Australian Government
Department of Health
Therapeutic Goods Administration

AusPAR Attachment 2

Extract from the Clinical Evaluation Report for Apixaban

Proprietary Product Name: Eliquis

Sponsor: Bristol-Myers Squibb Australia Pty Ltd

First round CER report: 31 July 2014
Second round CER report: 31 December 2014

TGA Health Safety Regulation

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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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List of abbreviations

Abbreviation	Meaning
AE	Adverse event
ALT	Alanine aminotransferase
aPTT	Activated partial thromboplastin time
ASA	Acetylsalicylic acid
AST	Aspartate aminotransferase
$AUC_{0\text{-}inf}$	Area under the curve from time 0 to infinity
AXA	Anti-factor Xa activity
BID	Twice daily
BMS	Bristol-Myers Squibb
BMS-562247	Apixaban
BMS-730823	Major metabolite of apixaban
BUN	Blood urea nitrogen
CBC	Complete blood cell count
CI	Confidence interval
CIAC	Central Independent Adjudication Committee
CK	Creatine kinase
CL	Clearance
CL_{NR}	Non-renal clearance
CL_R	Renal clearance
CrCl	Creatinine clearance
CRF	Case report form
CRNMB	Clinically relevant non-major bleeding
CUS	Compression ultrasound
D5W	5% dextrose in water

Abbreviation	Meaning
DAE	Discontinuation due to adverse event
DBP	Diastolic Blood Pressure
DSMB	Data Safety Monitoring Board
DVT	Deep vein thrombosis
F	Bioavailability
F1.2	Prothrombin fragment F1.2
FSH	Follicle-stimulating hormone
FXa	Factor Xa
GCP	Good Clinical Practice
Hb	Haemoglobin
HCG	Human chorionic gonadotropin
HIV	Human immunodeficiency virus
ICAC	Independent Central Adjudication Committee
ICH	International Conference on Harmonization
INR	International normalized ratio
IVRS	Interactive Voice Response System
k_a	Absorption rate constant
LMWH	Low molecular weight heparin
MB	Major bleeding
MedDRA	Medical Dictionary for Regulatory Activities
mPT	Modified prothrombin time
NSAID	Nonsteroidal anti-inflammatory drug
PD	Pharmacodynamic(s)
PE	Pulmonary embolism
p-gp	p-glycoprotein

Abbreviation	Meaning
PK	Pharmacokinetic(s)
PLS	Perfusion lung scan
QD	Once daily
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SBP	Systolic Blood Pressure
SMC	Study Management Committee
SSRI	Selective serotonin reuptake inhibitor
TAT	Thrombin-antithrombin III complex
TEAE	Treatment emergent adverse event
TC	Treatment compliance
UFH	Unfractionated heparin
ULN	Upper limit of normal
VKA	Vitamin K antagonist
VTE	Venous thromboembolism
WBC	White blood cell
WOCBP	Women of childbearing potential
%CV	Coefficient of variability expressed as a percentage
%DEV	Percentage deviation from the nominal value

1. Introduction

1.1. Submission type

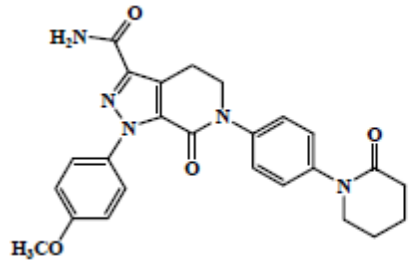
This is a Category 1, Type C submission for extension of indications for Eliquis (apixaban) 2.5 mg and 5 mg film coated tablets.

1.2. Drug class and therapeutic indication

Apixaban is a reversible, direct and highly selective inhibitor of FXa. It does not require antithrombin III for antithrombotic activity. Apixaban inhibits free and clotbound FXa, and prothrombinase activity. Apixaban has no direct effects on platelet aggregation, but indirectly inhibits platelet aggregation induced by thrombin. By inhibiting FXa, apixaban prevents thrombin generation and thrombus development. Preclinical studies of apixaban in animal models have demonstrated antithrombotic efficacy in the prevention of arterial and venous thrombosis at doses that caused negligible prolongation of prothrombin time and bleeding time in rabbits and dogs, but more than 2-fold increases in prothrombin time and bleeding time in rats.

Apixaban has the following structural formula (Figure 1):

Figure 1: Chemical structure



The approved indication is:

> *Eliquis is indicated for the prevention of venous thromboembolic events (VTE) in adult patients who have undergone elective total hip or total knee replacement surgery.*
>
> *Eliquis is indicated for the prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation and at least one additional risk factor for stroke.*

The proposed additional indications are:

> *Eliquis is indicated for the treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE).*
>
> *Eliquis is indicated for the prevention of recurrent DVT and PE.*

1.3. Dosage forms and strengths

The following dosage forms and strengths are currently registered:

- Eliquis 2.5 mg (apixaban) film coated tablet, blister pack, AUST R 172244
- Eliquis 5 mg (apixaban) film coated tablet, blister pack, AUST R 193474

No new dosage forms or strengths are proposed.

1.4. Dosage and administration

Treatment of DVT and PE:

> *The recommended dose of Eliquis is 10 mg taken orally twice daily for 7 days, followed by 5 mg taken orally twice daily.*

Prevention of Recurrent DVT and PE:

> *The recommended dose of Eliquis is 2.5 mg taken orally twice daily after at least 6 months of treatment for DVT or PE.*

2. Clinical rationale

The sponsor provides the following information in the Clinical Overview:

'*PE is the most serious complication of DVT, as the embolised blood clot lodges in the lung vasculature and obstructs blood flow through the lungs. This reduces oxygenation of the blood and increases mechanical strain on the heart, leading to cardiopulmonary compromise, which has a high risk of death. If a large thrombus acutely obstructs the pulmonary vasculature, sudden death is a common outcome, with approximately 300,000 deaths reported annually in the US, a number that exceeds that of deaths from myocardial infarction (MI) (170,000/year) and stroke (158,000/year)*'

In comparison with subjects who have experienced a provoked VTE (for example, after surgery) 'The rate of recurrent VTE is higher in unprovoked VTE, 10% reported after 1 year compared to only 1% after 1 year in provoked VTE.'

In studies for the indication of prevention of recurrent DVT and PE 'Subjects who discontinued active anticoagulant treatment (placebo arm) experienced symptomatic VTE recurrence rates of 7.1% (EINSTEIN EXT) and 8.8% (AMPLIFY EXT) over 12 months of study duration.'

The sponsor has summed up the clinical rationale in the Clinical Overview with:

'*Because bleeding is an important barrier to the use of long-term anticoagulation therapy for prevention of recurrent VTE in patients with unprovoked VTE, there remains an unmet medical need for this large group of patients.*

For VTE treatment, apixaban has demonstrated efficacy that was non-inferior to enoxaparin/warfarin, and bleeding across all categories (unlike with rivaroxaban) that was significantly less frequent, including a 69% risk reduction in MB. In preventing a recurrent DVT or PE, apixaban was markedly superior to placebo in subjects with both unprovoked and provoked VTE, with a minimal increase in bleeding for the 2.5 mg BD dose compared to placebo.

The data from the apixaban VTE treatment clinical development program has demonstrated that it fills the recognized unmet medical need for treating and preventing recurrent VTE.'

3. Contents of the clinical dossier

3.1. Scope of the clinical dossier

The submission contained the following clinical information:

- Five clinical pharmacology studies, including five that provided pharmacokinetic data and one that provided pharmacodynamic data.
- There were three studies evaluating the taste properties of oral formulations over a two year period (Study CV185061, Study CV185083 and Study CV185105)

- One population pharmacokinetic/ pharmacodynamic analyses.
- Two pivotal efficacy/safety studies.
- One dose-finding study.

3.2. Paediatric data

The submission did not include paediatric data.

A Paediatric Investigation Plan has been approved in the EU. The plan provides for pharmacokinetic, efficacy and safety studies in the paediatric population. There is also provision for a liquid formulation. However, the studies in children have been deferred until May 2015 at the earliest.

In the US, the sponsor has full waivers for the following indications:

- Stroke prevention in non-valvular atrial fibrillation
- VTE prevention in hip or knee replacement surgery

3.3. Good clinical practice

GCP appears to have been adhered to for all the clinical studies reported in the submission.

4. Pharmacokinetics

4.1. Studies providing pharmacokinetic data

Table 1 shows the studies relating to each pharmacokinetic topic and the location of each study summary.

Table 1: Submitted pharmacokinetic studies.

PK topic	Subtopic	Study ID
	Bioequivalence - Single dose	Study B0661007
		Study CV185111
	Food effect	Study B0661019
		Study CV185091
PK interactions	Prasugrel	CV185073
Population PK analyses	Target population	Study PMAR-00312

None of the pharmacokinetic studies had deficiencies that excluded their results from consideration.

4.2. Summary of pharmacokinetics

The information in the following summary is derived from conventional pharmacokinetic studies unless otherwise stated.

4.2.1. Pharmacokinetics in healthy subjects

4.2.1.1. Bioavailability relative to an oral solution or micronised suspension

Administration of apixaban 5 mg oral solution by oral syringing was bioequivalent to administration as a 5 mg tablet, crushed and suspended in D5W by nasogastric tube (both fasted) (Study 185111): ratio (90%) CI crushed tablet/oral solution for $AUC_{0\text{-}inf}$ was 0.950 (0.905 to 0.997).

Apixaban 5 mg oral solution (0.4 mg/mL) was bioequivalent when administered by nasogastric tube when followed by D5W, compared with by mouth using an oral syringe (Study CV185091): ratio (90% CI) nasogastric/oral was 0.968 (0.926 to 1.011) for $AUC_{0\text{-}inf}$ and 0.953 (0.873 to 1.040) for C_{max}.

4.2.1.2. Influence of food

Administration of apixaban 5 mg oral solution along with nasogastric enteral feeds resulted in decreased bioavailability (Study CV185111): ratio (90%) CI oral solution + feed/oral solution fasted for $AUC_{0\text{-}inf}$ was 0.813 (0.766 to 0.863).

The bioavailability of a standard commercial 5 mg tablet was reduced by food (Study B0661019,). $AUC_{0\text{-}inf}$ was reduced by 20% and C_{max} by 15%. The ratio (90% CI) fed/fasted was 79.93% (75.19%, 84.97%) for $AUC_{0\text{-}inf}$ and 85.13% (79.32% to 91.35%) for C_{max}.

Apixaban 5 mg oral solution (0.4 mg/mL) was bioequivalent for $AUC_{0\text{-}inf}$ when administered by nasogastric tube when followed by infant formula, compared with by mouth using an oral syringe (Study CV185091): ratio (90% CI) nasogastric/oral were 0.922 (0.899 to 0.947) for $AUC_{0\text{-}inf}$. However C_{max} was decreased by 20%: ratio (90% CI) nasogastric/oral 0.805 (0.749 to 0.865) for C_{max}.

4.2.1.3. Effect of administration timing

Administration of apixaban in the evening resulted in a 46% decrease in ka relative to administration in the morning or afternoon (Study PMAR-00312). This would not be expected to be clinically relevant.

4.2.1.4. Distribution

4.2.1.4.1. Volume of distribution

The effect of baseline body weight on Vc/F was less than directly proportional, with a 24% reduction for a 50 kg subject and a 20% increase for a 120 kg subject relative to the reference subject with a body weight of 85 kg (Study PMAR-00312).

4.2.1.5. Metabolism

There were no new data relating to metabolism.

4.2.1.6. Excretion

4.2.1.6.1. Renal clearance

In a population model of apixaban in VTE subjects the proportion of total clearance that was renal (CLR/F) was calculated to be approximately 42%. In subjects with impaired renal function, CLR/F increased with increasing cCrCL up to a breakpoint of 150 mL/min (consistent with normal renal function) with a linear relationship (Study PMAR-00312).

4.2.1.7. Intra- and inter-individual variability of pharmacokinetics

The inter-individual variability (expressed as CV%) for ke was 23.3 and for V/F was 23.5 (Study PMAR-00312).

4.2.2. Pharmacokinetics in the target population

Study PMAR-00312 was conducted in the target population (see Sections 4.2.2.1.3, 4.2.2.2.1, and 4.2.2.5).

4.2.3. Pharmacokinetics in other special populations

4.2.3.1. Pharmacokinetics according to age

CLNR/F was reduced in older (for example, a 40 year old and 80 year old male VTE treatment subject would have 11% higher and 7% lower CLNR/F relative to a reference VTE treatment male subject who is 60 years old; resulting in 7% higher and 4% lower CL/F, respectively (Study PMAR-00312).

4.2.3.2. Pharmacokinetics in other special population / according to other population characteristic

Female subjects had 22.3% lower CLNR/F relative to male subjects, resulting in a 13% lower CL/F (Study PMAR-00312).

Asian race and concomitant use of strong or moderate CYP3A4/p-gp inhibitors resulted in decreases of 16.8% and 20.3% in CL/F, respectively (Study PMAR-00312).

4.2.4. Pharmacokinetic interactions

4.2.4.1. Pharmacokinetic interactions demonstrated in human studies

Apixaban bioavailability was unaltered by concomitant prasugrel (Study CV185073): ratio (90% CI) apixaban + prasugrel / apixaban were 1.041 (0.979 to 1.107) for $AUC_{0-\tau}$ and 1.045 (0.975 to 1.122) for C_{max}. However, exposure to the active metabolite of prasugrel (R-138727) was slightly reduced by concomitant apixaban: ratio (90% CI) apixaban + prasugrel/prasugrel were 0.978 (0.940 to 1.017) for $AUC_{0-\tau}$ and 0.885 (0.789 to 0.991) for C_{max}. In Study CV185073, mean (SD) C_{min} was 70.18 (25.3) ng/mL and was not affected by concomitant prasugrel.

4.3. Evaluator's overall conclusions on pharmacokinetics

The submission contained data relating to the development of a liquid formulation as part of a Paediatric Investigation plan. The data indicate that the liquid formulation is suitable for both oral and nasogastric administration and is bioequivalent to the commercially available tablets. Food affects the bioavailability of the potential liquid formulation and this should be considered should there be an application to register that formulation. The bioavailability of the 5 mg tablet also appears to be decreased by food and this should be considered along with any other data the sponsor has previously submitted with regard to that formulation.

