	606 (25.2%)
≥ 12 months	95 (3.9%)	83 (3.5%)

Table 10. Duration of treatment after randomisation in study Einstein-PE and the pooled analysis (Einstein-DVT and PE), safety population

	Study 11702 PE		Pooled analysis	
	Rivaroxaban 20 mg o.d. ^a N=2412 (100%)	Enox/VKA N=2405 (100%)	Rivaroxaban 20 mg o.d. ^a N=4130 (100%)	Enox/VKA N=4116 (100%)
Overall actual treatment duration (days)				
missing	0	0	0	0
Mean \pm SD	216.9 \pm 99.1	214.9 \pm 99.1	207.6 \pm 95.9	203.8 \pm 97.4
Median (IQR)	183 (179-352)	182 (178-351)	183 (179-269)	182 (178-266)
Range	1 - 403	1 - 385	1 - 403	1 - 390

a 15 mg b.i.d. for 3 weeks, followed by 20 mg o.d.

Table 11. Duration of actual study treatment after randomisation until intended end of treatment - Population Safety, pooled studies Einstein-DVT and Einstein-PE, Study PH 36746

Total treatment duration categories	Rivaroxaban	Enoxaparin/VKA
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	1029 (24.9%)	1002 (24.3%)

In study PH 36715, which presented the results of an integrated safety analysis for 172 rollover subjects who participated in studies Einstein DVT or Einstein PE and then in study Einstein Extension, and who took rivaroxaban in both parts, the 172 subjects had a median treatment duration with rivaroxaban of 364 days (range: 183 to 644 days). Of these, 132 (76.7%) had a cumulative rivaroxaban treatment duration of at least 12 months, 43 (25.0%) of at least 15 months, 24 (14.0%) of at least 18 months and 3 (1.7%) of at least 21 months. In terms of actual treatment duration, 23.3% (40/172) had a rivaroxaban treatment duration of >0 months to <12 months, 62.8% (108/172) of ≥ 12 months to <18 months, and 14.0% (24/172) of ≥ 18 months.

The extent of exposure to rivaroxaban in the pooled safety analysis of rivaroxaban in subjects in the Phase I clinical trials (applicable for study PH36686) is presented in Table 12 below.

Table 12. Extent of exposure to rivaroxaban (all subjects valid-for-safety, n=1419)

	All n=1419	Rivaroxaban				
		< 10 mg n=77	10 mg n=539	15 mg n=123	20 mg n=338	> 20 mg n=342
1 day n(%)	1135 (80.0)	70 (90.9)	480 (89.1)	81 (65.9)	227 (67.2)	277 (81.0)
2-7 days n(%)	247 (17.4)	7 (9.1)	39 (7.2)	42 (34.1)	111 (32.8)	48 (14.0)
8-10 days n(%)	37 (2.6)	0 (0.0)	20 (3.7)	0 (0.0)	0 (0.0)	17 (5.0)
> 10 days n(%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Comments: Overall, the study drug exposure in the Einstein-PE study is adequate to assess if the safety profile is consistent with that reported in the Product Information.

8.3. Adverse events

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

8.3.1.1. Pivotal study

An overview of the number and percentage of subjects with AEs in each treatment group is presented in Table 13. The percentages of subjects with any AEs were comparable between treatment groups (81.2% [1959/2412] and 80.2% [1928/2405] in the rivaroxaban and enoxaparin/VKA groups, respectively). The percentages of subjects with any TEAEs (i.e. AEs in the period from randomisation until 2 days after the last dose of study drug) were comparable between treatment groups (80.3% [1937/2412] and 79.0% [1901/2405], respectively).

Table 13. Summary of adverse events - safety population, Study Einstein-PE

Incidence of	Rivaroxaban	Enox/VKA
	20 mg o.d. ^a N=2412 (100%)	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%)

All AEs in study 11702 PE were coded using MedDRA Version 14.1 terms.

a 15 mg b.i.d. for 3 weeks, followed by 20 mg o.d.

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.

Abbreviations: AE = adverse event; b.i.d. = twice daily; o.d. = once daily; TE = treatment-emergent; SAE = serious adverse event; Enox = enoxaparin; VKA = vitamin K antagonist

TEAEs that occurred in $\geq 2\%$ of subjects in either treatment group are presented in the dossier. The most commonly reported TEAEs in the rivaroxaban group were epistaxis (9.0% vs. 8.2% in the enoxaparin/VKA group), headache (8.0% vs. 7.2%), chest pain (7.6% vs. 7.7%), nasopharyngitis (7.5% vs. 7.9%), and dyspnoea (6.7% vs. 5.7%). TEAEs with higher incidence rates in the rivaroxaban treatment group by $\geq 1\%$ compared to the enoxaparin/VKA group were menorrhagia (3.0% vs. 1.9%), dyspnoea (6.7% vs. 5.7%), and pruritus (2.2% vs. 1.1%).

8.3.1.2. Other studies

8.3.1.2.1. Study PH 36746

The percentages of subjects with any AEs were comparable between treatment groups (74.1% [3062/4130] and 73.7% [3035/4116] in the pooled rivaroxaban and enoxaparin/VKA groups, respectively), as were the percentages of subjects with any TEAEs (73.0% [3015/4130] and 72.4% [2981/4116], respectively). The most commonly reported TEAEs in the pooled rivaroxaban group were epistaxis (7.4% vs. 6.6% in the pooled enoxaparin/VKA group), headache (6.9% vs. 5.9%), nasopharyngitis (6.8% vs. 6.8%), cough (5.5% vs. 5.3%), and chest pain (5.3% vs. 5.2%).

8.3.1.2.2. Study PH36686

Incidences of subjects with TEAEs by system organ class (SOC) and preferred term in the pooled Phase I studies are presented in the dossier. The percentages of subjects with any TEAEs were 37.7% (535/1419) and 27.1% (49/181) in the pooled rivaroxaban and placebo groups, respectively. The percentages of subjects with any TEAEs across the doses of rivaroxaban were 24.7% (19/77), 37.3% (201/539), 35.8% (44/123), 44.1% (149/338), and 35.7% (122/342), in pooled rivaroxaban dose groups of < 10mg, 10mg, 15mg, 20mg and >20mg, respectively. The most commonly reported TEAEs by preferred term in the pooled rivaroxaban group were headache (12.8% vs. 4.4% in the pooled placebo group), nasopharyngitis (4.1% vs. 0.6%), and fatigue (2.5% vs. 1.7%).

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

8.3.2.1. Pivotal study

The incidences of any treatment-related TEAEs were comparable between treatment groups (32.2% [776/2412] and 32.6% [784/2405] in the rivaroxaban and enoxaparin/VKA groups, respectively). Treatment-related TEAEs that occurred in ≥1% of subjects in either treatment group are presented. The most commonly reported treatment-related TEAEs in the rivaroxaban group were epistaxis (7.2% vs. 6.6% in the enoxaparin/VKA group), haemoptysis (2.6% vs. 1.9%), menorrhagia (2.5% vs. 1.4%), and contusion (2.2% vs. 3.6%). TEAEs with higher incidence rates in the rivaroxaban treatment group by ≥1% compared to the enoxaparin/VKA group were menorrhagia (2.5% vs. 1.4%) and headache (1.5% vs. 0.5%).

The majority of treatment-related TEAEs were assessed as being either mild (21.4% [516/2412] in the rivaroxaban group vs. 23.3% [561/2405] in the enoxaparin/VKA group) or moderate (8.3% [200/2412] vs. 6.7% [160/2405]). The incidences of treatment-related TEAEs which were assessed as being severe were 2.5% [60/2412] in the rivaroxaban group and 2.6% [63/2405] in the enoxaparin/VKA group.

8.3.2.2. Other studies

8.3.2.2.1. Study PH 36746

The incidences of any treatment-related TEAEs were comparable between treatment groups (28.5% [1177/4130] and 28.6% [1178/4116] in the pooled rivaroxaban and enoxaparin/VKA groups, respectively). The most commonly reported treatment-related TEAEs in the pooled rivaroxaban group were epistaxis (5.8% vs. 5.2% in the pooled enoxaparin/VKA group), menorrhagia (2.4% vs. 1.2%), contusion (2.0% vs. 3.1%), and gingival bleeding (1.9% vs. 2.1%).

8.3.2.2.2. Study PH36686

Incidences of subjects with treatment-related TEAEs by preferred term in the pooled Phase I studies are presented. The percentages of subjects with any treatment-related TEAEs were 17.1% (242/1419) and 6.1% (11/181) in the pooled rivaroxaban and placebo groups, respectively. The percentages of subjects with any treatment-related TEAEs across the doses of rivaroxaban were 13.0% (10/77), 18.9% (102/539), 15.4% (19/123), 15.4% (52/338), and

17.3% (59/342), in rivaroxaban dose groups of < 10mg, 10mg, 15mg, 20mg and >20mg, respectively. The most commonly reported treatment-related TEAEs by preferred term in the pooled rivaroxaban group were headache (8.2% vs. 2.8% in the pooled placebo group), and fatigue (1.6% vs. 1.1%).