Apixaban bioavailability was unaltered by concomitant prasugrel.

The population PK study described the following covariate effects:

- Administration of apixaban in the evening resulted in a 46% decrease in ka relative to administration in the morning or afternoon.
- CLR/F accounted for approximately 42% of the total clearance and increased with increasing cCrCL up to a breakpoint of 150 mL/min with a linear relationship.
- CLNR/F was reduced in older (for example, a 40 year old and 80 year old male VTE treatment subject would have 11% higher and 7% lower CLNR/F relative to a reference VTE

treatment male subject who is 60 years old; resulting in 7% higher and 4% lower CL/F, respectively.

- Female subjects had 22.3% lower CLNR/F relative to male subjects, resulting in 13% lower CL/F.
- Asian race and concomitant use of strong or moderate CYP3A4/p-gp inhibitors resulted in decreases of 16.8% and 20.3% in CL/F, respectively.
- The effect of baseline body weight on Vc/F was less than directly proportional, with a 24% reduction for a 50 kg subject and a 20% increase for a 120 kg subject relative to the reference subject with a body weight of 85 kg.

5. Pharmacodynamics

5.1. Studies providing pharmacodynamic data

Table 2 shows the studies relating to each pharmacodynamic topic and the location of each study summary.

Table 2: Submitted pharmacodynamic studies.

PD Interactions	Prasugrel	CV185073
Population PD and PK-PD analyses	Target population	Study PMAR-00312

None of the pharmacodynamic studies had deficiencies that excluded their results from consideration.

5.2. Summary of pharmacodynamics

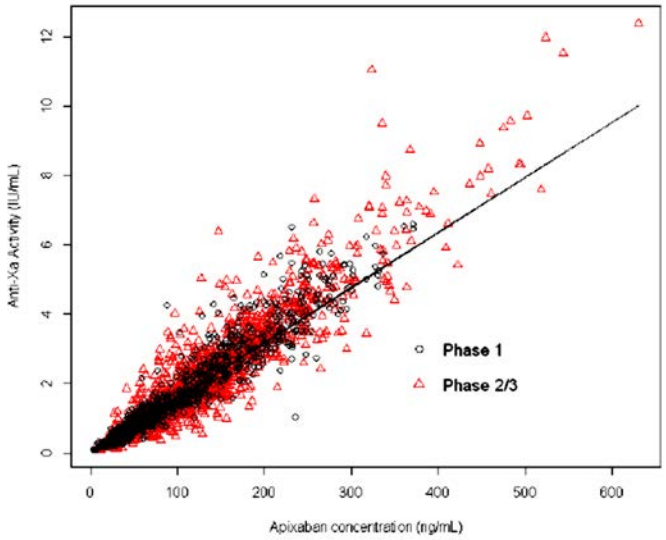
5.2.1. Mechanism of action

There were no new data relating to mechanism of action.

5.2.2. Relationship between drug concentration and pharmacodynamic effects

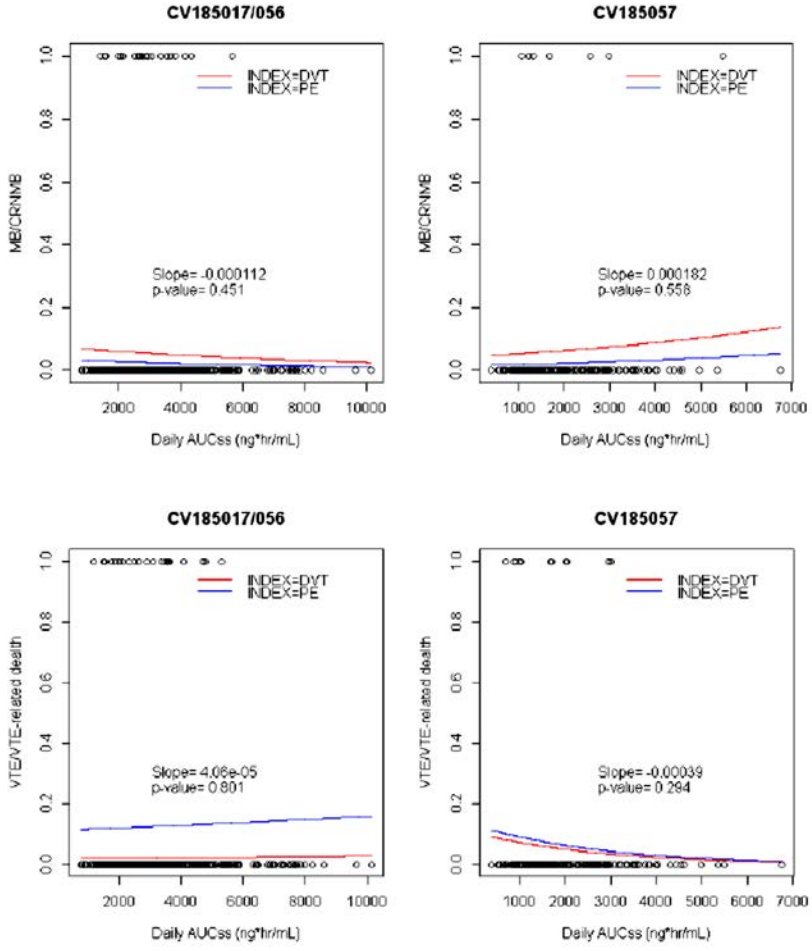
Study PMAR-00312 modelled the concentration response relationship of apixaban and AXA using a linear model. The slope parameter describing the linear relationship between apixaban plasma concentration and AXA was modelled separately for the Phase I studies, Study CV185017 and Study CV185056 and for Study CV185057: estimate (95% CI) 23.9 (22.8 to 25.0), 30.6 (29.3 to 31.9) and 26.7 (24.9 to 28.5) respectively. Overall there was an apparent linear relationship between predicted plasma concentration and AXA (Figure 2).

Figure 2: Apixaban Plasma Concentration vs AXA in LMWH Units



The logistic regression analysis of the PKPD relationship with MB/CRNMB or VTE/VTE-related death found no statistically significant relationship (Figure 3). However, the analysis was limited by the small numbers of events (MB/CRNMB or VTE/VTE-related death).

Figure 3: Fitted Logistic Regression Line for MB/CRNMB (top) and VTE and VTE-related Death (bottom)



Source: ePharmacology step ID 469346. INDEX=index event; DVT=deep vein thrombosis; PE=pulmonary embolism; P-value is for the slope estimate of logistic regression.

5.2.3. Pharmacodynamic interactions

Study CV185073 demonstrated no significant PD interaction between apixaban and prasugrel. Apixaban did not have any independent effect on platelet aggregation (Figure 4). Prasugrel did not have any effect on the anti-Xa activity of apixaban (Figure 5). There was no effect on International Normalised Ratio (INR) or Prothrombin Time (PT). However, the results for aPTT were not reported.

Figure 4: Day 4 Mean (+/- SD) Platelet Aggregation Values versus Time on a Linear Scale

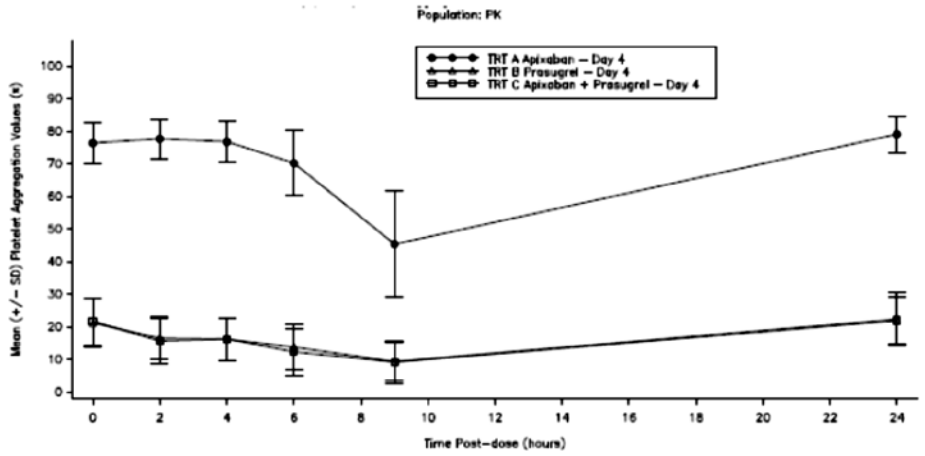
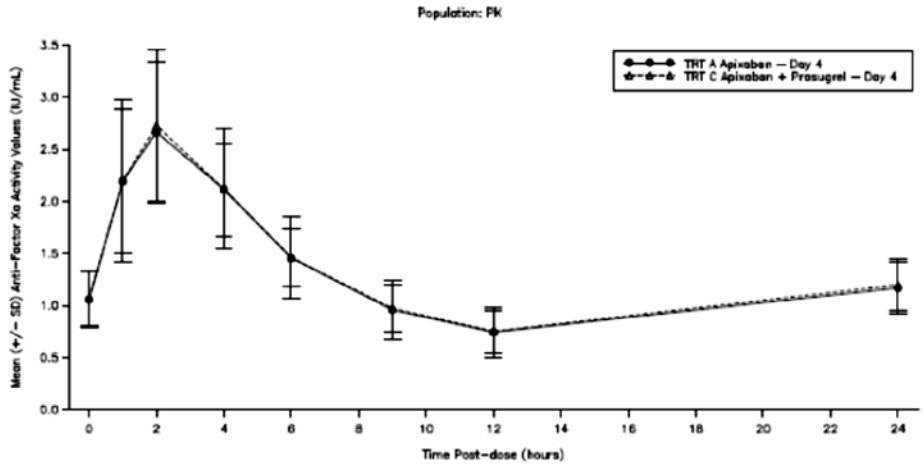
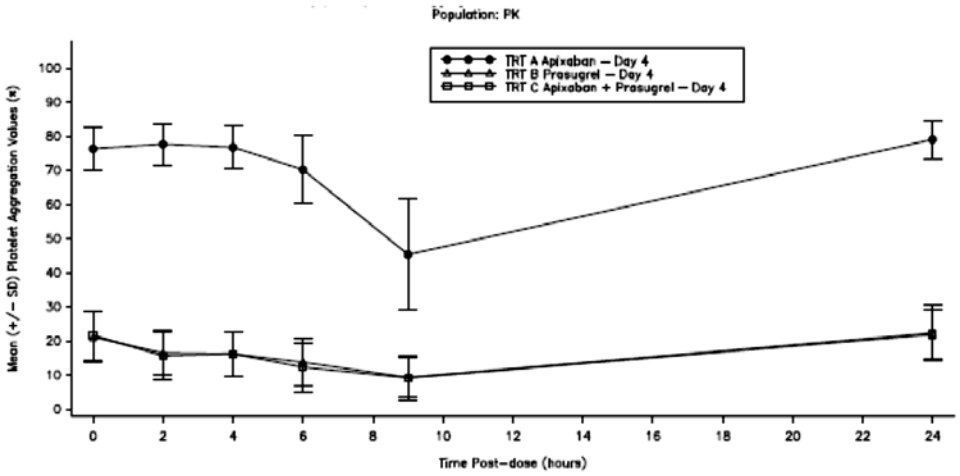


Figure 5: Day 4 Mean (+/- SD) Anti-FXa Activity versus Time on a Linear Scale



There was a decrease in ADP dependent platelet aggregation in the apixaban group at the 9 hour time point (Figure 6). This was not clinically or statistically significant and the sponsor did not have an explanation for the phenomenon.

Figure 6: Day 4 Mean (+/- SD) Platelet Aggregation Values versus Time on a Linear Scale



PK=Pharmacokinetics, TRT=Treatment, SD=Standard deviation

5.3. Evaluator's overall conclusions on pharmacodynamics

The sponsor has developed a valid model to explain the plasma concentration response relationship for AXA in the dose range proposed for the treatment of VTE and prevention of recurrent VTE. This model has been used to generate the data presented in Table 1 of the Product Information document. The data generated in Table 1 are a product of both the model and the patient characteristics. Hence there would be expected to be some variability in the distributions of the parameters, especially since they are presented at median, 5th and 95th centiles. However, there was less variability in the pharmacodynamic outcome variables. In the opinion of the evaluator, the data as presented in Table 1 is preferable to a version that did not give an indication of the variability.

The sponsor has also demonstrated no clinically relevant PD interaction with prasugrel at the dose ranges used in clinical practice.

6. Dosage selection for the pivotal studies

6.1. Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE)

6.1.1. Dose finding studies

6.1.1.1. Study CV185017

6.1.1.1.1. Study design, objectives, locations and dates

Study CV185017 was an open label, randomised, parallel group Phase II, study in subjects with acute proximal or extensive calf-vein thrombosis, comparing three dose levels of apixaban with conventional therapy (LMWH or fondiparinux and VKA). The study was conducted at 64 centres in 11 countries from December 2005 to February 2007.

6.1.1.1.2. Inclusion and exclusion criteria

The inclusion criteria included:

- Male or female aged 18 (or legal age of consent) to 90 years

- Confirmed acute symptomatic DVT, ie, proximal vein or extensive calf-vein thrombosis that involved at least the upper third part of the deep calf veins (trifurcation area) without concomitant symptomatic PE
- Women of childbearing potential must have agreed to use an adequate method of contraception during the study and for 1 week after the study and must have had a negative serum or urine pregnancy test at study entry

The exclusion criteria included:

- Pregnancy or breast-feeding
- Thrombectomy, insertion of a caval filter, or use of a fibrinolytic agent to treat the current episode of DVT
- More than 24 hours of pre-randomization treatment with therapeutic dosages of UFH, LMWH, or fondaparinux or more than a single starting dose of VKA before randomization
- Active bleeding or high risk for bleeding, contraindicating treatment with LMWH, fondaparinux, or VKA
- Any other contraindication listed in the labeling of warfarin, acenocoumarol, phenprocoumon, enoxaparin, tinzaparin, or fondaparinux
- Life expectancy < 6 months
- Bacterial endocarditis
- Uncontrolled hypertension (systolic blood pressure > 200 mm Hg or diastolic blood pressure > 110 mm Hg)
- Creatinine clearance < 30 mL/min
- Impaired liver function (ALT > 3 xULN).
- Use of VKA for indications other than DVT
- Use of ASA > 165 mg/day
- Legal lower age limitations (country specific)
- Use of azole antifungals (for example, ketoconazole), human immunodeficiency virus (HIV) protease inhibitors (for example, ritonavir), or macrolide antibiotics (eg, erythromycin) - use of topical azole antifungal agents was permitted

6.1.1.1.3. Study treatments

The study treatments were:

1. Apixaban 5 mg, twice daily
2. Apixaban 10 mg, twice daily
3. Apixaban 20 mg, once daily
4. Open label conventional therapy: Initially LMWH or fondaparinux followed by VKA (warfarin, phenprocoumon or acencoumarol)

Subjects treated with apixaban were blinded to dose. Apixaban was administered orally. There was a 12 week treatment phase, and a 30 day follow-up phase.