8.3.3. Deaths and other serious adverse events

8.3.3.1. Pivotal study

The total number of deaths reported and adjudicated was 63 (2.6%) in the rivaroxaban group and 51 (2.1%) in enoxaparin/VKA group. The most frequently reported primary causes for death (by CIAC¹⁸) in the rivaroxaban group were cancer (0.9% [22/2412] in rivaroxaban group vs. 1.0% [23/2405] in enoxaparin/VKA group), infectious disease (0.4% [9/2412] vs. 0.2% [6/2405]), and unexplained death for which PE could not be ruled out (0.3% [8/2412] vs. 0.2% [6/2405]).

The incidence rate of treatment-emergent death (i.e. deaths between treatment randomisation and 2 days after stopping the study drug) was 1.2% (28/2412) in the rivaroxaban group and 0.8% (20/2405) in the enoxaparin/VKA group. The most frequently reported primary causes for death (by CIAC) in this period in the rivaroxaban group were cancer (0.4% [10/2412] in rivaroxaban group vs. 0.2% [4/2405] in enoxaparin/VKA group), unexplained death for which PE could not be ruled out (0.3% [8/2412] vs. 0.2% [5/2405]), and infectious disease (<0.1% [2/2412] vs. 0.2% [4/2405]).

Overall, 20.9% of subjects (504/2412) in the rivaroxaban group and 20.7% of subjects (497/2405) in the enoxaparin/VKA group reported any SAEs. The percentages of subjects with any treatment-emergent SAEs (TESAEs) (i.e. SAEs in the period from randomisation until 2 days after the last dose of study drug) were 19.5% (471/2412) and 19.3% (463/2405) in the rivaroxaban and enoxaparin/VKA groups, respectively. TESAEs that occurred in ≥0.5% of subjects in either treatment group are presented. The most frequently reported TESAEs in the rivaroxaban treatment group were chest pain (0.8% vs. 1.1% in the enoxaparin/VKA group), pneumonia (0.8% vs. 0.8%), and dyspnoea (0.7% vs. 0.5%).

Overall, 4.6% of subjects (112/2412) in the rivaroxaban group and 4.9% of subjects (118/2405) in the enoxaparin/VKA group reported any treatment-related TESAEs. The most frequently reported treatment-related TESAEs in the rivaroxaban treatment group were menorrhagia (0.4% vs. <0.1% in the enoxaparin/VKA group), anaemia (0.3% vs. <0.1%), and haematuria (0.3% vs. 0.4%).

8.3.3.2. Other studies

8.3.3.2.1. Study PH 36746

The total number of deaths reported was 104 (2.5%) in the pooled rivaroxaban group and 103 (2.5%) in the pooled enoxaparin/VKA group. The most frequently reported primary causes for death (preferred term) in the pooled rivaroxaban group were pulmonary embolism (0.2% [7/4130] in pooled rivaroxaban group vs. <0.1% [3/4116] in the pooled enoxaparin/VKA group), and sepsis (0.2% [9/4130] vs. <0.1% [2/4116])¹⁹.

The incidence rate of treatment-emergent death (i.e. deaths between treatment randomisation and 2 days after stopping the study drug) was 1.1% (45/4130) in the pooled rivaroxaban group and 0.9% (39/4116) in the pooled enoxaparin/VKA group. No primary causes for death (by preferred term) occurred at an incidence rate of > 0.01% in the pooled rivaroxaban group.

¹⁸ The causes of death in study Einstein-PE were listed by "cause of death by CIAC" and "AE term by investigator"

¹⁹ The causes of death in study PH36746 were listed by SOC and preferred terms, while the causes of deaths in study Einstein-PE were listed by "cause of death by CIAC" and "AE term by investigator"

Overall, 17.6% of subjects (726/4130) in the pooled rivaroxaban group and 18.2% of subjects (751/4116) in the pooled enoxaparin/VKA group reported any SAEs. The percentages of subjects with any TESAEs were 16.4% (678/4130) and 16.9% (696/4116) in the pooled rivaroxaban and enoxaparin/VKA groups, respectively. The most frequently reported TESAEs in the pooled rivaroxaban treatment group were chest pain (0.6% vs. 0.7% in the pooled enoxaparin/VKA group), pneumonia (0.6% vs. 0.7%), and anaemia (0.5% vs. 0.3%).

Overall, 3.7% of subjects (154/4130) in the pooled rivaroxaban group and 4.1% of subjects (169/4116) in the pooled enoxaparin/VKA group reported any treatment-related TESAEs. The most frequently reported treatment-related TESAEs in the pooled rivaroxaban treatment group were menorrhagia (0.3% vs. <0.1 % in the pooled enoxaparin/VKA group), anaemia (0.3% vs. 0.1%), and haematuria (0.3% vs. 0.4%).

8.3.3.2.2. Study PH 36715

In this integrated safety analysis of the rollover subjects from the Einstein-DVT or Einstein-PE studies to the Einstein Extension study, of the 172 subjects who were valid for safety analysis, a total of 28 (16.3%) had TESAEs. The most frequently reported TESAEs by SOC were cardiac disorders (5 events; 2.9%) and infections and infestations (4 events; 2.3%). All other SOCs had incidence rates below 2.0%. There were no TESAEs by preferred term that had > 1 event reported. Analyses of the occurrence of TESAEs by time interval showed that 24 events (14.0%; 24/172) occurred in the interval of >0 months to <12 months and 4 events (3.0%; 4/132) in the interval of ≥12 months to <15 months. No further TESAEs occurred after 15 months of treatment.

Out of the 172 subjects analysed, 50 subjects had an index event of PE at baseline. Among these 50 subjects, a total of 10 (20.0%) had TESAEs. There were 2 (4.0%) TESAEs each in the SOCs of “cardiac disorders” and “respiratory, thoracic and mediastinal disorders”. All other SOCs had incidence rates of 2.0% (i.e. 1 event). Analyses of the occurrence of TESAEs by time interval in these 50 subjects showed that 9 events (18.0%; 9/50) occurred in the interval of >0 months to <12 months and 1 event (2.6%; 1/39) in the interval of ≥12 months to <15 months. No further TESAEs occurred after 15 months of treatment.

8.3.3.2.3. Study PH36686

No deaths occurred among the 1600 subjects of this pooled Phase I studies evaluation. Overall, 11 SAEs were reported by 10 subjects. None of the SAEs were considered treatment-related.

8.3.4. Discontinuation due to adverse events

8.3.4.1. Pivotal study

The incidence rate of any AEs resulting in permanent discontinuation of study drug was 5.1% (123/2412) in the rivaroxaban group and 4.1% (99/2405) in the enoxaparin/VKA group. The most frequently reported AEs resulting in permanent discontinuation of study drug in the rivaroxaban group were anaemia (0.2% vs. <0.1% in the enoxaparin/VKA group), ischaemic stroke (0.2% vs. 0%), and rash (0.2% vs. 0.1%).

The incidence rate of any AEs resulting in hospitalisation or prolonged hospitalisation was 17.6% (425/2412) in the rivaroxaban group and 17.9% (430/2405) in the enoxaparin/VKA group. The most frequently reported AEs resulting in hospitalisation or prolonged hospitalisation in the rivaroxaban group were chest pain (0.9% vs. 1.1% in the enoxaparin/VKA group), pneumonia (0.8% vs. 0.8%), dyspnoea (0.7% vs. 0.5%), sepsis (0.5% vs. <0.1%), and pleural effusion (0.4% vs. 0.5%).

8.3.4.2. Other studies

8.3.4.2.1. Study PH 36746

The incidence rate of any AEs resulting in permanent discontinuation of study drug was 5.0% (208/4130) in the pooled rivaroxaban group and 4.4% (180/4116) in the pooled enoxaparin/VKA group. The most frequently reported AEs resulting in permanent discontinuation of study drug in the pooled rivaroxaban group were anaemia (0.3% vs. <0.1%% in the pooled enoxaparin/VKA group), and haematuria (0.2% vs. <0.1%).

The incidence rate of any AEs resulting in hospitalisation or prolonged hospitalisation was 15.0% (618/4130) in the pooled rivaroxaban group and 15.6% (641/4116) in the pooled enoxaparin/VKA group. The most frequently reported AEs resulting in hospitalisation or prolonged hospitalisation in the pooled rivaroxaban group were chest pain (0.6% vs. 0.7% in the pooled enoxaparin/VKA group), pneumonia (0.5% vs. 0.7%), dyspnoea (0.5% vs. 0.4%), and anaemia (0.4% vs. 0.3%).

8.3.4.2.2. Study PH36686

Overall, 22 (1.4%; 22/1600) subjects were discontinued from the pooled Phase I studies due to AEs. The only AEs resulting in study discontinuation that were considered related to rivaroxaban were those of pressure on left ear, and of tinnitus in left ear (both reported by the same subject) and that of elevated ALT.