Pre-randomization treatment with therapeutic doses of UFH, LMWH, or fondaparinux was allowed for up to a maximum of 24 hours. In addition, a single, pre-randomization starting dose of VKA was also allowed.

For subjects in the open-label comparator group the allowable LMWH regimens were:

- Tinzaparin 175 IU/kg once daily, subcutaneously
- Enoxaparin 1.5 mg/kg once daily, subcutaneously
- Enoxaparin 1.0 mg/kg twice daily, subcutaneously

If fondaparinux were selected instead of LMWH, it was to be administered subcutaneously at a dose 7.5 mg once daily (or 5.0 mg if body weight was < 50 kg or 10.0 mg if body weight was > 100 kg).

For subjects in the open-label comparator group warfarin, acenocoumarol, and phenprocoumon were the only allowed VKAs. The VKA was administered once daily in the evening. Treatment with the VKA was to be started as soon as possible, but not later than 48 hours, after randomization. The VKA dosages were to be adjusted to maintain the INR within the therapeutic range (target, 2.5; range, 2.0 - 3.0). The INR was initially to be measured every 2 to 3 days and, when stable, at least once monthly. Treatment with VKA was continued for 12 weeks.

Use of ASA in doses > 165 mg/day was prohibited. The combination of any dose of ASA plus clopidogrel (75 mg) was prohibited. Use of azole antifungals (for example, ketoconazole), HIV protease inhibitors (for example, ritonavir), or macrolide antibiotics (for example, erythromycin) was not allowed, and it was recommended that use of these potent CYP 3A4 inhibitors be discontinued for 2 weeks before study participation.

6.1.1.1.4. Efficacy variables and outcomes

The primary efficacy outcome measure was the composite of adjudicated symptomatic VTE (that is, recurrent DVT or fatal or non-fatal PE) and deterioration (increase) of the thrombotic burden as assessed by repeat bilateral compression ultrasound (CUS) and perfusion lung scan (PLS) and adjudicated by the CIAC. The Week 12 results were classified as improvement, no relevant change, or deterioration.

The secondary efficacy outcome measures were:

- Deterioration, improvement, and no relevant change on proximal thrombus based on CUS in subjects who presented with symptomatic DVT. For there to be deterioration there was an increase in diameter of 4 mm or more; for improvement the thrombus disappeared (full compressibility or compressed diameter was reduced to 2 mm or less) or the diameter decreased by more than 50% at the week 12 assessment; and no relevant change included other changes that could not be scored as improvement or deterioration.
- Deterioration, improvement, and no relevant change on composite lung thrombus score based on PLS in subjects presenting with symptomatic DVT. Deterioration was defined as when the lobe score was decreased with a value exceeding 0.25 for any individual lobe or for the overall score, that is, the weighted sum over the six lobes. Improvement was when all lobes had a lobe score of 1 or the perfusion defect decreased by more than 50% compared to the baseline scan at the week 12 assessment. No relevant change was when other changes that could not be scored as improvement or deterioration.
- Incidence of symptomatic recurrent VTEs (that is, recurrent DVT or fatal or non-fatal PE)

The primary safety outcome measure was the composite of major and clinically relevant non-major bleeding. Major bleeding was defined as an overt bleeding with one or more of:

- Associated with a fall in Hb of 2 g/dL or more, or
- Leading to transfusion of two or more units of packed red blood cells or whole blood
- Bleeding that occurred in a critical site (intracranial, intra-spinal, intraocular, pericardial, intra-articular, intramuscular with compartment syndrome, retroperitoneal)
- Contributing to death.

Other safety variables were: AEs, clinical laboratory evaluations and vital signs.

The schedule of study visits was summarized. Baseline bilateral CUS of the legs and a PLS were obtained within 36 hours after randomization.

6.1.1.1.5. Randomisation and blinding methods

Subjects were randomized to study group using IVRS in a 1:1:1:1 ratio. Blinding to dose level was maintained in the apixaban groups by using double dummies.

6.1.1.1.6. Analysis populations

The primary efficacy data set included all subjects in the randomized data set who had measurements of CUS and PLS at both baseline and Week 12.

6.1.1.1.7. Sample size

The sample size was not based on demonstrating either superiority or non-inferiority but was intended to be sufficient to indicate the most appropriate dosing strategy to take forward into Phase III. With 130 subjects randomized to each group, the half-width of the 95% confidence intervals (CI) for the differences between treatment groups in the proportion of subjects with the composite endpoint during the Treatment Period would be approximately 10%, assuming the rate of the composite endpoint was approximately 5% for all of the treatment groups.

6.1.1.1.8. Statistical methods

Hypothesis tests were performed using 95% CI for the difference in proportions affected by the efficacy endpoints.

6.1.1.1.9. Participant flow

There were 520 subjects randomized to treatment: 130 to apixaban 5 mg BD, 134 to apixaban 10 mg BD, 128 to apixaban 20 mg QD group, and 128 to the LMWH/VKA group. There were 17 (13.1%) discontinuations in the apixaban 5 mg group twice daily, 12 (9.0%) in the 10 mg twice daily, 21 (16.4%) in the 20 mg daily and 10 (7.8%) in the LMWH/VKA group. The commonest cause for discontinuation was adverse event: 9 (6.9%) subjects in the apiaxaban 5 mg group, 5 (3.7%) in the 10 mg, 11 (8.6%) in the 20 mg and 4 (3.1%) in the LMWH/VKA.

6.1.1.1.10. Baseline data

There were 323 (62.1%) males, 197 (37.9%) females and the age range was 18 to 89 years. There were 195 (37.5%) subjects aged ≥ 65 years. The demographic characteristics of the study groups were similar. The DVT/PE characteristics of the treatment groups were also similar. Overall there were 354 (68.1%) subjects with abnormal PLS at baseline indicating a high proportion of subjects may have had asymptomatic PE. In the open-label group, 24 (19.0%) subjects received enoxaparin 1.5 mg/kg once daily, 72 (57.1%) received enoxaparin 1.0 mg/kg twice daily and 31 (24.6%) received tinzaparin 175 iu/kg.

6.1.1.1.11. Results for the primary efficacy outcome

Although there was no significant difference between the treatment groups, the apixaban 20 mg once daily group had lowest rate of symptomatic recurrent VTE or deterioration: the event rate (95% CI) was 6.0 (2.4 to 11.9) % for 5 mg twice daily, 5.6 (2.3 to 11.2) % for 10 mg twice daily, 2.6 (0.5 to 7.4) % for 20 mg once daily and 4.2 (1.4 to 9.6) % for LMWH/VKA (Table 3). The difference in rate (95% CI) apixaban – LMWH/VKA was 1.7 (- 4.4 to 8.2) % for 5 mg twice daily, 1.4 (- 4.6 to 7.5) % for 10 mg twice daily and -1.7 (- 7.3 to 3.6) for 20 mg daily.

Table 3: Summary of Symptomatic Recurrent VTE/Deterioration during the Treatment Period - Primary Subjects

	APIX BID 5mg (N=117)	APIX BID 10mg (N=125)	APIX QD 20mg (N=116)	Any APIX (N=358)	LMWH/Fond and VKA (N=118)
Symptomatic Recurrent VTE / Deterioration, n	7	7	3	17	5
Event rate (%)	6.0	5.6	2.6	4.7	4.2
95% CI	(2.4, 11.9)	(2.3, 11.2)	(0.5, 7.4)	(2.8, 7.5)	(1.4, 9.6)
Individual Components *					
Fatal PE, n	0	0	1	1	0
Non-Fatal PE, n	0	0	0	0	1
Symptomatic Recurrent DVT, n	3	4	1	8	2
Deterioration, n	4	3	1	8	2
Comparisons to Control Group					
Difference (%) (APIX - LMWH)	1.7	1.4	-1.7		
95% CI	(-4.4, 8.2)	(-4.6, 7.5)	(-7.3, 3.6)		
No Change, n **	21	16	22	59	18
Event rate (%)	17.9	12.8	19.0	16.5	15.3
95% CI	(11.5, 26.1)	(7.5, 20.0)	(12.3, 27.3)	(12.8, 20.7)	(9.3, 23.0)
Improvement, n ***	89	102	91	282	95
Event rate (%)	76.1	81.6	78.4	78.8	80.5
95% CI	(67.3, 83.5)	(73.7, 88.0)	(69.9, 85.5)	(74.2, 82.9)	(72.2, 87.2)

*. Intent-to-treat analysis. If a subject has multiple events, only the most severe one will be counted. Individual components are presented in decreasing order of severity.
**. If a subject does not have a recurrent VTE, and the results from his/her ultrasound tests are normal, and perfusion lung scan results are normal or no relevant change, then the subject is categorized as 'no change' on the primary endpoint
***. If a subject does not have a recurrent VTE, and the results from his/her perfusion lung scan and ultrasound tests have at least one improvement and no deterioration, then the subject is categorized as 'Improvement' on the primary endpoint.

However, the greatest rate of improvement was in the 10 mg twice daily group: the event rate (95% CI) was 76.1 (67.3 to 83.5) % for 5 mg twice daily, 81.6 (73.7 to 88.0) for 10 mg twice daily, 78.4 (69.9 to 85.5) % for 20 mg once daily and 80.5 (72.2 to 87.2) % for LMWH/VKA.

6.1.1.1.12. Results for other efficacy outcomes

- Deterioration, improvement, and no relevant change on proximal thrombus based on CUS in subjects who presented with symptomatic DVT is summarised:
  - Deterioration was infrequent: two (1.7%) subjects in the 5 mg twice daily group, three (2.4%) in the 10 mg twice daily group, one (0.9%) in the 20 mg once daily and two (1.7%) in the LMWH/VKA group
  - Improvement was reported in 82 (70.1%) subjects in the 5 mg twice daily group, 90 (72.0%) in the 10 mg twice daily group, 84 (72.4%) in the 20 mg once daily and 77 (65.3%) in the LMWH/VKA group
  - No relevant change was reported in 33 (28.2%) subjects in the 5 mg twice daily group, 29 (23.2%) in the 10 mg twice daily group, 30 (25.9%) in the 20 mg once daily and 36 (30.5%) in the LMWH/VKA group
- Deterioration, improvement, and no relevant change on composite lung thrombus score based on PLS in subjects presenting with symptomatic DVT is summarised:
  - Deterioration was infrequent: four (3.4%) subjects in the 5 mg twice daily group, one (0.8%) in the 10 mg twice daily group, none (0.0%) in the 20 mg once daily and none (0.0%) in the LMWH/VKA group
  - Improvement was reported in 47 (40.2%) subjects in the 5 mg twice daily group, 47 (37.6%) in the 10 mg twice daily group, 45 (38.8%) in the 20 mg once daily and 52 (44.1%) in the LMWH/VKA group
  - No relevant change was reported in 29 (24.8%) subjects in the 5 mg twice daily group, 38 (30.4%) in the 10 mg twice daily group, 33 (28.4%) in the 20 mg once daily and 28 (23.7%) in the LMWH/VKA group
- The incidence of symptomatic recurrent VTEs (ie, recurrent DVT or fatal or non-fatal PE) is also summarised:

- Symptomatic recurrent VTE occurred in three (2.6%) subjects in the 5 mg twice daily group, four (3.2%) in the 10 mg twice daily group, two (1.7%) in the 20 mg once daily and three (2.5%) in the LMWH/VKA group

6.1.2. Evaluator's conclusions on dose finding for treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE)

There are some issues with the dose finding study. The definition of symptomatic PE was not included in the protocol. The comparator group included subjects treated with tinzaparin, which is not available in Australia. However, in the opinion of the evaluator, these issues do not detract from the value of the study as a dose finding study.

All three dosing apixaban regimens had similar efficacy. For convenience of dosing, the 20 mg once daily would have been the most advantageous dosing regimen to take into Phase III. However, this would have been a different dosing strategy compared to the dosing regimens for the currently approved indications (once daily as opposed to twice daily).

The dosing regimen actually taken into the Phase III study was: Apixaban 10 mg twice daily for 7 days, then 5 mg twice daily; placebo warfarin and enoxaparin.

7. Clinical efficacy

7.1. Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE)

7.1.1. Pivotal efficacy studies

7.1.1.1. Study CV185056

7.1.1.1.1. Study design, objectives, locations and dates

Study CV185056 was a randomised, active controlled, parallel group, double blind, triple-dummy efficacy and safety study in subjects with acute symptomatic proximal DVT or acute symptomatic PE. The study was conducted at 358 centres in 28 countries (including Australia, Canada, and the USA) from August 2008 to March 2013.

7.1.1.1.2. Inclusion and exclusion criteria

The inclusion criteria included:

- Men and women, aged ≥ 18 years, who had an unprovoked index event or a provoked index event with a risk for recurrence
- Subjects who had acute symptomatic proximal DVT with evidence of proximal thrombosis that involved at least the popliteal vein or a more proximal vein, demonstrated by imaging with:
  - CUS including grey-scale or colour-coded Doppler; or
  - Ascending contrast venography.

  Or
- Subjects who had acute symptomatic PE with evidence of thrombosis demonstrated by imaging as follows:
  - An intraluminal filling defect in segmental or more proximal branches on spiral CT scan; or
  - An intraluminal filling defect or a sudden cut-off of vessels more than 2.5 mm in diameter on the pulmonary angiogram; or

  - A perfusion defect of at least 75% of a segment with a local normal ventilation result (high-probability) on ventilation/perfusion lung scan

- The index DVT and/or PE was adjudicated by the Independent Central Adjudication Committee (ICAC) according to the Adjudication Manual. Investigators were encouraged to assemble and submit imaging dossiers to the ICAC as soon as possible during the period that extended from the beginning of the screening period up to two weeks after randomization.
- Women of childbearing potential must have been using an adequate method of contraception to avoid pregnancy throughout the study.

The Exclusion criteria included:

- Women who were pregnant or breastfeeding
- Target Disease Exceptions:
  - Subjects with a provoked index event without the existence of a persistent risk factor for recurrence
  - < 6 months of anticoagulation planned for the most recent DVT or PE (index event)
  - Thrombectomy, insertion of a caval filter, or use of a fibrinolytic agent to treat the concurrent episode of VTE
  - Active bleeding or high risk for bleeding contraindicating treatment with LMWH and a VKA;
  - Subjects with cancer who were treated for ≥6 months with LMWH therapy
  - Subjects with contraindications according to the local prescribing information of enoxaparin or warfarin.
- Medical History and Concurrent Diseases:
  - Subjects with an indication, other than VTE, intended for long term treatment with a VKA such as: mechanical valve; atrial fibrillation or atrial flutter with moderate to high risk of systemic thromboembolism.
  - Conditions for which serious bleeding could have occurred: intracranial bleeding, intraocular bleeding, gastrointestinal bleeding and/or endoscopically verified ulcer disease, head trauma or other major trauma, major surgery, ischemic stroke, neurosurgery, gross haematuria, evidence of poor healing of a major wound or major trauma, planned major surgery during trial, intracranial neoplasm, arteriovenous malformation or aneurysm, overt major bleeding, documented haemorrhagic tendencies or blood dyscrasias
  - Active and clinically significant liver disease (for example, hepatorenal syndrome)
  - Life expectancy < 6 months
  - Bacterial endocarditis
  - Uncontrolled hypertension: SBP > 180 mm Hg or DBP > 100 mm Hg
- Physical and Laboratory Test Findings: platelet count < 100×109 cells/L; haemoglobin < 90 g/L; serum creatinine > 221 μmol/L; CrCl < 25 mL/min; ALT or AST > 2xULN; total bilirubin > 1.5xULN.
- Allergies and Adverse Drug Reactions: heparin induced thrombocytopenia; or allergic reaction to UFH, LMWH, fondaparinux or any VKA.
- Prohibited Treatments and/or Therapies:

- DVT or PE treatment with more than two doses of fondaparinux or a LMWH that was labelled for once daily dosing, or more than three doses of a LMWH that was labelled for twice daily dosing, or continuous infusion of UFH for more than 36 hours, before the first administration of study drug;
- DVT or PE treatment with more than 2 doses of oral VKA therapy before the first administration of study drug;
- ASA > 165 mg/day at randomization;
- Subjects who required dual antiplatelet therapy (such as ASA plus clopidogrel or ASA plus ticlopidine) at randomization

7.1.1.1.3. Study treatments

1. Apixaban 10 mg twice daily for 7 days, then 5 mg twice daily; placebo warfarin and enoxaparin.
2. Enoxaparin 1 mg/kg 12 hourly until INR ≥2, warfarin dosed to target range 2.0 to 3.0; placebo apixaban.

Treatment was for 6 months, followed by a 30 day follow-up period. INR measurements were performed using an encrypted point of care device that provided sham INR measurements for the apixaban group.

The following treatments were prohibited during the treatment period:

- Potent inhibitors of cytochrome CYP3A4 (such as azole antifungals [itraconazole and ketoconazole], macrolide antibiotics [clarithromycin and telithromycin], protease inhibitors [ritonavir, indinavir, nelfinavir, atazanavir, and saquinavir], and nefazodone)
- Aspirin > 165 mg/day.
- Dual antiplatelet therapy such as concomitant (simultaneous) use of both aspirin and a thienopyridine (such as clopidogrel, ticlopidine).
- Other antithrombotic agents (for example, UFH, LMWH, direct thrombin inhibitors, fondaparinux)
- Glycoprotein IIb/IIIa inhibitors (for example, abciximab, eptifibatide, tirofiban)

7.1.1.1.4. Efficacy variables and outcomes

The primary efficacy outcome measure was the incidence of an adjudicated composite of symptomatic, recurrent VTE (nonfatal DVT or nonfatal PE) or VTE-related death during 6 months of therapy. The secondary efficacy outcome measures were:

- Incidence of adjudicated composite of recurrent symptomatic VTE and all-cause death
- Incidence of adjudicated composite of recurrent symptomatic VTE and CV-related death
- Incidence of adjudicated composite of recurrent symptomatic VTE, VTE-related death and major bleeding
- Incidence of adjudicated symptomatic non-fatal DVT
- Incidence of adjudicated symptomatic non-fatal PE
- Incidence of adjudicated VTE-related death
- Incidence of adjudicated CV-related death
- Incidence of all-cause death

In addition to the protocol specified endpoints, the following endpoints were investigated:

- Time to first occurrence of an adjudicated composite of recurrent symptomatic VTE (nonfatal DVT or nonfatal PE) and all-cause death
- Time to first occurrence of an adjudicated composite of recurrent symptomatic VTE (nonfatal DVT or nonfatal PE) and VTE-related death
- Incidence of adjudicated composite of recurrent symptomatic VTE, myocardial infarction, stroke, CV-related death, major bleeding, CRNMB

There was ICAC review and adjudication for all VTE events without awareness of treatment allocation. The required tests to demonstrate the presence of DVT were ultrasonography or venography. The tests to confirm pulmonary embolism were ventilation perfusion scan, spiral CT or pulmonary angiography. All deaths were assessed on the basis of a clinical summary, an autopsy-report (if available), reports of diagnostic tests (if these were performed), all other relevant information for the ICAC such as additional laboratory values, copies of SAE pages if applicable and good quality copies of diagnostic tests (if these were available).

The primary safety outcome measure was the incidence of adjudicated major bleeding during the treatment period. The secondary safety outcome measure was adjudicated composite of major or CRNMB during the treatment period. In addition to the protocol-specified endpoints, secondary safety endpoints included:

- Adjudicated minor bleeding during the treatment period
- Total adjudicated bleeding defined as adjudicated major, CRNMB, or minor bleeding during the treatment period
- CRNMB
- Time to first adjudicated major bleeding during the treatment period
- Time to first adjudicated composite of major or CRNMB during the treatment period

Other safety measures were AEs, laboratory tests, vital signs and ECGs.

7.1.1.1.5. Randomisation and blinding methods

Subjects were randomized using a central IVRS in a 1:1 ratio. Randomization was stratified by the type of disease (symptomatic proximal DVT only or symptomatic PE with or without DVT) at baseline. Blinding was maintained by using placebos for enoxaparin, warfarin and apixaban (depending upon treatment group).

7.1.1.1.6. Analysis populations

The primary efficacy data set used for analyses of event rates consisted of all randomized subjects with a non-missing primary endpoint. Non-inferiority was tested using the per-protocol dataset. The primary efficacy population was used as a sensitivity analysis. The safety dataset included all treated subjects.

7.1.1.1.7. Sample size

The sample size calculation was based on a test of non-inferiority with the margin for non-inferiority being the upper 95% CI for the RR being < 1.8. Assuming that 3% of subjects in the enoxaparin/warfarin group have VTE (nonfatal DVT or nonfatal PE)/ VTE-related death over 6 months of therapy, a sample size of 4094 subjects (in total and randomized 1:1) would have 90% power for a 1-sided α of 0.025 test of non-inferiority assuming true RR of 1. Assuming 15% subjects discontinued treatment early, 2408 subjects per group would be required.

7.1.1.1.8. Statistical methods

Non-inferiority was based the upper 95% CI for the RR being < 1.8 and a risk difference < 0.035. Non-inferiority based on CIs was assessed for the primary efficacy outcome measure using

estimated RR (95% CI) using a stratified analysis. Hypotheses tests (1-sided p-values for noninferiority) were based on the Yanagawa, Tango and Hiejima (YTH) test. Hypotheses test of superiority for efficacy endpoints were based on the Cochran-Mantel-Haenszel (CMH) test stratified by the type of index event (DVT or PE with/without DVT).

Multiplicity was addressed by using the following hierarchical approach to hypothesis testing:

1. Non-inferiority for VTE/VTE-related death
2. Superiority for Major Bleeding
3. Superiority for VTE/VTE-related death
4. Superiority for Major Bleeding/CRNM Bleeding

7.1.1.1.9. Participant flow

A total of 5614 subjects were enrolled in the study, 5395 were randomised to treatment and 5365 (99.4%) received at least one dose of study treatment: 2676 received apixaban and 2689 received warfarin. The 6 months of study treatment was completed by 2314 (86.0%) subjects in the apixaban group and 2291 (84.7%) in the enoxaparin/warfarin (Table 4). The majority of discontinuations were due to death, AE or thrombotic event. The per-protocol population included 2257 (83.9%) subjects in the apixaban group and 2235 (82.7%) in the enoxaparin/warfarin.

Table 4: Overall Summary of Subject Disposition (Randomized Subjects)

Number (%) of Subjects	Apixaban	Enoxaparin/ Warfarin	Total[a]
Subjects enrolled			5614
Subjects randomized	2691	2704	5395
Subjects treated	2676 (99.4)	2689 (99.4)	5365 (99.4)
Subjects who completed 6 months of study treatment	2314 (86.0)	2291 (84.7)	4605 (85.4)
Subjects who discontinued from study treatment[b]	377 (14.0)	413 (15.3)	790 (14.6)
Reason for discontinuation from study treatment			
Death	20 (0.7)	26 (1.0)	46 (0.9)
Adverse event	150 (5.6)	182 (6.7)	332 (6.2)
DVT	15 (0.6)	17 (0.6)	32 (0.6)
PE	9 (0.3)	11 (0.4)	20 (0.4)
Bleeding	18 (0.7)	46 (1.7)	64 (1.2)
MI	3 (0.1)	1 (<0.1)	4 (<0.1)
Stroke	5 (0.2)	1 (<0.1)	6 (0.1)
Thrombocytopenia	2 (<0.1)	0	2 (<0.1)
Venous thromboembolic event[c]	2 (<0.1)	3 (0.1)	5 (<0.1)
Arterial thromboembolic event	2 (<0.1)	2 (<0.1)	4 (<0.1)
Other	94 (3.5)	101 (3.7)	195 (3.6)
Subject withdrew consent or unwilling to provide consent	49 (1.8)	49 (1.8)	98 (1.8)
Lost to follow-up	14 (0.5)	14 (0.5)	28 (0.5)
Poor/non-compliance	20 (0.7)	23 (0.9)	43 (0.8)
Pregnancy	3 (0.1)	2 (<0.1)	5 (<0.1)
Subject did not meet or no longer meets study inclusion/exclusion criteria	13 (0.5)	9 (0.3)	22 (0.4)
Administrative reason by sponsor	1 (<0.1)	1 (<0.1)	2 (<0.1)
Other	107 (4.0)	107 (4.0)	214 (4.0)

Source: Table 14.1.1.2.1 and Table 14.1.1.2.2.
The denominator to calculate each percentage was the total number of randomized subjects in each treatment group.
DVT=Deep vein thrombosis; MI=Myocardial infarction; N=Total number of subjects in respective group; PE=Pulmonary embolism.
a. Data from Site 648 (pertains to 5 subjects) were excluded from all summary tables, and were not included in any 'Randomization' counts. However, the data were included in the listings. The accuracy of the data collected could not be confirmed through source data verification.
b. Subjects who were randomized but never received any study treatment were also included and reason for not being treated was summarized under reason for discontinuation.
c. Venous thromboembolic events were events other than DVT or PE.

7.1.1.1.10. Major protocol violations/deviations

There were 1603 (59.6%) subjects in the apixaban group and 1589 (58.8%) in the enoxaparin/warfarin group with significant protocol deviations. For 1581 (58.85) subjects in the apixaban group and 1562 (57.8) in the enoxaparin/warfarin the deviation was use of a prohibited concomitant medication. For 111 (4.1%) subjects in the apixaban group and 134 (5.0%) in the enoxaparin/warfarin this was a non-study anti-coagulant. There were five (0.2%) subjects in the apixaban group and 17 (0.6%) in the enoxaparin/warfarin with active bleeding or high risk of bleeding at enrolment. The reasons for exclusion from the per-protocol analysis dataset were similar for the two treatment groups (Table 5).

Table 5: Reasons Subjects Excluded From Per-Protocol Population (as Defined by the Statistical Analysis Plan) (Randomized Subjects)

Reason	Apixaban N=2691	Enoxaparin/ Warfarin N=2704	Total N=5395
	n (%)	n (%)	n (%)
Overall	434 (16.1)	469 (17.3)	903 (16.7)
<80% compliance with intended study medications[a]	102 (3.8)	113 (4.2)	215 (4.0)
Thrombectomy, insertion of a caval filter, or use of a fibrinolytic agent to treat the index event of VTE	0	2 (<0.1)	2 (<0.1)
Use of anti-coagulant therapy exceeding the limit as specified in the protocol before the first administration of study medications	19 (0.7)	15 (0.6)	34 (0.6)
Error in treatment assignment resulting in a subject being dosed with an incorrect treatment[b]	5 (0.2)	8 (0.3)	13 (0.2)
Subject randomized but not dosed	15 (0.6)	15 (0.6)	30 (0.6)
Subject randomized but index VTE was not objectively confirmed by the adjudication committee	12 (0.4)	15 (0.6)	27 (0.5)
Subjects who discontinued treatment before the end of the intended treatment period without having had an incidence of the primary efficacy endpoint during the actual treatment period	346 (12.9)	375 (13.9)	721 (13.4)

Source: Table 14.2.2.3.
The denominator to calculate each percentage was the total number of treated subjects within each treatment group.
n=Number of subjects with observation; N=Total number of subjects; VTE=Venous thromboembolism.
a. Treatment compliance (TC) was defined as follows where number of tablets taken counts for apixaban/apixaban placebo (assuming that on the first day subjects did not take the morning dose):
For subjects who received >7 day treatment:
TC=([number of tablets taken]/[days from first dose to last dose of double blinded treatment × 2 + 12]) × 100%
For subjects who received ≤7 day treatment:
TC=([number of tablets taken]/[days from first dose to last dose of double blinded treatment × 4 - 2]) × 100%
b. Additionally, per the predefined per protocol criteria, 1 subject (284-1424) was not eligible for inclusion into the per protocol analysis dataset but was included in this analysis in error. This subject did not experience any efficacy events on trial and therefore this error had no impact on the overall interpretation of the data. This subject received apixaban. For details, refer to Errata.