8.4. Laboratory tests

8.4.1. Liver function

8.4.1.1. Pivotal study

Post-baseline incidence rates for various thresholds for the laboratory parameters of AST, ALT, AP, total bilirubin, direct bilirubin as well as concurrent combined elevations of: ALT and bilirubin, AST and bilirubin, and total bilirubin and direct bilirubin, are presented in the dossier.

Overall, there were no significant abnormalities of concern in the liver-related laboratory parameters.

The incidence rates of post-baseline ALT >3 x ULN were lower in the rivaroxaban treatment group than in the enoxaparin/VKA group (1.9% [45/2351] vs. 3.0% [70/2324] in enoxaparin/VKA group). The incidence rates of post-baseline ALT >5x ULN, > 8x ULN, > 10x ULN and >20x ULN were similar between treatment groups. For the laboratory parameters AP and AST, the incidence rates of post-baseline elevations were similar through the various thresholds in both treatment groups. For total bilirubin, the incidence rates of post-baseline elevations at the lowest defined threshold of >1.5 x ULN were higher in the rivaroxaban treatment group compared to the enoxaparin/VKA treatment group (1.9% [24/2352] vs. 1.5% [34/2327] in enoxaparin /VKA group), but similar between treatment groups for the other thresholds. For direct bilirubin, the incidence rates post-baseline elevations at the defined threshold of >1.5 x ULN and > 2x ULN were higher in the rivaroxaban treatment group compared to the enoxaparin/VKA treatment group (> 1.5x ULN: 3.1% [72/2351] vs. 2.0% [46/2319] in enoxaparin /VKA group; > 2x ULN: 1.4% [32/2351] vs. 0.6% [14/2319]), but similar between treatment groups for the other thresholds.

Post-baseline amylase elevations were uncommon. Post-baseline elevations of >3 x ULN occurred in 1 subject in each treatment group, and post-baseline elevations of >5 x ULN, >8x ULN and >10x ULN occurred in 1 subject for each threshold in the enoxaparin/VKA treatment group.

8.4.1.2. Other studies

8.4.1.2.1. Study PH 36746

Post-baseline incidence rates for various thresholds for the laboratory parameters of AST, ALT, AP, total bilirubin, and direct bilirubin in the pooled analysis are presented in the dossier. Overall, the liver-related laboratory results in the pooled analysis were comparable with those in study Einstein-PE.

8.4.1.2.2. Study PH36686

The incidences of high laboratory abnormalities for AST, ALT, AP and total bilirubin were 5.1% (70/1376), 10.2% (136/1334), 0.8% (11/1350), and 4.2% (52/1253), respectively. The incidences of high laboratory abnormalities for AST, ALT, AP and total bilirubin across rivaroxaban dose groups are presented in the dossier.

8.5. Post-marketing experience

The sponsor has provided post-marketing data from spontaneous reports received by Bayer Global Pharmacovigilance cumulatively from the approval of rivaroxaban in Canada on 15 September 2008 and in Europe on 30 September 2008 through to the cut-off date of this submission of 31 December 2011. The sponsor had stated that the results of the XAMOS study (Study 13802, a Phase IV Post-Marketing Surveillance study) had been previously presented as an interim analysis in the previous submission with study Einstein-DVT, and that as of database lock of this submission on 31 December 2011, no new data were available, and hence data from the XAMOS study are not included in this submission.

Overall, until 31 December 2011, 3404 spontaneous case reports (including 156 consumer reports) had been identified, and this included 6144 AEs, of which 3573 were SAEs. The most frequently reported SAEs were PE (n=339), DVT (n=318), haematoma (n=185), and haemorrhage (n=120). Until 31 December 2011, 91 death cases had been reported through spontaneous reporting. The most frequently reported AE associated with a fatal outcome was PE (n=39).

Bleeding-related AEs were identified through a search of the AE database for the preferred terms included in the MedDRA SMQ for Haemorrhages. A total of 1518 cases with at least one bleeding-related event were identified, of which 1108 cases were considered serious. The most frequent bleeding-related SAEs were haematoma (n=185), post-procedural haemorrhage (n=97), haemorrhage (n=120), gastrointestinal haemorrhage (n=90), and post procedural haematoma (n=70).

Comments: The post-marketing data is generally consistent with the known safety profile of rivaroxaban as stated in the currently-approved Australian PI for rivaroxaban.

8.6. Other safety issues

8.6.1. Bleeding events

8.6.1.1. Pivotal study

In study Einstein-PE, the principal safety outcome was clinically relevant bleeding events (i.e. the composite of major bleeding events or clinically relevant non-major bleeding events). Definitions of major bleeding events and of clinically relevant non-major bleeding events have been described in Section 8.1.

The incidence rate of the principal safety outcome was slightly lower in the rivaroxaban group (10.3% [249/2412]) compared to the enoxaparin/VKA treatment groups (11.4% [274/2405]). The hazard ratio (rivaroxaban vs. enoxaparin/VKA) was 0.900 (95% CI: 0.758 to 1.069; p-value for superiority: 0.2305). This result for the principal safety outcome was driven largely by that

for the component of major bleeding events rather than that for clinically relevant non-major bleeding events.

For the component of major bleeding events, the incidence rate was lower in the rivaroxaban treatment group (1.1% [26/2412]) compared to the enoxaparin/VKA treatment group (2.2% [52/2405]). The hazard ratio (rivaroxaban vs. enoxaparin/VKA) was 0.493 (95% CI: 0.308 – 0.789; p-value for superiority: 0.0032). However, the incidence rate of the component of clinically relevant non-major bleeding events was similar between treatment groups (9.5% [228/2412]) and 9.8% [235/2405] in the rivaroxaban and the enoxaparin/VKA treatment groups, respectively). Hazard ratio and test for statistical significance were not presented in the CSR. The Kaplan-Meier curves were generated for the cumulative rate of the principal safety outcome, major bleeding events, and all bleeding events.

In the rivaroxaban group, the majority of major bleeding events were in the category of non-fatal non-critical organ bleeding events (i.e. fall in haemoglobin [Hb] \geq 2 g/dL and/or transfusions \geq 2 units), with an incidence of 0.7% (17/2412) in the rivaroxaban treatment group vs. 1.0% (25/2405) in the enoxaparin/VKA treatment group. Major bleeding events in the category of non-fatal critical organ bleeding events occurred in 0.3% (7/2412) in the rivaroxaban group and 1.1% (26/2405) in the enoxaparin/VKA treatment group. There were 2 (< 0.1%) major bleeding events in the category of fatal major bleeding events in the rivaroxaban group (vs. 3 [0.1%] in the enoxaparin/VKA treatment group).

In the rivaroxaban group, the most frequently reported clinically relevant non-major bleeding events by organ site were urogenital bleeding events (2.2% [52/2412] vs. 2.5% [59/2405] in the enoxaparin/VKA treatment group), nasal bleeding events (1.9% [47/2412] vs. 1.7% [41/2405]), gastrointestinal bleeding events (1.6% [38/2412] vs. 0.7% [17/2405]), and uterine bleeding events (1.6% [38/2412] vs. 1.0% [25/2405]).

Subgroup analyses of bleeding events were performed for the principal safety outcome and for major bleeding events. Analyses of the principal safety outcome in the subgroups showed similar results as those in the overall safety population, with hazard ratios below or close to 1.00, except for the subgroups of patients with active cancer at baseline, those with more than one risk factor, and those in geographic regions of North America and of Israel. However, it is noted that these subgroups had low sample sizes and/or low event rates, making interpretation difficult. Treatment interactions p-values were not statistically significant for these subgroups²⁰. Treatment interactions p-values were not statistically significant for all subgroups except for the subgroup of subjects who had pre-randomisation treatment with LMWH/heparin/fondaparinux.

Analyses of the safety outcome of major bleeding events in the subgroups also showed similar results to that in the overall safety population, with hazard ratios below or close to 1.00, except for the subgroups of patients with active cancer at baseline, and those in geographic regions of Israel. However, these subgroups had low sample sizes and/or low event rates, making interpretation difficult. Treatment interactions p-values were not statistically significant for these subgroups. Treatment interactions p-values were not statistically significant for any subgroups except for the subgroup of age (< 65 vs. 65 to 75 vs. > 75 years old).

8.6.1.2. Other studies

8.6.1.2.1. Study PH 36746

The incidence rate of the principal safety outcome was lower in the pooled rivaroxaban group (9.4% [388/4130] and 10.0% [412/4116] in the pooled rivaroxaban and enoxaparin/VKA treatment groups, respectively). The hazard ratio (rivaroxaban vs. enoxaparin/VKA) was 0.925

²⁰ No interaction p-value was calculated for the subgroup of geographic region as no event occurred within a treatment group in one category of the subgroup.

(95% CI: 0.805 to 1.063; p-value for superiority: 0.2721). This result for the principal safety outcome was driven largely by that for the component of major bleeding events rather than that for clinically relevant non-major bleeding events.