Data from one study site (Site CV185056-0648 at Shefali Center, Paldi, Ahmedabad, India) were excluded following an internal audit which found that the site lacked appropriate source documentation for a number of data, despite repeated training.

7.1.1.1.11. Baseline data

There were 3167 (58.7%) males, 2228 (41.3%) females and the age range was 18 to 99 years. There were 1130 (20.9%) subjects aged 65 to < 75 years and 774 (14.3%) aged ≥ 75 years. The treatment groups were similar in baseline demographic characteristics and VTE risk factors. The treatment groups were similar in primary anticoagulant treatment prior to randomisation. The treatment groups were similar in prior antiplatelet treatment. The treatment groups were similar in concomitant anticoagulant medications received during the treatment period (Table 6). The index events were similar for the two treatment groups (Table 7).

Table 6: Concomitant Anticoagulant Medications Received During the Treatment Period, Excluding Day 1 and the Last 2 Days of Study Treatment

Generic Name	Apixaban N=2676	Enoxaparin/ Warfarin N=2689	Total N=5365
	n (%)	n (%)	n (%)
Heparinoid derivatives	167 (6.2)	179 (6.7)	346 (6.4)
VKA	90 (3.4)	100 (3.7)	190 (3.5)
Other	1 (<0.1)	1 (<0.1)	2 (<0.1)

Source: Table 14.4.2.4.3.
The denominator to calculate each percentage was the total number of treated subjects within each treatment group.
n=Number of subjects with observation; N=Total number of subjects; VKA=Vitamin k antagonist.

Table 7: Summary of Index Event (Randomized Subjects)

Number (%) of Subjects	Apixaban N=2691	Enoxaparin/ Warfarin N=2704	Total N=5395
Index event strata (IVRS)			
Proximal DVT	1778 (66.1)	1814 (67.1)	3592 (66.6)
PE[a]	913 (33.9)	890 (32.9)	1803 (33.4)
Index event (adjudicated)			
Proximal DVT	1749 (65.0)	1783 (65.9)	3532 (65.5)
PE[a]	930 (34.6)	906 (33.5)	1836 (34.0)
PE only	678 (25.2)	681 (25.2)	1359 (25.2)
PE + proximal DVT	252 (9.4)	225 (8.3)	477 (8.8)
Non-evaluable or not confirmed	12 (0.4)	15 (0.6)	27 (0.5)
Index event diagnostic method - DVT[b]			
CUS	1731 (98.9)	1771 (99.3)	3502 (99.2)
Ascending contrast venography	20 (1.1)	11 (0.6)	31 (0.9)
Computed tomography	2 (<0.1)	1 (<0.1)	3 (<0.1)
Index event diagnostic method - PE[b]			
Spiral computed tomography	810 (87.1)	804 (88.7)	1614 (87.9)
Ventilation-perfusion lung scanning	109 (11.7)	92 (10.2)	201 (10.9)
Pulmonary angiography	21 (2.3)	16 (1.8)	37 (2.0)

Source: Table 14.1.2.4, and Section 16.1.11.
The denominator to calculate each percentage was the total number of randomized subjects within each treatment group.
Index event strata (IVRS) were defined at site. Index event (adjudicated) was defined by the independent central adjudication committee.
CUS=Compression ultrasound; DVT=Deep vein thrombosis; IVRS=Interactive Voice Response System; N=Total number of subjects in respective groups; PE=Pulmonary embolism.
a. In the event a subject had both DVT and PE, the subject was classified to PE.
b. Each subject was counted only once in a category, but could be counted in more than 1 category. The denominator to calculate each percentage was the total number of randomized subjects within each treatment group and the adjudicated index event type.

7.1.1.1.12. Results for the primary efficacy outcome

Non-inferiority was demonstrated according to the predefined criteria (Table 8). There were 59 events in the apixaban population and 71 in the enoxaparin/warfarin. The RR (95% CI) for the primary efficacy outcome measure in the per-protocol population was 0.6611 (0.4243 to 1.0301) with the upper 95% CI being < 1.8 (the criterion for non-inferiority) and the risk difference (95% CI) was -0.0072 (-0.0150 to 0.0005) which was less than the non-inferiority criterion of 0.035. In the primary efficacy population the RR (95% CI) was 0.8390 (0.2965 to 1.1802), and the risk difference (95% CI) was -0.0044 (-0.0128 to 0.0040). However, by the same hypothesis tests, superiority was not demonstrated for apixaban.

The excess of events in the enoxaparin/warfarin group was primarily due to more non-fatal DVT in that group (Table 9).

Table 8: Analysis of Adjudicated VTE (Nonfatal DVT or Nonfatal PE)/VTE-Related Death

Symptomatic VTE (Nonfatal DVT or Nonfatal PE)/VTE-Related Death	Apixaban	Enoxaparin/Warfarin
Primary Analysis (Primary Efficacy Subjects)		
n/N1[a]	59/2609	71/2635
Event rate (95% CI)*	0.0226 (0.0169, 0.0283)	0.0269 (0.0208, 0.0331)
Relative risk (95% CI)†	0.8390 (0.5965, 1.1802)	
p-value for non-inferiority‡	<0.0001	
p-value for superiority†	0.3128	
Risk difference (95% CI)§	-0.0044 (-0.0128, 0.0040)	
p-value for non-inferiority‡	<0.0001	
p-value for superiority§	0.3090	
Sensitivity Analysis[b] (Randomized Subjects)		
n/N2	59/2691	71/2704
Event rate (95% CI)*	0.0219 (0.0164, 0.0275)	0.0263 (0.0202, 0.0323)
Relative risk (95% CI)†	0.8347 (0.5933, 1.1744)	
p-value for non-inferiority‡	<0.0001	
p-value for superiority†	0.299	
Risk difference (95% CI)§	-0.0044 (-0.0125, 0.0038)	
p-value for non-inferiority‡	<0.0001	
Primary Analysis (Per-Protocol Subjects)		
n/N3	32/2257	48/2235
Event rate (95% CI)*	0.0142 (0.0093, 0.0191)	0.0215 (0.0155, 0.0275)
Relative risk (95% CI)†	0.6611 (0.4243, 1.0301)	
p-value for non-inferiority‡	<0.0001	
Risk difference (95% CI)§	-0.0072 (-0.0150, 0.0005)	
p-value for non-inferiority‡	<0.0001	

Source: Table 14.2.3.1.1, Table 14.2.3.1.2, and Table 14.2.3.1.4.

* CI for single event rate was calculated based on the Wald asymptotic confidence limits.

† Relative risk, CI, and p-value were calculated based on CMH test stratified by index event strata.

‡ p-value was calculated based on the Yanagawa-Tango-Hiejima test stratified by index event strata for non-inferiority.

§ Risk difference, CI, and p-value were calculated based on the inverse variance method when there was at least 1 event of interest per treatment group and index event stratum, otherwise they were calculated based on the harmonic means method when there was at least 1 event of interest per index event stratum.

CI=Confidence interval; CMH=Cochran-Mantel-Haenszel; DVT=Deep vein thrombosis; n=Number of subjects with observation; N1=Total number of efficacy evaluable subjects in respective groups (Primary Efficacy Subjects); N2=Total number of randomized subjects in respective group; N3=Total number of per-protocol subjects in respective group; PE=Pulmonary embolism; VTE=Venous thromboembolism.

a. Subjects with missing endpoint information were excluded from the analysis.

b. Sensitivity analysis was based on randomized subjects without imputation.

Table 9: Adjudicated Primary Efficacy Endpoints (Nonfatal DVT, Nonfatal PE and VTE-Related Death) During the Intended Treatment Period (Randomized Subjects)

	Apixaban N=2691	Enoxaparin/Warfarin N=2704
Subjects with first event, n (%)[a]		
Nonfatal DVT	20 (0.7)	33 (1.2)
Nonfatal PE	27 (1.0)	23 (0.9)
VTE-related death	12 (0.4)	15 (0.6)
Subjects with event, n (%)[b]		
Nonfatal DVT	22 (0.8)	35 (1.3)
Nonfatal PE	27 (1.0)	25 (0.9)
VTE-related death	12 (0.4)	16 (0.6)
Total number of events, n[c]		
Nonfatal DVT	22	38
Nonfatal PE	27	25
VTE-related death	12	16

Source: Table 14.2.3.4.1.

DVT=Deep vein thrombosis; n=Number of subjects with observation; N=Total number of subjects in respective group; PE=Pulmonary embolism; VTE=Venous thromboembolism.

a. First event was the first primary event for each subject. Each subject was counted only once.

b. Each subject was counted only once in each event category but could have been counted in multiple categories.

c. Each subject could have been counted multiple times in each event category if multiple events occurred.

There was no difference in efficacy by index event type (Table 10). There was no statistically significant subgroup effect on primary efficacy outcome measure (Figure 10).

Table 10: Subgroup Analysis of Adjudicated VTE (Nonfatal DVT or Nonfatal PE)/VTE-Related Death During the Intended Treatment Period by Index Event Type (Primary Efficacy Subjects)

Index Event Stratum	Apixaban	Enoxaparin/Warfarin
PE with/without DVT, n/N1[a]	21/900	23/886
Event Rate (95% CI)*	0.0233 (0.0135, 0.0332)	0.0260 (0.0155, 0.0364)
Relative Risk (95% CI)†	0.8988 (0.5011, 1.6122)	
Risk Difference (95% CI)‡	-0.0026 (-0.0170, 0.0118)	
DVT only, n/N1[a]	38/1698	47/1736
Event Rate (95% CI)*	0.0224 (0.0153, 0.0294)	0.0271 (0.0194, 0.0347)
Relative Risk (95% CI)†	0.8266 (0.5419, 1.2610)	
Risk Difference (95% CI)‡	-0.0047 (-0.0151, 0.0057)	
p-value for test of treatment by index event stratum interaction§	0.8198	

Source: Table 14.2.3.1.3.1.

* CI for single event rate was calculated based on the Wald asymptotic confidence limits.

† Relative risk and CI were calculated based on CMH test.

‡ Risk difference and CI were calculated based on the binomial proportions and the asymptotic confidence limits.

§ p-value was based on a logistic model using Wald's chi-square test.

CI=Confidence interval; CMH=Cochran-Mantel-Haenszel; DVT=Deep vein thrombosis; n=Number of subjects with observation; N1=Total number of subjects in respective groups excluding subjects with missing endpoint information (primary efficacy subjects); PE=Pulmonary embolism; VTE=Venous thromboembolism.

a. Subjects with missing endpoint information were excluded from the analysis.

The subjects in the enoxaparin/warfarin range were within the target INR range for 61% of the time (Table 11).

Table 11: Proportion of Time in Specified INR Range During the Treatment Period (Randomized Subjects)

INR Range	Apixaban (Sham INR) N=2691	Enoxaparin/Warfarin N=2704
INR <2.0	16.14	22.94
2.0 ≤INR ≤3.0	78.30	60.93
INR >3.0	5.56	16.13
INR <0.8	0.00	0.01
0.8 ≤INR <1.8	6.04	13.06
1.8 ≤INR <2.0	10.10	9.87
2.0 ≤INR ≤3.0	78.30	60.93
3.0 <INR ≤3.2	2.57	5.23
3.2 <INR ≤5.0	2.98	10.19
5.0 <INR ≤9.9	0.01	0.69
INR >9.9	0.00	0.01

Source: Table 14.4.2.1.6.1.
Included INRs from first INR measurement after Day 15 through last INR measurement on or before last dose excluding the time period when study warfarin dosing was temporarily interrupted.
Rosendaal's linear interpolation methodology was used to determine the proportion of time in specified INR range.
INR=International normalized ratio.

7.1.1.1.13. Results for other efficacy outcomes

For the secondary efficacy outcome measures:

- Recurrent symptomatic VTE and all-cause death: 84 episodes in the apixaban group, 104 in the enoxaparin/warfarin, RR (95% CI) 0.8151 (0.6146 to 1.0812), p = 0.1554.
- Incidence (95% CI) of adjudicated composite of recurrent symptomatic VTE and CV-related death: 0.0234 (0.0176 to 0.0292) in the apixaban group and 0.0292 (0.0228 to 0.0357) in the enoxaparin/warfarin.
- Incidence (95% CI) of adjudicated composite of recurrent symptomatic VTE, VTE-related death and major bleeding: 0.0280 (0.0216 to 0.0343) in the apixaban group and 0.0448 (0.0369 to 0.0527) in the enoxaparin/warfarin.
- Incidence (95% CI) of adjudicated symptomatic non-fatal DVT: 0.0084 (0.0049 to 0.0119) in the apixaban group and 0.0133 (0.0089 to 0.0177) in the enoxaparin/warfarin.
- Incidence (95% CI) of adjudicated symptomatic non-fatal PE: 0.0104 (0.0065 to 0.0142) in the apixaban group and 0.0095 (0.0058 to 0.0132) in the enoxaparin/warfarin.
- Incidence (95% CI) of adjudicated VTE-related death: 0.0046 (0.0020 to 0.0072) in the apixaban group and 0.0061 (0.0031 to 0.0091) in the enoxaparin/warfarin.
- Incidence (95% CI) of adjudicated CV-related death: 0.0058 (0.0028 to 0.0087) in the apixaban group and 0.0087 (0.0052 to 0.0123) in the enoxaparin/warfarin.
- Incidence (95% CI) of all-cause death: 0.0157 (0.0109 to 0.0205) in the apixaban group and 0.0198 (0.0145 to 0.0251) in the enoxaparin/warfarin.
- Incidence (95% CI) of adjudicated composite of recurrent symptomatic VTE, myocardial infarction, stroke, CV-related death, major bleeding, CRNMB: 0.0699 (0.0602 to 0.0205) in the apixaban group and 0.1261 (0.0145 to 0.0251) in the enoxaparin/warfarin.

In the 30 day follow-up period the rates of events were similar for the two treatment groups except for non-fatal PE which was more common in the enoxaparin/warfarin group: event rate (95% CI) 0.0007 (0.0000 to 0.0018) in the apixaban compared to 0.0033 (0.0012 to 0.0055) in the enoxaparin/warfarin, p = 0.0345. There was no significant difference in event rates for non-

fatal DVT, VTE-related death, CV-related death, all-cause death, myocardial infarction or acute stroke.

For the following exploratory analyses:

- The Kaplan Meier plot for first occurrence of an adjudicated composite of recurrent symptomatic VTE (nonfatal DVT or nonfatal PE) and all-cause death indicated benefit by Day 30 that was maintained to Day 180 (Figure 7)
- The Kaplan Meier plot for first occurrence of an adjudicated composite of recurrent symptomatic VTE (nonfatal DVT or nonfatal PE) and VTE-related death indicated benefit by Day 30 that was maintained to Day 180 (Figure 7)

There were few subjects with renal impairment included in the study, but there did not appear to be any difference in efficacy in those subjects (Table 12).

Figure 7: Kaplan-Meier Plots for Efficacy Endpoints During the Intended Treatment Period - Randomized Subjects

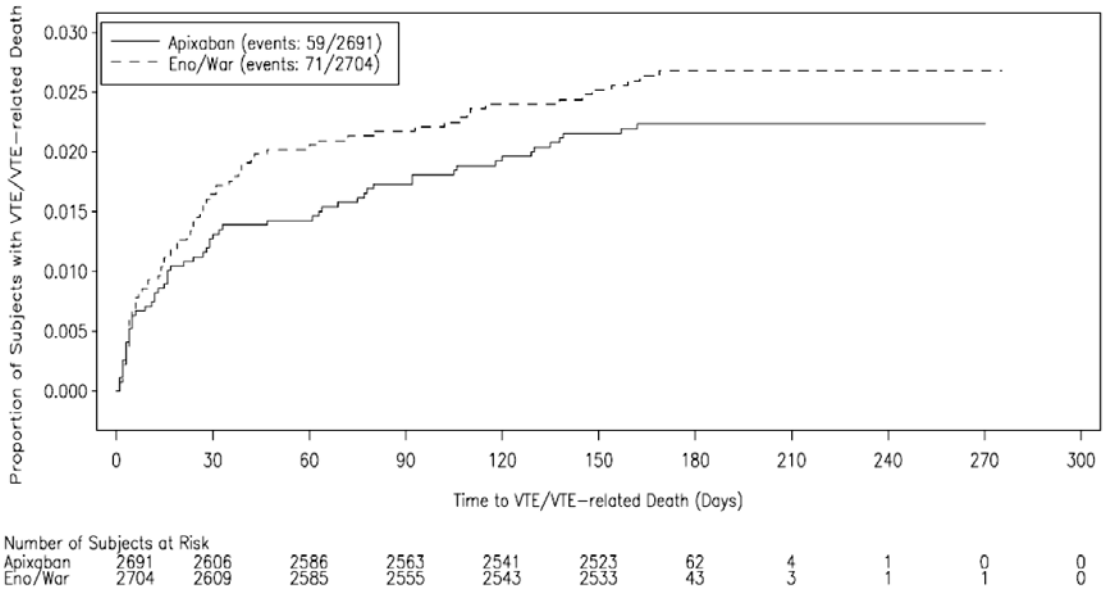


Table 12: Analysis of Adjudicated VTE/VTE-related Death during the Intended Treatment Period, by Renal Impairment Category II - Randomized Subjects

	Apixaban N=2691	Enoxaparin/Warfarin N=2704
RENAL IMPAIRMENT CATEGORY II		
SEVERE, n/N	2/14	1/14
EVENT RATE (95% CI) [1]	0.1429 (0.0000, 0.3262)	0.0714 (0.0000, 0.2063)
RELATIVE RISK (95% CI) [2]	1.8800 (0.2259, 15.6478)	
RISK DIFFERENCE (95% CI) [3]	0.0714 (-0.1712, 0.3140)	
MODERATE, n/N	5/155	6/144
EVENT RATE (95% CI) [1]	0.0323 (0.0044, 0.0601)	0.0417 (0.0090, 0.0743)
RELATIVE RISK (95% CI) [2]	0.7654 (0.2416, 2.4250)	
RISK DIFFERENCE (95% CI) [3]	-0.0056 (-0.0481, 0.0370)	
MILD, n/N	14/531	12/530
EVENT RATE (95% CI) [1]	0.0264 (0.0127, 0.0400)	0.0226 (0.0100, 0.0353)
RELATIVE RISK (95% CI) [2]	1.1702 (0.5473, 2.5022)	
RISK DIFFERENCE (95% CI) [3]	0.0015 (-0.0164, 0.0194)	

Subjects with missing endpoint information are excluded from the analysis.
Renal impairment: Normal: CrCL>80, Mild: 50<CrCL<=80, Moderate: 30<CrCL<=50, Severe: CrCL<=30, where CrCL (ml/min) is calculated as [(140-AGE)x(Weight at Baseline (kg))]/(Serum Creatinine at Baseline x 72) for male; for females multiply the results by 0.85.
[1] Confidence interval for single event rate is calculated based on the Wald asymptotic confidence limits.
[2] Relative risk and confidence interval are calculated based on CMH test stratified by index event strata within each subgroup.
[3] Within each subgroup, risk difference and confidence interval are calculated based on the inverse variance method when there is at least one event of interest per treatment group and index event stratum, otherwise they are calculated based on the harmonic means method when there is at least one event of interest per index event stratum.
[4] P-value is based on a logistic model using Wald's chi-square test.

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

There were no pooled analyses of efficacy for the indication of: treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE).

7.1.3. Evaluator's conclusions on clinical efficacy for treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE)

Non-inferiority was demonstrated for apixaban in comparison with conventional treatment according to the predefined criteria. There were 59 events in the apixaban population and 71 in the enoxaparin/warfarin. The RR (95% CI) for the primary efficacy outcome measure in the per-protocol population was 0.6611 (0.4243 to 1.0301) with the upper 95% CI being < 1.8 (the criterion for non-inferiority. In the primary efficacy population (used as a sensitivity analysis) the RR (95% CI) was 0.8390 (0.2965 to 1.1802), and the risk difference (95% CI) was - 0.0044 (-0.0128 to 0.0040). The secondary outcome measures were also supportive for similar efficacy of apixaban and conventional treatment.

The study design conformed with EMA guidance. The study population included appropriate at-risk groups and also included elderly subjects. The comparator treatment was the accepted standard of care, and dosing for enoxaparin was within commonly accepted treatment guidelines (Clexane Australian approved Product Information). However, some treatment guidelines preferentially recommend 1.5 mg/kg once daily for the initial management of DVT and PE (New Zealand Formulary and the British National Formulary). The evaluator does not consider that this would have affected the results of the trial. The warfarin dosing recommendations and the proportion of subjects within therapeutic INR in the warfarin group (61%) was consistent with other clinical trials in this population and with the general population of patients treated with warfarin in Australia (Dignan et. al. 2013). The outcome measures were in accordance with guidance (Guideline On Clinical Investigation Of Medicinal Products For The Prophylaxis Of Venous Thromboembolic Risk In Non-Surgical Patients [CPMP/EWP/6235/04]). The margin for non-inferiority was clinically relevant and was adhered to in the analysis. The statistical procedures were appropriate. The subgroup analysis was extensive and included clinically relevant groupings. The non-inferiority margin (the upper

95% CI for the RR being < 1.8 and a risk difference < 0.035) was clinically meaningful (representing a < 80% increase in risk), and the results were comfortably within this margin (the upper 95% CI being 1.0301, i.e. < 4% increase in risk, and < 0.5% increase in incidence).

In the opinion of the evaluator, the inclusion of the Kaplan Meier plot for time to first DVT or PE or VTE-related death in the PI is appropriate because it presents primary outcome measure in a manner that informs prescribers of the magnitude, timing and durability of the treatment effect.

7.2. Prevention of recurrent DVT and PE

7.2.1. Pivotal efficacy studies

7.2.1.1. Study CV185057

7.2.1.1.1. Study design, objectives, locations and dates

Study CV185057 was a randomised, double blind, placebo controlled, parallel group, Phase III study of two dose regimens of apixaban in comparison with placebo in subjects with symptomatic proximal DVT or PE. The study was conducted at 328 centres in 28 (including Australia, Canada, UK and the US) from May 2008 to August 2012.

7.2.1.1.2. Inclusion and exclusion criteria

The inclusion criteria included:

- Men and women, ages 18 years or greater.
- An unprovoked index event or a provoked index event with a risk for recurrence.
- An objectively documented index event of symptomatic proximal DVT or symptomatic PE;
  - Symptomatic proximal DVT was defined as symptomatic DVT with evidence of proximal thrombosis that involved at least the popliteal vein or a more proximal vein, demonstrated by imaging with compression ultrasound (CUS), including grey-scale or colour-coded Doppler, or ascending contrast venography
  - Symptomatic PE with evidence of thrombosis demonstrated by imaging as follows:
    - an intraluminal filling defect in segmental or more proximal branches on spiral computed tomography (CT) scan; or
    - an intraluminal filling defect or a sudden cut-off of vessels more than 2.5 mm in diameter on the pulmonary angiogram; or
    - a perfusion defect of at least 75% of a segment with a local normal ventilation result (high-probability) on ventilation/perfusion lung scan.
- Completed approximately 6 to 12 months of standard anticoagulant therapy, or completed assigned CV185056 (AMPLIFY) study treatment, for the treatment of the index event.
- No objectively documented symptomatic recurrence of VTE after the index event.
- WOCBP must have been using an adequate method of contraception to avoid pregnancy throughout the study in such a manner that the risk of pregnancy was minimized.

Subjects were randomized within approximately 7 days of the last dose of their initial 6 to 12 month treatment. If a VKA was used as standard anticoagulant therapy, then an INR must have been documented as ≤ 2 before randomization. If the subject received CV185056 (AMPLIFY) study treatment, then a blinded INR must have been documented as ≤ 2 before randomization.

The exclusion criteria included:

- Women who were pregnant or breastfeeding

- Medical History and Concurrent Diseases
  - Subjects with a provoked index event without the existence of a persistent risk factor for recurrence.
  - More than 12 months of anticoagulation planned for the most recent DVT or PE.
  - Subjects with indications for long-term treatment with a VKA, such as: mechanical valve; atrial fibrillation or atrial flutter with moderate to high risk of systemic thromboembolism; multiple episodes of unprovoked DVT or PE; documented anti-phospholipid antibodies, AT III deficiency, protein C deficiency, protein S deficiency, homozygous factor V Leiden, or homozygous prothrombin gene mutation.
  - Subjects with cancer who were treated indefinitely with anticoagulation therapy.
  - Conditions for which serious bleeding could have occurred: intracranial bleeding; intraocular bleeding; gastrointestinal bleeding and/or endoscopically verified ulcer disease; head trauma or other major trauma; major surgery; stroke of any type; neurosurgery; gross haematuria; evidence of poor healing of a major wound or major trauma; planned major surgery during trial; intracranial neoplasm, arteriovenous malformation or aneurysm; overt major bleeding; documented haemorrhagic tendencies or blood dyscrasias.
  - Active and clinically significant liver disease (for example, hepatorenal syndrome).
  - Life expectancy < 12 months.
  - Bacterial endocarditis.
  - Uncontrolled hypertension: SBP > 180 mmHg or DBP > 100 mmHg.
- Physical and Laboratory Test Findings: platelet count < $100x10^9$ cells/L; haemoglobin < 90 g/L; serum creatinine > 221 µmol/L; calculated creatinine clearance < 25 mL/min; ALT or AST > 2xULN; total bilirubin > 1.5xULN
- Prohibited Treatments and/or Therapies:
  - ASA > 165 mg/day at randomization
  - Dual antiplatelet therapy (such as ASA plus clopidogrel or ASA plus ticlopidine) at randomization
  - Any oral direct factor Xa inhibitor, any oral direct thrombin inhibitor, or any investigational antithrombotic agent during the period between the onset of the index event to randomization.

7.2.1.1.3. Study treatments

The study treatments were:

1. Apixaban 2.5 mg (and placebo 5 mg) twice daily
2. Apixaban 5 mg (and placebo 2.5 mg) twice daily
3. Placebo 2.5 mg and placebo 5 mg twice daily

Treatment was administered orally for 12 months with a 1 month follow-up period.

The following medications or therapies were prohibited during the study treatment period:

- Potent inhibitors of cytochrome CYP3A4 (eg, azole antifungals [itraconazole and ketoconazole], macrolide antibiotics [clarithromycin and telithromycin], protease inhibitors [ritonavir, indinavir, nelfinavir, atazanavir, and saquinavir], and nefazodone)
- Aspirin > 165 mg/day

- Dual antiplatelet therapy such as concomitant (simultaneous) use of both aspirin and a thienopyridine (for example, clopidogrel, ticlopidine)
- Other antithrombotic agents (for example, UFH, LMWH, direct thrombin inhibitors, fondaparinux)
- Glycoprotein IIb/IIIa inhibitors (for example, abciximab, eptifibatide, tirofiban)

7.2.1.1.4. Efficacy variables and outcomes

The primary efficacy outcome measure was the incidence of an adjudicated composite of symptomatic, recurrent VTE (nonfatal DVT or nonfatal PE) or all-cause death. The secondary efficacy outcome measures were:

- Incidence of adjudicated composite of recurrent symptomatic VTE or VTE-related death
- Incidence of adjudicated composite of recurrent symptomatic VTE or CV-related death
- Incidence of adjudicated symptomatic nonfatal DVT
- Incidence of adjudicated symptomatic nonfatal PE
- Incidence of adjudicated VTE-related death
- Incidence of adjudicated CV-related death
- Incidence of all-cause death

Kaplan-Meier plots were displayed by treatment group based on the:

- Time to first adjudicated event of the composite of symptomatic, recurrent VTE (nonfatal DVT or nonfatal PE) or all-cause death
- Time to first adjudicated event of the composite of symptomatic, recurrent VTE or VTE-related death

The safety outcome measures were: major bleeding, CRNMB, minor bleeding, AEs, vital signs, ECGs, and laboratory blood tests.