For the component of major bleeding events, the incidence rate was lower in the pooled rivaroxaban treatment group (1.0% [40/4130]) compared to the pooled enoxaparin/VKA treatment group (1.7% [72/4116]). The hazard ratio (rivaroxaban vs. enoxaparin/VKA) was 0.539 (95% CI: 0.366 – 0.794; p-value for superiority: 0.0018). The incidence rate of clinically relevant non-major bleeding events was similar between pooled treatment groups (8.6 % [357/4130]) and 8.7% [357/4116] in the pooled rivaroxaban and the enoxaparin/VKA treatment groups, respectively). Hazard ratio and test for statistical significance were not presented in the CSR. The Kaplan-Meier curve for the cumulative rate of the principal safety outcome, major bleeding events, and all bleeding events in the pooled treatment groups are presented in the dossier.

In the pooled rivaroxaban group, the majority of major bleeding events were in the category of non-fatal non-critical organ bleeding events (i.e. fall in haemoglobin [Hb] \geq 2 g/dL and/or transfusions \geq 2 units), with an incidence of 0.7% (27/4130) in the pooled rivaroxaban treatment group vs. 0.9% (37/4116) in the pooled enoxaparin/VKA treatment group. Major bleeding events in the category of non-fatal critical organ bleeding events occurred in 0.2% (10/4130) in the pooled rivaroxaban group and 0.7% (29/4116) in the pooled enoxaparin/VKA treatment group. There were 3 (< 0.1%) major bleeding events in the category of fatal major bleeding events in the pooled rivaroxaban group (vs. 8 [0.2%] in the pooled enoxaparin/VKA treatment group).

In the pooled rivaroxaban group, the most frequently reported clinically relevant non-major bleeding events by organ site were urogenital bleeding events (2.1% [87/4130] vs. 2.1% [88/4116] in the pooled enoxaparin/VKA treatment group), uterine bleeding events (1.6% [67/4130] vs. 1.0% [41/4116]), nasal bleeding events (1.5% [62/4130] vs. 1.4% [56/4116]), and gastrointestinal bleeding events (1.2% [49/4130] vs. 0.8% [31/4116]).

Subgroup analyses of bleeding events for the principal safety outcome and for major bleeding events are presented in the dossier. Analyses of the principal safety outcome in the subgroups showed similar results to that in the overall safety population, with hazard ratios below or close to 1.00, except for the subgroups of patients in geographic regions of Eastern Europe, of North America and of Israel. However, it is noted that these subgroups had low sample sizes and/or low event rates, making interpretation difficult. Treatment interactions p-values were not statistically significant for this subgroup category of geographic region. Treatment interactions p-values were not statistically significant for all subgroups except for the subgroup of age group (< 60 years vs. \geq 60 years).

Analyses of the safety outcome of major bleeding events in the subgroups showed similar results to that in the overall safety population, with hazard ratios below or close to 1.00, except for the subgroups of patients in study centres with both acenocoumarol and warfarin study treatment patients. However, this subgroup had low event rates, making interpretation difficult. Treatment interactions p-values were not statistically significant for this subgroup category. Treatment interactions p-values were not statistically significant for all subgroups except for the subgroup of age (< 60 vs. \geq 60 years old) and of fragility.

8.6.1.2.2. Study PH36715

Of the 172 rollover subjects, a total of 25 (14.5%) had treatment-emergent clinically relevant bleeding events. Out of these, 2 (1.2%) were major bleeding events and 23 (13.4%) were clinically relevant non-major bleeding events. The major bleeding events were reported as 1 event of bleeding affecting the uterus and 1 event of bleeding affecting the abdomen. The clinically relevant non-major bleeding events were mainly urogenital bleeding (4.7%; 8/172) and nasal bleeding (3.5%, 6/172).

Analyses of the occurrence of treatment-emergent clinically relevant bleeding events by time interval showed that the majority of these events occurred in the interval of >0 months to <12 months (23 out of the 25 events; 13.4% [23/172]). Two events (1.5%; 2/172) occurred in the interval of ≥12 months to <15 months. No further clinically relevant bleeding events occurred after 15 months of treatment.

Out of the 172 subjects analysed, 50 subjects had an index event of PE at baseline. Among these 50 subjects a total of 7 (14.0%) had treatment-emergent clinically relevant bleeding events. Out of these, 1 (2.0%) was major bleeding event, and 6 (12.0%) were clinically relevant non-major bleeding events. The major bleeding event was reported as 1 event of bleeding affecting the abdomen. The clinically relevant non-major bleeding events were urogenital bleeding (4.0%; 2/50), gastrointestinal bleeding (4.0%; 2/50), nasal bleeding (4.0%; 2/50) and rectal bleeding (2.0%, 1/50). Analyses of the occurrence of these events by time interval showed that all 7 events occurred in the interval of >0 months to <12 months.

8.6.1.2.3. *Studies PH36707 and PH36708*

Results of the analyses on multiple bleeding events in studies PH36707 and PH36708 are summarised in the dossier. In study Einstein-PE (study PH36707), 26/2412 (1.1%) subjects in the rivaroxaban group and 52/2405 (2.2%) subjects in the enoxaparin/VKA treatment group had major bleeding events. Out of these 26 subjects in the rivaroxaban group, all 26 had one single bleeding event each. Out of the 52 subjects in the enoxaparin/VKA treatment group, the majority (88.5%; 46/52) had one single bleeding event each. The remaining 11.5% (6/52) had 2 bleeding events each. For the principal safety outcome (i.e. clinically relevant bleeding), 249/2412 (10.3%) subjects in the rivaroxaban group and 274/2405 (11.4%) subjects in the enoxaparin/VKA treatment group had clinically relevant bleeding. Out of the 249 subjects in the rivaroxaban group, the majority (90.4%; 225/249) had one single bleeding event each. The maximum number of multiple clinically relevant bleeding events was 3 events occurring in a subject (reported in 4 out of the 249 subjects; 1.6%). Out of the 274 subjects in the enoxaparin/VKA treatment group, the majority (86.1%; 236/274) had one single bleeding event each. The maximum number of multiple clinically relevant bleeding events was 3 events occurring in a subject (reported in 1 out of the 274 subjects; 0.4%). In study Einstein-PE, the incidence rate of all confirmed bleeding events was 31.4% (757/2412) in the rivaroxaban group and 32.2% (774/2405) in the enoxaparin/VKA treatment group. Out of the 757 subjects in the rivaroxaban group, the majority (66.4%; 503/757) had one single bleeding event. Three subjects (0.4%) had > 5 confirmed bleeding events per subject. Out of the 774 subjects in the enoxaparin/VKA treatment group, the majority (64.3%; 498/774) had one single bleeding event. Five subjects (0.6%) had > 5 confirmed bleeding events per subject.

Results of the analyses on multiple bleeding events in study PH36708 for the pooled studies Einstein-DVT and Einstein PE showed similar results.

Comments: The sponsor had not provided any interpretation or conclusion on the results, and had stated that these 2 reports were purely technical reports and that “No safety conclusions are described in this report. After medical review of the data, results and conclusions will be summarized under separate cover”. It is not critical that the separate reports be provided now in order that a recommendation can be made with regards to this submission. However it will be raised as a question as to when the separate report will be expected.

8.6.1.2.4. *Studies PH36705 and PH36718*

In study Einstein-PE (Study PH36705), the most frequently used co-medications at baseline were statins (15.8% [380/2412] in the rivaroxaban group vs. 15.1% [362/2405] in the enoxaparin/VKA group), ASA (10.5% [253/2412] vs. 9.8% [235/2405]), NSAIDs (10.0% [240/2412] vs. 9.6% [230/2405]), and CYP3A4 inhibitors (6.3% [153/2412] vs. 6.9% [165/2405]).

The incidences of treatment emergent major bleeding in subjects on these co-medications at baseline in study Einstein-PE are presented. The incidences of major bleeding events were higher in subjects on these co-medications at baseline, compared to those who were not, in both treatment groups. However, the incidences of major bleeding events were lower in the rivaroxaban group compared to the enoxaparin/VKA group irrespective of the use of these co-medications at baseline.

The incidences of clinically relevant bleeding events and of all confirmed bleeding events in subjects on these co-medications at baseline are presented in the dossier. The incidences of clinically relevant bleeding events and of all confirmed bleeding events were higher in subjects on these co-medications at baseline, compared to those who were not, in both treatment groups. The incidences of clinically relevant bleeding events and of all confirmed bleeding events were higher in the rivaroxaban group compared to the enoxaparin/VKA group in subjects on statins or NSAIDs at baseline.

The corresponding incidences for the pooled analysis (PH 36718) are presented, and results were similar to those in study PH 36705.

8.6.1.2.5. *Studies PH36706 and PH36711*

The distribution of baseline and peak prothrombin time (measured by Neoplastin) by bleeding events in the safety population of study Einstein-PE (study PH36706) showed that the prothrombin times appeared comparable between subjects without bleeding events and those with bleeding events.

The distribution of baseline and peak prothrombin time (measured by Neoplastin) by bleeding events in the pooled safety population of studies Einstein-DVT and Einstein-PE (study PH36711) showed again that the prothrombin times appeared comparable between subjects without bleeding events and those with bleeding events.