7.2.1.1.5. Randomisation and blinding methods

Subjects were randomized to treatment in a 1:1:1 ratio, by IVRS and stratified by the type index event (symptomatic proximal DVT only or symptomatic PE with or without DVT) and by previous treatment (enoxaparin/warfarin in Study CV185056, apixaban in Study CV185056, or standard therapy). Blinding was maintained by placebo for the 2.5 and 5 mg tablets.

7.2.1.1.6. Analysis populations

The efficacy analysis was based on the ITT population: subjects were categorized to the group to which they were assigned by the IVRS, regardless of the treatment actually received.

The safety data set (as-treated) consisted of all treated subjects: randomised subjects who received at least one dose of study drug.

7.2.1.1.7. Sample size

The sample size calculation was based on the primary efficacy outcome measure. The probability of VTE/VTE-related death for subjects receiving active treatment (apixaban) of 2% and placebo of 6% at 12 months was based on the Van Gogh Extension study. The assumed background rate of non-VTE related deaths was 0.82%, giving a relative risk of 2.82%/6.82% = 0.4135. To give a 90% power, with a level of significance of 0.05 a sample size of 810 subjects would be required in each group.

7.2.1.1.8. Statistical methods

Hypothesis tests were based on the Cochran–Mantel–Haenszel test, using 95% CI. Missing data for the primary efficacy outcome measure were imputed as having had a primary efficacy outcome event.

7.2.1.1.9. Participant flow

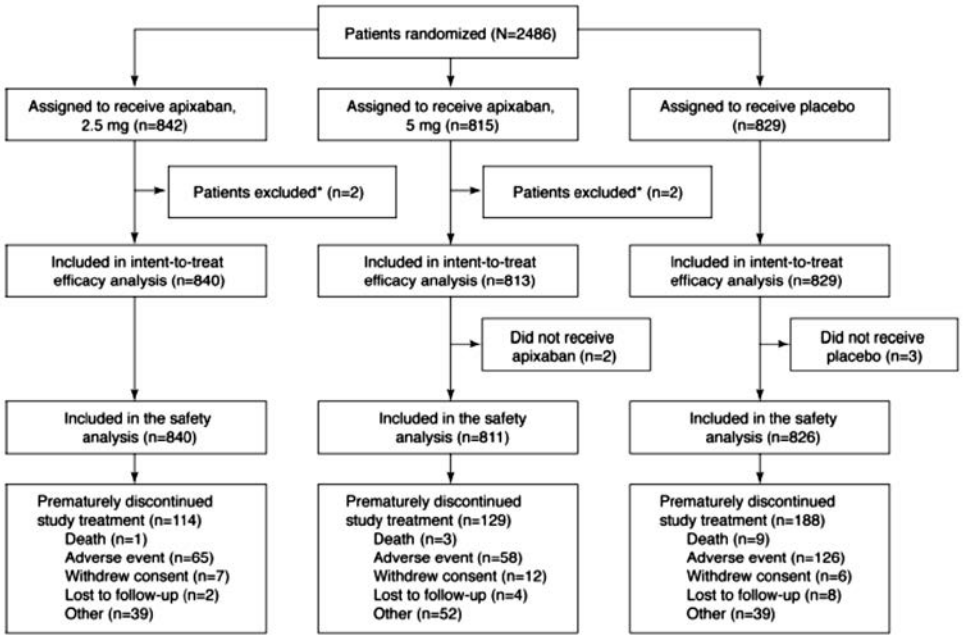
A total of 2711 subjects were enrolled and 2482 were randomised. There were 840 randomised to apixaban 2.5 mg, 813 to apixaban 5 mg and 829 to placebo. A total of 2477 subjects received treatment: 840 in the apixaban 2.5 mg group, 811 in the 5 mg and 826 in the placebo (Table 13). There were 2051 (82.6%) subjects that completed the study: 726 (86.4%) in the apixaban 2.5 mg group, 684 (84.1%) in the 5 mg and 641 (77.3%) in the placebo (Figure 8). Discontinuation due to VTE was more common in the placebo group, and due to bleeding was more common in the apixaban groups. Discontinuation due to DVT occurred for 5 (0.6%) subjects in the apixaban 2.5 mg group, 8 (1.0%) in the 5 mg and 57 (6.9%) in the placebo; due to PE for 4 (0.55) subjects in the apixaban 2.5 mg group, 2 (0.2%) in the 5 mg and 18 (2.2%) in the placebo; and due to bleeding in 8 (1.0%) subjects in the apixaban 2.5 mg group, 8 (1.0%) in the 5 mg and 3 (0.4%) in the placebo.

Table 13: Overall Summary of Subject Disposition (Randomized Subjects)

Number (%) of Subjects	Apixaban	Enoxaparin/ Warfarin	Total[a]
Subjects enrolled			5614
Subjects randomized	2691	2704	5395
Subjects treated	2676 (99.4)	2689 (99.4)	5365 (99.4)
Subjects who completed 6 months of study treatment	2314 (86.0)	2291 (84.7)	4605 (85.4)
Subjects who discontinued from study treatment[b]	377 (14.0)	413 (15.3)	790 (14.6)
Reason for discontinuation from study treatment			
Death	20 (0.7)	26 (1.0)	46 (0.9)
Adverse event	150 (5.6)	182 (6.7)	332 (6.2)
DVT	15 (0.6)	17 (0.6)	32 (0.6)
PE	9 (0.3)	11 (0.4)	20 (0.4)
Bleeding	18 (0.7)	46 (1.7)	64 (1.2)
MI	3 (0.1)	1 (<0.1)	4 (<0.1)
Stroke	5 (0.2)	1 (<0.1)	6 (0.1)
Thrombocytopenia	2 (<0.1)	0	2 (<0.1)
Venous thromboembolic event[c]	2 (<0.1)	3 (0.1)	5 (<0.1)
Arterial thromboembolic event	2 (<0.1)	2 (<0.1)	4 (<0.1)
Other	94 (3.5)	101 (3.7)	195 (3.6)
Subject withdrew consent or unwilling to provide consent	49 (1.8)	49 (1.8)	98 (1.8)
Lost to follow-up	14 (0.5)	14 (0.5)	28 (0.5)
Poor/non-compliance	20 (0.7)	23 (0.9)	43 (0.8)
Pregnancy	3 (0.1)	2 (<0.1)	5 (<0.1)
Subject did not meet or no longer meets study inclusion/exclusion criteria	13 (0.5)	9 (0.3)	22 (0.4)
Administrative reason by sponsor	1 (<0.1)	1 (<0.1)	2 (<0.1)
Other	107 (4.0)	107 (4.0)	214 (4.0)

Source: Table 14.1.1.2.1 and Table 14.1.1.2.2.
The denominator to calculate each percentage was the total number of randomized subjects in each treatment group.
DVT=Deep vein thrombosis; MI=Myocardial infarction; N=Total number of subjects in respective group; PE=Pulmonary embolism.
a. Data from Site 648 (pertains to 5 subjects) were excluded from all summary tables, and were not included in any 'Randomization' counts. However, the data were included in the listings. The accuracy of the data collected could not be confirmed through source data verification.
b. Subjects who were randomized but never received any study treatment were also included and reason for not being treated was summarized under reason for discontinuation.
c. Venous thromboembolic events were events other than DVT or PE.

Figure 8: Subject Disposition Flow Diagram



Source: Table 14.1.1.2.1, Table 14.1.1.2.2 and Section 16.1.11.

Two subjects in the 2.5 mg apixaban group and 2 subjects in the 5 mg apixaban group were excluded from all the analyses because verifiable source documentation was lacking.

7.2.1.1.10. Major protocol violations/deviations

Protocol deviations were balanced between the treatment groups. The commonest protocol deviations were: incomplete eligibility labs before randomization; and non-study anti-coagulant.

7.2.1.1.11. Baseline data

There were 1424 (57.4%) males, 1058 (42.6%) females, and the age range was 18 to 94 years. There were 490 (19.7%) subjects aged 65 to < 75 years and 329 (13.3%) aged ≥ 75 years. The treatment groups were similar in demographic characteristics, VTE characteristics and VTE risk factors. The treatment groups were similar in index events. Prior VKAs were used by 540 (64.3%) subjects in the 2.5 mg group, 521 (64.1%) in the 5 mg and 520 (62.7%) in the placebo. Prior antiplatelet agents were used by 120 (14.3%) subjects in the 2.5 mg group, 96 (11.8%) in the 5 mg and 107 (13.0%) in the placebo. One or more concomitant medications were used by 707 (84.2%) subjects in the 2.5 mg group, 681 (84.0%) in the 5 mg and 706 (85.5%) in the placebo. There were 836 (33.7%) who had previously participated in Study CV185056 (AMPLIFY): 282 (33.6%) in the apixaban 2.5 mg group, 272 (33.5%) in the 5 mg and 282 (34.0%) in the placebo.

7.2.1.1.12. Results for the primary efficacy outcome

Both apixaban treatment regimens were superior to placebo. There were 19 events in the apixaban 2.5 mg group, 14 in the 5 mg and 77 in the placebo. In addition, there were 13 imputed events in the apixaban 2.5 mg group, 20 in the 5 mg and 19 in the placebo. The RR (95% CI) compared to placebo for apixaban 2.5 mg was 0.3283 (0.2225 to 0.4844) and for apixaban 5 mg was 0.3615 (0.2475 to 0.5281). The Risk difference (95% CI) compared to placebo was - 0.0779 (- 0.1032 to - 0.0526) for apixaban 2.5 mg and - 0.0740 (- 0.0997 to - 0.0482) for apixaban 5 mg. All these hypothesis tests were significant to $p < 0.0001$.

All of the event types were more common in the placebo group (Table 14). For both DVT and PE separately, the apixaban groups had fewer events compared with placebo (Table 15). There was no subgroup effect.

Table 14: Adjudicated Primary Efficacy Endpoints (Nonfatal DVT, Nonfatal PE and All-Cause Death) During the Intended Treatment Period (Randomized Subjects) - Without Imputation

	Apixaban 2.5 mg (N=840)	Apixaban 5 mg (N=813)	Placebo (N=829)
Subjects with first event, n (%)[a]			
Nonfatal DVT	6 (0.7)	7 (0.9)	53 (6.4)
Nonfatal PE	7 (0.8)	4 (0.5)	13 (1.6)
All-cause death	6 (0.7)	3 (0.4)	11 (1.3)
CV-related death[b]	0 (0.0)	0 (0.0)	3 (0.4)
VTE-related death	1 (0.1)	3 (0.4)	7 (0.8)
Subjects with event, n (%)[c]			
Nonfatal DVT	6 (0.7)	8 (1.0)	53 (6.4)
Nonfatal PE	8 (1.0)	4 (0.5)	15 (1.8)
All-cause death	7 (0.8)	4 (0.5)	14 (1.7)
CV-related death[b]	0 (0.0)	0 (0.0)	3 (0.4)
VTE-related death	2 (0.2)	3 (0.4)	7 (0.8)
Total number of events, n[d]			
Nonfatal DVT	6	8	54
Nonfatal PE	8	4	15
All-cause death	7	4	14
CV-related death[b]	0	0	3
VTE-related death	2	3	7

Source: Table 14.2.3.4.1.
No imputation was done for the endpoints summarized in this table. Only subjects who had an event during the intended treatment period were counted.
CV=Cardio vascular; DVT=Deep vein thrombosis; n=Number of subjects with observation; N=Total number of subjects in respective group; PE=Pulmonary embolism; VTE=Venous thromboembolism.
a. First event was the first primary event for each subject. Each subject was counted only once.
b. CV-related death in this table is presented excluding VTE-related death.
c. Each subject was counted only once in each event category but could have been counted in multiple categories.
d. Each subject could have been counted multiple times in each event category if multiple events occurred.

Table 15: Subgroup Analysis of Adjudicated VTE (Nonfatal DVT or Nonfatal PE)/ All-Cause Death During the Intended Treatment Period by Index Event Type – With Imputation (Randomized Subjects)

Index Event Stratum	Apixaban 2.5 mg	Apixaban 5 mg	Placebo
PE with/without DVT, N[a]	296	286	278
n (number of imputed events)	13 (3)	11 (7)	32 (9)
Event rate (95% CI)*	0.0439 (0.0206, 0.0673)	0.0385 (0.0162, 0.0607)	0.1151 (0.0776, 0.1526)
Relative risk (95% CI)†	0.3815 (0.2045, 0.7117)	0.3341 (0.1719, 0.6496)	
Risk difference (95% CI)‡	-0.0712 (-0.1154, -0.0270)	-0.0766 (-0.1203, -0.0330)	
DVT only, N[a]	544	527	551
n (number of imputed events)	19 (10)	23 (13)	64 (10)
Event rate (95% CI)*	0.0349 (0.0195, 0.0504)	0.0436 (0.0262, 0.0611)	0.1162 (0.0894, 0.1429)
Relative risk (95% CI)†	0.3007 (0.1827, 0.4949)	0.3757 (0.2369, 0.5960)	
Risk difference (95% CI)‡	-0.0812 (-0.1121, -0.0503)	-0.0725 (-0.1044, -0.0406)	
p-value for test of treatment by index event stratum interaction§	0.7652		

Source: Table 14.2.3.1.2.1 and Table 14.2.3.1.4.1.
* CI for single event rate was calculated based on the Wald asymptotic confidence limits.
† Relative risk, risk difference, and associated CIs were based on stratified analyses with initial diagnosis as the stratification factor. Differences between treatment arms were assessed using the CMH test.
‡ Risk difference and CI comparing each apixaban dose group with placebo group were calculated based on the binomial proportions and the asymptotic confidence limits.
§ p-value for the test of the treatment by index event stratum interaction was based on a logistic model using Wald's chi-square test.
Number of imputed events was calculated by subtracting number of adjudicated events with imputation from the number of adjudicated events without imputation.
CI=Confidence interval; CMH=Cochran–Mantel–Haenszel; DVT=Deep vein thrombosis; n=Number of subjects with observation; N=Total number of subjects in respective group; PE=Pulmonary embolism; VTE=Venous thromboembolism.
a. Subjects with missing endpoint information were classified as having an event during the intended treatment period.