8.6.2. *Cardiovascular events*

8.6.2.1. *Pivotal study*

All pre-defined cardiovascular events (acute coronary syndromes, ischemic stroke, transient ischaemic attack [TIA], non-CNS systemic embolism and vascular death) were adjudicated by the CIAC. Analyses were done for the incidence rates of on-treatment and off-treatment cardiovascular events, respectively. On-treatment events were those events that had an onset not later than 1 day after the last intake of study medication. Off-treatment events were events that had an onset >1 day after last intake of study medication up to 30 days after stop of study medication (i.e. end of observational period of study).

The incidence rates of on-treatment and off-treatment cardiovascular events are presented in the dossier. The overall incidence of on-treatment cardiovascular events was similar between treatment groups (1.5% [35/2412] in the rivaroxaban group and 1.5 % [37/2405] in the enoxaparin/VKA group). The incidence of on-treatment cardiovascular deaths was higher in the rivaroxaban group compared to the enoxaparin/VKA group (0.3% [7/2412] vs. 0.1 % [3/2405]). However the results needed to be interpreted with care due to the low event rates in both treatment groups. The incidences of off-treatment cardiovascular events and of cardiovascular deaths were numerically higher in the rivaroxaban group compared to the enoxaparin/VKA group (off-treatment cardiovascular events: 0.4% [9/2206] in the rivaroxaban group vs. 0.1 % [3/2197] in the enoxaparin/VKA group; off-treatment cardiovascular deaths: 0.2% [4/2206] vs. 0% [0/2197]), although interpretation was limited by low event rates.

8.6.2.2. *Other studies*

8.6.2.2.1. *Study PH 36746*

The incidence rates of on-treatment and off-treatment cardiovascular events in the pooled treatment groups were similar to those in study Einstein-PE.

8.6.3. Liver-related laboratory test abnormalities and hepatic disorder adverse events

8.6.3.1. Pivotal study

Liver-related laboratory test abnormalities have been presented in Section 8.4.1.

Adverse events of the hepatic system were identified from the clinical database using the MedDRA Standardised MedDRA Query (SMQ) for "hepatic disorders". The incidence rates of hepatic disorder AEs, hepatic disorder SAEs, and hepatic disorder AEs resulting in permanent discontinuation of study drug are presented in the dossier. The incidence rate of hepatic disorder AEs was lower in the rivaroxaban treatment group than in the enoxaparin/VKA treatment group (8.3% [199/2412] in rivaroxaban group vs. 12.4% [299/2405] in enoxaparin/VKA group). The incidence rate of hepatic disorder SAEs was also lower in the rivaroxaban treatment group than in the enoxaparin/VKA treatment group (1.0% [23/2412] vs. 1.5% [36/2405]). The incidence rates of hepatic disorder AEs resulting in permanent discontinuation of study drug were comparable between the rivaroxaban and enoxaparin/VKA groups (0.5% [11/2412] and 0.3% [7/2405], respectively).

8.6.3.2. Other studies

8.6.3.2.1. Study PH 36746

The incidence rates of hepatic disorder AEs, treatment-emergent hepatic disorder SAEs, and hepatic disorder AEs resulting in permanent discontinuation of study drug in the pooled treatment groups showed similar pattern to that found in study Einstein-PE, with lower incidences of hepatic disorder AEs and of hepatic disorder SAEs in the pooled rivaroxaban treatment group than in the pooled enoxaparin/VKA treatment group (hepatic disorder AEs: 6.8% [282/4130] in pooled rivaroxaban group vs. 11.2% [460/4116] in pooled enoxaparin/VKA group; hepatic disorder SAEs: 0.9% [36/4130] vs. 1.5% [60/4116]). The incidence rates of hepatic disorder AEs resulting in permanent discontinuation of study drug were comparable between the pooled rivaroxaban and enoxaparin/VKA groups (0.4% [18/4130] and 0.3% [13/4116] respectively).

8.6.4. Other adverse events of interest

Although not stated in the protocol as AEs of interest, the CSR for study Einstein-PE presented AEs identified by the MedDRA preferred terms of thrombocytopenia, pancreatitis, renal failure, and hypersensitivity. As these were also presented in study PH 36746 for the pooled studies Einstein-PE and Einstein-DVT, they will be summarised together in this section.

The incidence rates of thrombocytopenia reported as TEAEs, as TESAEs and as TEAEs resulting in permanent discontinuation of study drug in study Einstein-PE and for the pooled analysis (study PH 36746) were low and comparable in both treatment groups.

With regards to the incidence rates of acute pancreatitis, no patients in the rivaroxaban group reported acute pancreatitis as TEAEs, TESAEs, or as a TEAE that resulted in permanent discontinuation of study drug, in both study Einstein-PE and the pooled analysis.

The incidence rates of renal failure reported as TEAEs, as TESAEs and as TEAEs resulting in permanent discontinuation of study drug in study Einstein-PE and for the pooled analysis (study PH 36746) were low and comparable in both treatment groups.

The incidence rates of anaphylactic reactions/severe cutaneous reactions reported as TEAEs, as TESAEs and as TEAEs resulting in permanent discontinuation of study drug in study Einstein-PE and for the pooled analysis (study PH 36746) were also low and comparable in both treatment groups.

8.7. Evaluator's overall conclusions on clinical safety

Overall, in study Einstein-PE, the incidences of all-causality TEAEs, treatment-related TEAEs, all-causality TESAEs and treatment-related TESAEs were comparable between the 2 treatment groups (Table 14).

Table 14. Incidence of AEs and most commonly-reported AEs in study Einstein-PE and pooled analysis of studies Einstein-PE and DVT, safety population

	Study Einstein-PE		Pooled analysis (studies Einstein-PE and Einstein-DVT)	
	Rivaroxaban N=2412	enoxaparin/VKA N=2405	Pooled Rivaroxaban N=4130	Pooled enoxaparin/VKA N=4116
Incidence of all-causality TEAEs	80.3%	79.0%	73.0%	72.4%
Incidence of treatment-related TEAEs	32.2%	32.6%	28.5%	28.6%
Incidence of all deaths	2.6%	2.1%	2.5%	2.5%
Incidence of all-causality SAEs	19.5%	19.3%	16.4%	16.9%
Incidence of treatment-related TESAEs	4.6%	4.9%	3.7%	4.1%
Most commonly reported all-causality TEAEs in the rivaroxaban group	epistaxis (9.0% vs. 8.2% in the enoxaparin/VKA group) headache (8.0% vs. 7.2%) chest pain (7.6% vs. 7.7%) nasopharyngitis (7.5% vs. 7.9%) dyspnoea (6.7% vs. 5.7%).		epistaxis (7.4% vs. 6.6 % in the pooled enoxaparin/VKA group) headache (6.9% vs. 5.9%) nasopharyngitis (6.8% vs. 6.8%) cough (5.5% vs. 5.3%) chest pain (5.3% vs. 5.2%).	
Most commonly reported treatment-related TEAEs in the rivaroxaban group	epistaxis (7.2% vs. 6.6% in the enoxaparin/VKA group) haemoptysis (2.6% vs. 1.9%) menorrhagia (2.5% vs. 1.4%) contusion (2.2% vs. 3.6%).		epistaxis (5.8% vs. 5.2% in the pooled enoxaparin/VKA group) menorrhagia (2.4% vs. 1.2%) contusion (2.0% vs. 3.1%) gingival bleeding (1.9% vs. 2.1%).	
Most commonly reported all-causality TESAEs in the rivaroxaban group	chest pain (0.8% vs. 1.1% in the enoxaparin/VKA group) pneumonia (0.8% vs. 0.8%) dyspnoea (0.7% vs. 0.5%).		chest pain (0.6% vs. 0.7% in the pooled enoxaparin/VKA group) pneumonia (0.6% vs. 0.7%) anaemia (0.5% vs. 0.3%).	
Most commonly reported treatment-related TESAEs in the rivaroxaban group	menorrhagia (0.4% vs. <0.1 % in the enoxaparin/VKA group) anaemia (0.3% vs. <0.1%) haematuria (0.3% vs. 0.4%).		menorrhagia (0.3% vs. <0.1 % in the pooled enoxaparin/VKA group) anaemia (0.3% vs. 0.1%) haematuria (0.3% vs. 0.4%).	

The safety results of the study were also consistent with the known adverse effects of rivaroxaban. The AEs elicited in this pivotal study are known adverse effects of rivaroxaban stated in the currently-approved Australian PI for rivaroxaban.

Safety results in the pooled analysis of studies Einstein-PE and Einstein-DVT were consistent with those of study Einstein-PE. Safety results in the pooled Phase I studies (study PH36686) did not show any obvious dose-related increase in incidences of all-causality TEAEs and treatment-related TEAEs. Analyses of the rollover subjects from the Einstein-DVT or Einstein-PE studies to the Einstein Extension study (study PH 36715) did not show any obvious increase in incidences of TESAEs with duration of treatment.

The most commonly occurring treatment-related TEAEs in the rivaroxaban group in study Einstein-PE were bleeding-related AEs of epistaxis, haemoptysis and menorrhagia. The most commonly occurring treatment-related TESAEs in the rivaroxaban group were menorrhagia and anaemia. These were known adverse effects of rivaroxaban stated in the currently-approved Australian PI for rivaroxaban. The incidence rates of these treatment-related TEAEs and TESAEs were higher in the rivaroxaban group than in the enoxaparin/VKA group (Table 14).

However, analyses of the AE of interest of bleeding events in both study Einstein-PE and the pooled analysis of studies Einstein-PE and Einstein-DVT showed that the overall incidence of clinically relevant bleeding events (composite of major and clinically relevant non-major bleeding events) was slightly lower in the rivaroxaban group compared to the enoxaparin/VKA group. The incidence of the component of major bleeding events was lower in the rivaroxaban group compared to the enoxaparin/VKA group, yielding hazard ratios of about 0.5, and statistically significant p-values for superiority (rivaroxaban over enoxaparin/VKA) in both study Einstein-PE and the pooled analysis. The incidence of the component of clinically relevant non-major bleeding events was comparable between treatment groups in both study Einstein-PE and the pooled analysis. In addition, the majority of major bleeding events in the rivaroxaban group (in both study Einstein-PE and the pooled analysis of studies Einstein-PE and Einstein-DVT) were in the category of non-fatal non-critical organ bleeding events. The number of fatal major bleeding events in the rivaroxaban group was numerically lower compared to the enoxaparin/VKA treatment group (study Einstein-PE: 2 [$< 0.1\%$] vs. 3 [0.1%] in the enoxaparin/VKA treatment group; pooled analysis: 3 [$< 0.1\%$] vs. 8 [0.2%]).

Subgroup analyses of the principal safety outcome and of major bleeding events in both study Einstein-PE and the pooled analysis showed similar results to that in the overall safety population, with hazard ratios below or close to 1.00, except for certain subgroups with low sample sizes and/or low event rates, which makes interpretation difficult. Treatment interactions p-values were not statistically significant for the majority of the subgroups.

Subgroup analyses in study Einstein-PE showed that for major bleeding events, the hazard ratios of rivaroxaban versus enoxaparin/VKA in the younger age groups (age < 65 years and age 65 to 75 years) were all < 1.0 (i.e. in favour of rivaroxaban over enoxaparin/VKA), although treatment interaction p-values were statistically significant (this was supported by subgroup analyses in the pooled analysis of studies Einstein-PE and Einstein-DVT for major bleeding events, showing that the hazard ratios of rivaroxaban versus enoxaparin/VKA in the age groups of < 60 years was < 1.0 , although treatment interactions p-value was statistically significant for this age subgroup category (age < 60 years vs. ≥ 60 years). These suggested that although there was a statistically significant difference between the younger and the older age groups, subjects on rivaroxaban nonetheless had a lower risk of major bleeding events compared to those on enoxaparin/VKA across the age groups.

When clinically relevant non-major bleeding events were factored in (i.e. principal safety outcome which was a composite of major and clinically relevant non-major bleeding events), subgroup analyses in both study Einstein-PE and the pooled analysis of studies Einstein-PE and

Einstein-DVT suggested that subjects aged <60 years and on rivaroxaban had about 1.1x higher risk of major or clinically relevant non-major bleeding events compared to those on enoxaparin/VKA. In the pooled analysis, the treatment interactions p-value was statistically significant for this age subgroup category (age < 60 years vs. ≥ 60 years), suggesting that there was a statistically significant difference between the younger and older age groups. However, in study Einstein-PE, the p-value was not statistically significant for this age subgroup category.

Analyses of bleeding events in 172 rollover subjects to study Einstein Extension showed that in these subjects, who had a median treatment duration with rivaroxaban of 364 days and among whom about 75% had a cumulative rivaroxaban treatment duration of at least 12 months, and about 25% of at least 15 months, the majority of clinically relevant bleeding events were non-major bleeding events and only a minority were major bleeding events. The majority of these bleeding events occurred within the first 12 months, and no bleeding events were reported after 15 months of treatment, suggesting the incidence of these bleeding events did not increase with duration of treatment.

Analyses on the incidence of multiple bleeding events showed that in both study Einstein-PE and the pooled analysis of studies Einstein-PE and Einstein-DVT, the majority of subjects with clinically relevant bleeding events, major bleeding events, or all confirmed bleeding events had single bleeding event. The incidence rate of multiple bleeding events affecting the principal safety outcome and all confirmed bleeding events were also comparable between treatment groups.

Analyses on the effect of co-medications on the incidence of bleeding events (studies PH36705 and PH36718) suggested that subjects on statins, ASA, NSAIDs or CYP3A4 inhibitors at baseline had a higher incidence of major bleeding events, clinically relevant bleeding events, and all confirmed bleeding events compared to those who were not. The interactions of NSAIDs and CYP3A4 inhibitors with rivaroxaban are known drug interactions stated in the currently approved PI for rivaroxaban. The currently approved PI stated that “No clinically significant pharmacokinetic or pharmacodynamic interactions were observed when rivaroxaban was co-administered with 500 mg acetylsalicylic acid” although it was also stated under the precaution section of the PI that “Care should be taken if patients are treated concomitantly with platelet aggregation inhibitors (e.g. clopidogrel and acetylsalicylic acid) as it may lead to an increased bleeding risk”. No mention of drug interaction with statins are stated in the PI except that “There were no mutual pharmacokinetic interactions between rivaroxaban and midazolam (substrate of CYP 3A4), digoxin (substrate of P-gp) or atorvastatin (substrate of CYP 3A4 and P-gp).” The sponsor is not currently proposing to make any changes to the PI using data derived from studies PH36705 and PH36718, but had stated that these analyses were exploratory and that results and conclusions will be described in a separate report. It is not critical that the separate report be provided now in order that a recommendation can be made with regards to this submission.

The potential use of prothrombin time as a PD marker for bleeding events was explored in studies PH36706 and PH36711, but results had not been analysed with statistical tests and were exploratory at the time of submission. The sponsor had stated that results and conclusions will be described in a separate report. It is not critical that the separate report be provided now in order that a recommendation can be made with regards to this submission.

Analyses of liver laboratory test results and of hepatic disorder AEs and SAEs in both study Einstein-PE and the pooled analysis of studies Einstein-PE and Einstein-DVT yielded results consistent with the known adverse effect of rivaroxaban in causing liver laboratory test abnormalities, and did not raise additional significant concerns on the risk of hepatic injury with rivaroxaban use. The incidence rates of post-baseline increases in ALT, AST and AP were lower or comparable in the rivaroxaban treatment group versus those in the enoxaparin/VKA group. Incidence rates of post-baseline elevations in total and direct bilirubin levels were higher in the rivaroxaban group compared to the enoxaparin/VKA group at lower thresholds of elevations

(>1.5 x ULN for total bilirubin; >1.5 x ULN and > 2x ULN for direct bilirubin), but were similar between treatment groups for the higher thresholds. Analyses of hepatic disorder AEs and SAEs in both study Einstein-PE and the pooled analysis of studies Einstein-PE and Einstein-DVT showed lower incidence rates in the rivaroxaban treatment group than in the enoxaparin/VKA treatment group.

Analyses of cardiovascular events and cardiovascular deaths showed that while overall incidence of on-treatment cardiovascular events was similar between treatment groups, the incidence of on-treatment cardiovascular deaths, off-treatment cardiovascular events and off-treatment cardiovascular deaths were higher in the rivaroxaban group compared to the enoxaparin/VKA group. However, the event rates were low, making interpretation difficult.

9. First round benefit-risk assessment

9.1. First round assessment of benefits

The benefit of rivaroxaban in the proposed usage is:

- Potential treatment of PE and prevention of recurrent DVT and PE

According to a report by the Australia and New Zealand Working Party on the Management and Prevention of Venous Thromboembolism (2008), an estimated 15000 to 23000 Australians experienced VTE in 2008²¹. Retrospective studies report mortality rates following VTE of 5–23%²². Worldwide, PE is the third most common cause of death from cardiovascular disease after heart attack and stroke²³.

Standard treatment for acute DVT or PE usually involves initial use of parenteral anticoagulants such as LMWH (e.g. enoxaparin), unfractionated heparin or fondaparinux. Per oral administration of vitamin K antagonists such as warfarin is then started in overlap with the parenteral anticoagulants. As VKAs can interact with various other drugs and food, treatment with VKAs requires ongoing coagulation laboratory monitoring and dose adjustments to keep the INR in the optimal therapeutic window of 2.0 – 3.0. The sponsor had stated that rivaroxaban was developed as an alternative anticoagulant to the parenteral anticoagulant/VKA treatment regimen, as it is an oral, direct-acting antithrombotic agent with a predictable dose-response relationship, and can be administered without the need for laboratory monitoring of its anti-coagulant effect and subsequent dose-adjustments. As the currently-approved PI for rivaroxaban does not make any reference to a need for anticoagulation laboratory monitoring with the use of rivaroxaban, and this submission does not include any data on this benefit of rivaroxaban over current treatment regimen, this evaluation will only comment on the efficacy claim of rivaroxaban for the treatment of PE and prevention of recurrent DVT and PE, without reference to the benefit of rivaroxaban in not requiring anticoagulation laboratory monitoring.

The study design of the pivotal study submitted, study Einstein-PE, was good, and design elements, including efficacy endpoints, were consistent with the TGA-adopted EMA guidelines on the clinical investigation of medicinal products for the treatment of venous thromboembolic disease. This TGA-adopted EMA guideline recommend that VTE Phase III trials should primarily address clinical outcome in the form of recurrent, symptomatic VTE (non-fatal DVT and/or non-fatal PE), deaths and bleeding episodes. The study primary efficacy endpoint was the composite endpoint of recurrent DVT/PE or deaths from PE, while the main secondary endpoint evaluated

²¹ Access Economics, The burden of venous thromboembolism in Australia: Report for the Australian and New Zealand Working Party on the Management and Prevention of Venous Thromboembolism. 2008

²² Goldhaber SZ, Pulmonary embolism. *Lancet*, 363:1295–305, 2004

²³ Goldhaber SZ, Bounameaux H, Pulmonary embolism and deep vein thrombosis. *Lancet*, 379(9828):1835-46, May 2012.

the composite outcome of recurrent DVT/PE or all-cause deaths. The secondary endpoint labelled “net clinical benefit 1” evaluated the composite outcome of recurrent DVT/PE, deaths from PE, or major bleeding events. The secondary endpoint labelled “net clinical benefit 2” evaluated the composite outcome of recurrent DVT/PE, deaths from PE, major bleeding events, or cardiovascular events/deaths.

Overall, the efficacy results in the pivotal study managed to show non-inferiority of rivaroxaban compared with enoxaparin/VKA, a currently accepted standard treatment regimen for PE, across all these primary and secondary efficacy outcomes. In addition, the incidence rates of the individual components of recurrent PE, recurrent DVT and all-cause deaths were comparable between treatment groups, and the incidence rate of major bleeding event was lower in the rivaroxaban group compared to the enoxaparin/VKA group. The efficacy results in study Einstein-PE were supported by similar efficacy results in the pooled analysis of studies Einstein-PE and Einstein-DVT.

9.2. First round assessment of risks

The main risks of rivaroxaban in the proposed usage are:

- Bleeding
- Hepatic laboratory abnormalities

The potential risks of rivaroxaban listed above were all known adverse effects of rivaroxaban. The safety results of the pivotal study were consistent with the known adverse effects of rivaroxaban stated in the currently-approved Australian PI.

The most commonly occurring treatment-related TEAEs in the rivaroxaban group were bleeding-related AEs of epistaxis, haemoptysis and menorrhagia. These are known adverse effects of rivaroxaban stated in the currently-approved Australian PI for rivaroxaban, and are consistent with the known pharmacodynamic of rivaroxaban.

When compared to enoxaparin/VKA, a currently accepted standard treatment regimen for PE, the incidence rate of major bleeding events was lower in subjects on rivaroxaban group and that of clinically relevant non-major bleeding events was comparable between treatment groups. Taking both major and clinically relevant non-major bleeding events together as a composite endpoint, the overall incidence was lower in subjects on rivaroxaban. In addition, the majority of major bleeding events in the rivaroxaban group were in the category of non-fatal non-critical organ bleeding events. Analyses of bleeding events in rollover subjects to study Einstein Extension showed no evidence that the incidence of these bleeding events increase with duration of treatment. Analyses on the incidence of multiple bleeding events showed that the majority of subjects with bleeding events had single bleeding event instead of multiple bleeding events and that the incidence rate of multiple bleeding events were comparable with that in the enoxaparin/VKA group.

Subgroup analyses for major bleeding events in both study Einstein-PE and the pooled analysis of studies Einstein-PE and Einstein-DVT suggested that although there was a statistically significant difference between the younger and the older age groups, subjects on rivaroxaban nonetheless had a lower risk of major bleeding events compared to those on enoxaparin/VKA across the age groups.

Analyses of hepatic laboratory test results and of hepatic disorder AEs and SAEs in both study Einstein-PE and the pooled analysis of studies Einstein-PE and Einstein-DVT yielded results consistent with the known adverse effect of rivaroxaban in causing hepatic laboratory test abnormalities, and did not raise additional significant concerns on the risk of hepatic injury with rivaroxaban use.

9.3. First round assessment of benefit-risk balance

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

The efficacy results in the pivotal study showed non-inferiority of rivaroxaban compared with enoxaparin/VKA, a currently accepted standard treatment regimen for PE, across all efficacy endpoints: composite endpoint of recurrent VTE or deaths from PE, composite endpoint of recurrent VTE or all-cause deaths, composite endpoint of recurrent VTE, deaths from PE, or major bleeding events, and composite endpoint of recurrent VTE, deaths from PE, major bleeding events, or cardiovascular events/deaths. In addition, the incidence rates of the individual components of recurrent PE, recurrent DVT and all-cause deaths were comparable between rivaroxaban and enoxaparin/VKA.

The potential risks of rivaroxaban elicited in study Einstein-PE were bleeding and hepatic laboratory test abnormalities, which were all known adverse effects of rivaroxaban. When compared to enoxaparin/VKA, the incidence rate of major bleeding events was lower in subjects on rivaroxaban group and that of clinically relevant non-major bleeding events was comparable between rivaroxaban and enoxaparin/VKA. Taking both major and clinically relevant non-major bleeding events together as a composite endpoint, the overall incidence was lower in subjects on rivaroxaban. There is also no evidence suggesting potential liver injury by rivaroxaban, and the adverse effect of liver laboratory test abnormalities could be monitored by routine laboratory assessment.

With regards to benefit-risk balance in the younger or older age groups, subgroup analyses in study Einstein-PE were difficult to interpret due to low event rates/sample sizes in some subgroups, but no interaction test p-value for any subgroup analyses on the primary efficacy endpoint of symptomatic recurrent VTE was statistically significant. Subgroup analyses on the safety endpoint of major bleeding events showed that although there was a statistically significant difference between younger and older subjects (in favour of older subjects), there was nevertheless a lower risk of major bleeding events in younger subjects on rivaroxaban compared to those on enoxaparin/VKA. Insert all information].

10. First round recommendation regarding authorisation

It is recommended that the application for extension of indication of rivaroxaban for treatment of pulmonary embolism be approved.

This is subject to a satisfactory response to the clinical questions raised in Section 11.

11. Clinical questions

11.1. Pharmacokinetics

1. Please provide comments on the results of Study 15921 that appear to differ from the effect of food on rivaroxaban stated in the currently approved PI.

The results of this study using a Japanese breakfast showed that AUC and C_{max} of rivaroxaban after single administration of 15mg rivaroxaban were similar in the fasted state and the fed state. This appeared to be different from those of other food effect studies on rivaroxaban. In the currently approved PI, it was stated that "Intake with food does not affect rivaroxaban AUC or C_{max} at the 10 mg dose", but that "Oral bioavailability of Xarelto 20 mg tablet is reduced to 66% under fasting conditions. When Xarelto 20 mg tablet is taken with food mean AUC is increased by 39% compared to tablet taken under fasting conditions". There was no mention of food effect on 15mg tablet, but it is noted that the currently approved PI states that "Xarelto 10 mg tablets

can be taken with or without food. Intake with food does not affect rivaroxaban AUC or C_{max} at the 10 mg dose. Xarelto 15 mg and 20 mg tablets should be taken with food.", suggesting that food had been found to have an effect on the bioavailability of Xarelto 15mg tablets.

2. Please provide justification for the conclusion for Study 13238 that "a comparable exposure was observed in subjects with CYP induction receiving an adapted dosing regimen and subjects without CYP induction receiving the usual 15 mg b.i.d. / 20 mg o.d. dosing regimen".

The PK results of this study showed that the median rivaroxaban AUC(0-24)_{ss} and median C_{max,ss} were both lower in this study compared to those of the pooled study results from subjects of the Phase II studies (who were not on strong CYP3A4 inducers and treated with the usual 15 mg b.i.d. / 20 mg o.d. dosing regimen), as well as those predicted by the simulations in study 15539, in both the initial and extended treatment periods.

11.2. Efficacy

1. Please provide details on the protocol violations in study Einstein-PE.

The sponsor had stated in the CSR of Einstein-PE that, among all randomised subjects, 12 subjects (0.5%; 12/2420) and 5 subjects (0.2%; 5/2413) in the rivaroxaban group and the enoxaparin/VKA group, respectively, had protocol violations. No further details were given on the nature of the protocol violations, although a listing of all protocol deviations, and protocol deviations that were reasons for exclusions from analysis sets were provided.

2. Please provide a timeline as to the availability of finalised results for studies PH36705, PH36718, PH36706, PH36711, PH36707, PH36708, PH36709, PH36710 and PH 36686.

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

Overall, the sponsor has adequately addressed all the questions posed in the first round of evaluation. In this section on the evaluation of the sponsor's responses to the questions posed in the first round of evaluation, each question and the rationale for the question will be re-stated for ease of reference, followed by the evaluation.

Pharmacokinetics Question 1

Please provide comments on the results of Study 15921 which appear to differ from the currently approved PI regarding the effect of food on rivaroxaban.

Rationale for question: "The results of this study using a Japanese breakfast showed that AUC and C_{max} of rivaroxaban after single administration of 15 mg rivaroxaban were similar in the fasted state and the fed state. This appeared to be different from those of other food effect studies on rivaroxaban. In the currently approved PI, it was stated that "Intake with food does not affect rivaroxaban AUC or C_{max} at the 10 mg dose", but that "Oral bioavailability of Xarelto 20 mg tablet is reduced to 66% under fasting conditions. When Xarelto 20 mg tablet is taken with food mean AUC is increased by 39% compared to tablet taken under fasting conditions". There was no mention of food effect on 15 mg tablet, but it is noted that the currently approved PI states that "Xarelto 10 mg tablets can be taken with or without food. Intake with food does not affect rivaroxaban AUC or C_{max} at the 10 mg dose. Xarelto 15 mg and 20 mg tablets should be taken with food", suggesting that food had been found to have an effect on the bioavailability of Xarelto 15 mg tablets."

The response by the sponsor adequately clarified the reason for the recommendation in the proposed PI that the 15 mg dose be taken with food. In their response, the sponsor confirmed that dedicated food effect studies performed according to the FDA CDER guidelines were conducted for rivaroxaban 10 mg tablet and 20 mg tablet, but not 15 mg tablet. Results of these confirmatory food effect studies showed that no food effect was observed for the 10 mg tablet, but that after administration of the 20 mg tablet with food, AUC was increased by 39% as compared to administration under fasting condition. The food effect study 15921 on the 15 mg tablet was conducted based on a request from the Japanese Health Authorities, and showed no effect of food on the PK parameters of AUC and C_{max} of rivaroxaban 15 mg tablet. However, the sponsor stated that there were also limited data available from various Phase I studies with different populations (young, elderly, Japanese, Caucasian) receiving rivaroxaban 15 mg in either fasted or fed state, and that in these pooled analyses, a trend towards an apparent effect of food on the PK parameters of rivaroxaban 15 mg was observed. The sponsor had stated that this could have resulted from the comparison of different populations participating in different studies. The sponsor had stated that their overall interpretation of the data was that a relevant effect of food was unlikely for rivaroxaban 10mg and 15 mg, but that in order to provide harmonised posology recommendations per indication, the 15 mg dose was recommended to be taken with food.

Overall, this rationale provided by the sponsor for the recommendation in the proposed PI that the 15 mg dose be taken with food is reasonable. The pooled analyses suggested a possible food effect on rivaroxaban 15mg, and in the absence of any confirmatory food effect study for rivaroxaban 15mg, it is reasonable to recommend that 15 mg dose be taken with food.

Pharmacokinetics Question 2

Please provide justification for the conclusion for Study 13238 that "a comparable exposure was observed in subjects with CYP induction receiving an adapted dosing regimen and subjects without CYP induction receiving the usual 15 mg b.i.d. / 20 mg o.d. dosing regimen".

Rationale for question: "The PK results of this study showed that the median rivaroxaban AUC(0-24)_{ss} and median C_{max,ss} were both lower in this study compared to those of the pooled study results from subjects of the Phase II studies (who were not on strong CYP3A4 inducers and treated with the usual 15 mg b.i.d. / 20 mg o.d. dosing regimen), as well as those predicted by the simulations in study 15539, in both the initial and extended treatment periods."

The response by the sponsor satisfactorily addressed the question. In their response, the sponsor confirmed that the results of study 13283 (in subjects on strong CYP3A4 inducers and treated with the adapted 30mg b.i.d./ 20 mg b.i.d. dosing regimen) showed that the median rivaroxaban AUC(0-24)_{ss} and median C_{max,ss} in these subjects were lower compared to those of the pooled study results (study 12143) from subjects of the Phase II studies (who were not on strong CYP3A4 inducers and were treated with the usual 15 mg b.i.d. / 20 mg o.d. dosing regimen), as well as those predicted by the simulations in study 15539 (based on the same study population as study 12143), in both the initial and extended treatment periods. However, the sponsor has stated that there were demographic differences between the study populations which had to be taken into account. The sponsor provided data which showed that the patients in study 13238 were younger, had a lower lean body mass and lower serum creatinine concentration than those in the above-mentioned phase II studies (see Table 15 below).

Table 15. Comparison of covariates of the population from this evaluation (IMP13812) vs. the population of the VTE treatment elevation (IMP12143). Median (min/max).

Covariate	IMP13812 ^a	IMP12143 / IMP15539 ^b
AGE [years]	37 (22/79)	61 (18/94)
LBM [kg]	46.15 (30.3/65.4)	55.5 (32.3/92.9)
SCRE [mg/dL]	0.67 (0.41/1.00)	0.93 (0.26/2.36)

LBM: lean body mass; SCRE: serum creatinine concentration

IMP13812: Study 13812 (a sub-study of study 13283), is a PK/PD modelling study using data from study 13238

The sponsor has stated that population PK model had identified effects on clearance and on volume of distribution when compared to a median reference subject aged 61 years with a lean body mass of 56 kg and a serum creatinine concentration of 0.94 mg/dL: with an increase of age by 1 year, clearance decreased by 0.692% and volume of distribution decreased by 0.486%; with an increase of serum creatinine by 0.1 mg/dL, clearance decreased by 2.69%; with an increase of lean body mass by 1 kg, volume of distribution increased by 0.818%. The sponsor was of the opinion that due to the lower age, lower lean body mass and lower serum creatinine concentration in the study population of 13238, a higher individual clearance, and hence lower AUC was expected, in addition to the effect of the strong CYP3A4/P-gp inducer.

Efficacy Question 1

Please provide details on the protocol violations in study Einstein-PE.

Rationale for question: You have stated in the CSR of Einstein-PE that, among all randomised subjects, 12 subjects (0.5%; 12/2420) and 5 subjects (0.2%; 5/2413) in the rivaroxaban group and the enoxaparin/VKA group, respectively, had protocol violations. No further details were given on the nature of the protocol violations, although a listing of all protocol deviations, and protocol deviations that were reasons for exclusions from analysis sets were provided.

The sponsor provided the requested details on the nature of the protocol violations for these subjects. The additional data provided did not raise any concerns impacting the recommendation for this submission.

The additional data provided showed that out of the 12 subjects in the rivaroxaban group, 7 subjects did not have confirmed acute symptomatic PE with or without symptomatic DVT, 3 subjects had concomitant use of strong CYP3A4 inhibitors or strong CYP3A4 inducers, 1 subject had other indication for VKA than DVT and/or PE, and 1 subject whose pre-randomisation local laboratory haematology results were not received prior to randomisation. Out of the 5 subjects in the enoxaparin/VKA group 3 subjects did not have confirmed acute symptomatic PE with or without symptomatic DVT, 1 subject was treated with anticoagulant therapy other than specified in the protocol, and 1 subject had creatinine clearance less than 30 ml/min.

Efficacy Question 2

Please provide a timeline as to the availability of finalised results for studies PH36705, PH36718, PH36706, PH36711, PH36707, PH36708, PH36709, PH36710 and PH36686.

This question was later clarified by the evaluator, via TGA, to the sponsor that the question was raised because in each of the 9 studies, the sponsor had stated that they were “technical reports” and that “After medical review of the data, results and conclusions will be described under separate cover”. The question was therefore seeking for the timeline when these “separate cover” reports describing the results and conclusions will be available.

In their response, the sponsor satisfactorily clarified that these study reports were described as “technical reports” as they were exploratory, and that their results were intended to generally support, “for exploratory and supplementary purposes”, the conclusions presented in the summary documents in Module 2 of the submission, and hence no individual conclusions was presented for the individual study reports. This was the intended meaning of the generic statement of “After medical review of the data, results and conclusions will be described under separate cover”.

The summary documents in Module 2 of the submission, and these 9 study reports had been previously reviewed in the first round of evaluation, and did not raise any concerns impacting the recommendation for this submission.

13. Second round benefit-risk assessment

13.1. Second round assessment of benefits

After consideration of the responses to clinical questions, the benefits of rivaroxaban in the proposed usage are unchanged from those identified in Section 9.1.

13.2. Second round assessment of risks

After consideration of the responses to clinical questions, the risks of rivaroxaban in the proposed usage are unchanged from those identified in Section 9.2.

13.3. Second round assessment of benefit-risk balance

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

14. Second round recommendation regarding authorisation

It is recommended that the application for extension of indication of rivaroxaban for treatment of pulmonary embolism be approved.

15. References

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