7.2.1.1.13. Results for other efficacy outcomes

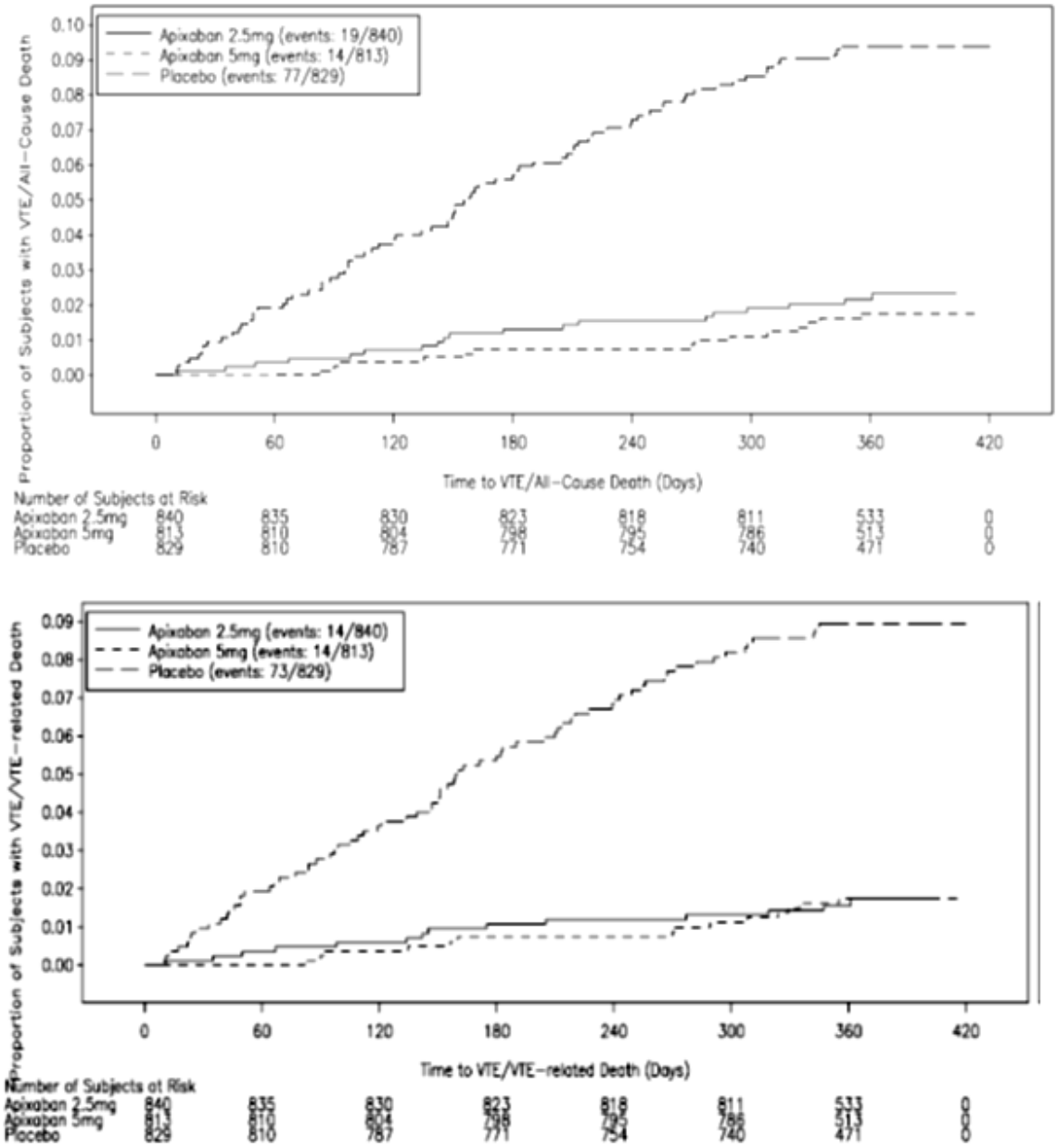
The results for the secondary efficacy outcomes were:

- The incidence of adjudicated composite of recurrent symptomatic VTE or VTE-related death (with imputation) was: event rate (95% CI) 0.0321 (0.0202 to 0.0441) for apixaban 2.5 mg, 0.0418 (0.0281 to 0.0556) for apixaban 5 mg and 0.1110 (0.0896 to 0.1324) for placebo. Risk difference (95% CI) compared with placebo - 0.0790 (- 0.1035 to - 0.0545) for apixaban 2.5 mg and - 0.0691 (- 0.0945 to - 0.0437) for apixaban 5 mg, $p < 0.0001$.
- The incidence of adjudicated composite of recurrent symptomatic VTE or CV-related death (with imputation) was: event rate (95% CI) 0.0167 (0.0080 to 0.0253) for apixaban 2.5 mg, 0.0172 (0.0083 to 0.0262) for apixaban 5 mg and 0.0881 (0.0688 to 0.1073) for placebo. Risk difference (95% CI) compared with placebo - 0.0715 (- 0.0926 to - 0.0504) for apixaban 2.5 mg and - 0.0700 (- 0.0912 to -0.0489) for apixaban 5 mg, $p < 0.0001$.
- The incidence of adjudicated symptomatic nonfatal DVT (with imputation): event rate (95% CI) 0.0226 (0.0126 to 0.0327) for apixaban 2.5 mg, 0.0344 (0.0219 to 0.0470) for apixaban 5 mg and 0.0869 (0.0677 to 0.1060) for placebo. Risk difference (95% CI) compared with placebo - 0.0642 (- 0.0858 to - 0.0426) for apixaban 2.5 mg and - 0.0523 (- 0.0752 to - 0.0294) for apixaban 5 mg, $p < 0.0001$.
- The incidence of adjudicated symptomatic nonfatal PE (with imputation) was: event rate (95% CI) 0.0274 (0.0163 to 0.0384) for apixaban 2.5 mg, 0.0308 (0.0189 to 0.0426) for apixaban 5 mg and 0.0446 (0.0306 to 0.0587) for placebo. Risk difference (95% CI) compared with placebo - 0.0162 (- 0.0337 to 0.0013) for apixaban 2.5 mg and -0.0127 (- 0.0308 to 0.0054) for apixaban 5 mg, $p > 0.05$.
- The incidence of adjudicated VTE-related death (with imputation) was: event rate (95% CI) 0.0202 (0.0107 to 0.0298) for apixaban 2.5 mg, 0.0295 (0.0179 to 0.0412) for apixaban 5 mg and 0.0314 (0.0195 to 0.0432) for placebo. Risk difference (95% CI) compared with placebo - 0.0113 (- 0.0266 to 0.0039) for apixaban 2.5 mg and - 0.0019 (- 0.0185 to 0.0148) for apixaban 5 mg, $p > 0.05$.
- The incidence of adjudicated CV-related death (with imputation) was: event rate (95% CI) 0.0202 (0.0107 to 0.0298) for apixaban 2.5 mg, 0.0295 (0.0179 to 0.0412) for apixaban 5 mg and 0.0350 (0.0225 to 0.0475) for placebo. Risk difference (95% CI) compared with placebo - 0.0145 (- 0.0303 to 0.0012) for apixaban 2.5 mg and - 0.0052 (- 0.0223 to 0.0119) for apixaban 5 mg, $p > 0.05$.
- The incidence of all-cause death (with imputation) was: event rate (95% CI) 0.0262 (0.0154 to 0.0370) for apixaban 2.5 mg, 0.0308 (0.0189 to 0.0426) for apixaban 5 mg and 0.0398 (0.0265 to 0.0531) for placebo. Risk difference (95% CI) compared with placebo - 0.0131 (- 0.0303 to 0.0041) for apixaban 2.5 mg and - 0.0085 (- 0.0263 to 0.0094) for apixaban 5 mg, $p > 0.05$.

In the follow-up period there was a greater proportion of subjects in the apixaban 5 mg group with symptomatic VTE (nonfatal DVT or nonfatal PE)/ all-cause death: four (0.5%) subjects in the apixaban 2.5 mg group, eight (1.0%) in the 5 mg and three (0.4%) in the placebo. This may represent an unmasking effect rather than a rebound effect.

The Kaplan-Meier indicated a sustained treatment effect during the 12 month treatment period (Figure 9).

Figure 9: Kaplan-Meier Plots for Efficacy Endpoints During the Intended Treatment Period - Randomized Subjects



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

There were no pooled analyses of efficacy for the indication of: prevention of recurrent DVT and PE.

7.2.3. Evaluator's conclusions on clinical efficacy for prevention of recurrent DVT and PE

Both apixaban treatment regimens were superior to placebo with no apparent difference in efficacy between the apixaban doses. There were 19 events in the apixaban 2.5 mg group, 14 in the 5 mg and 77 in the placebo. In addition, there were 13 imputed events in the apixaban 2.5 mg group, 20 in the 5 mg and 19 in the placebo. The RR (95% CI) compared to placebo for apixaban 2.5 mg was 0.3283 (0.2225 to 0.4844) and for apixaban 5 mg was 0.3615 (0.2475 to 0.5281). The Risk difference (95% CI) compared to placebo was - 0.0779 (- 0.1032 to - 0.0526)

for apixaban 2.5 mg and - 0.0740 (- 0.0997 to - 0.0482) for apixaban 5 mg. All these hypothesis tests were significant to $p < 0.0001$. The secondary efficacy outcome measures were also supportive of superiority.

The study design conformed with EMA guidance. The study population included appropriate at-risk groups and also included elderly subjects. The comparator treatment was placebo, which is appropriate because 'no treatment' is an accepted standard of care. The outcome measures were in accordance with guidance. The statistical procedures were appropriate. The subgroup analysis was extensive and included clinically relevant groupings.

8. Clinical safety

8.1. Studies providing evaluable safety data

The following studies provided evaluable safety data:

8.1.1. Pivotal efficacy studies

In the pivotal efficacy studies, the following safety data were collected:

- Major or CRNMB during the treatment period
- AEs, laboratory tests, vital signs and ECGs.

8.1.2. Pivotal studies that assessed safety as a primary outcome

There were no pivotal studies that assessed safety alone as the primary outcome.

8.1.3. Dose-response and non-pivotal efficacy studies

The dose-response study provided safety data, as follows:

- Major and CRNMB.
- AEs, clinical laboratory evaluations and vital signs.

8.1.4. Other studies evaluable for safety only

Clinical pharmacology studies:

- AEs, clinical laboratory tests and ECGs.

8.2. Pivotal studies that assessed safety as a primary outcome

There were no pivotal studies that assessed safety alone as the primary outcome.

8.3. Patient exposure

In Study CV185017 there were 128 subjects exposed to apixaban 5 mg twice daily, 133 to 10 mg twice daily and 124 to 20 mg once daily, for up to 12 weeks.

In Study CV185056 there were 2676 subjects exposed to apixaban, with 244 exposed for more than 172 days. The median duration of exposure was 168 days.

In Study CV185057 there were 840 subjects exposed to apixaban 2.5 mg twice daily; with 58 (6.9%) exposed for > 367 days, and the median exposure was 360 days. There were 811 subjects exposed to apixaban 5 mg twice daily; with 38 (4.7%) exposed for > 367 days, and the median exposure was 360 days.

8.4. Adverse events

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

8.4.1.1. Pivotal studies

In Study CV185056, TEAEs were reported in 1795 (67.1%) subjects in the apixaban group and 1923 (71.5%) in the enoxaparin/warfarin. The commonest TEAE was headache, reported in 169 (6.3%) subjects in the apixaban group and 168 (6.2%) in the enoxaparin/warfarin (Table 16). In the follow-up period TEAEs were reported in 195 (7.5%) subjects in the apixaban group and 217 (8.2%) in the enoxaparin/warfarin.

Table 16: Summary of the Most Frequently Reported (≥2% in Either Treatment Group) Adverse Events With Onset During the Treatment Period (Treated Subjects)

System Organ Class Preferred Term	Apixaban N=2676	Enoxaparin/Warfarin N=2689
	n (%)	n (%)
Total subjects with an event	1795 (67.1)	1923 (71.5)
Infections and infestations		
Nasopharyngitis	104 (3.9)	98 (3.6)
Urinary tract infection	95 (3.6)	85 (3.2)
Bronchitis	55 (2.1)	57 (2.1)
Gastrointestinal disorders		
Diarrhoea	100 (3.7)	106 (3.9)
Nausea	81 (3.0)	107 (4.0)
Constipation	74 (2.8)	87 (3.2)
Vomiting	50 (1.9)	70 (2.6)
Musculoskeletal and connective tissue disorders		
Pain in extremity	122 (4.6)	131 (4.9)
Back pain	80 (3.0)	88 (3.3)
Arthralgia	75 (2.8)	86 (3.2)
Musculoskeletal chest pain	58 (2.2)	50 (1.9)
Nervous system disorders		
Headache	169 (6.3)	168 (6.2)
Dizziness	66 (2.5)	69 (2.6)
Respiratory, thoracic and mediastinal disorders		
Epistaxis	77 (2.9)	146 (5.4)
Dyspnoea	72 (2.7)	77 (2.9)
Cough	61 (2.3)	58 (2.2)
Pulmonary embolism	44 (1.6)	56 (2.1)
General disorders and administration site conditions		
Oedema peripheral	96 (3.6)	113 (4.2)
Fatigue	58 (2.2)	50 (1.9)
Pyrexia	56 (2.1)	57 (2.1)
Investigations		
Gamma-glutamyltransferase increased	38 (1.4)	57 (2.1)
Blood creatine phosphokinase increased	33 (1.2)	78 (2.9)
Alanine aminotransferase increased	31 (1.2)	105 (3.9)
Vascular disorders		
Hypertension	71 (2.7)	69 (2.6)
Deep vein thrombosis	42 (1.6)	66 (2.5)
Haematoma	35 (1.3)	76 (2.8)
Injury, poisoning and procedural complications		
Contusion	49 (1.8)	97 (3.6)
Metabolism and nutrition disorders		
Hypercholesterolaemia	28 (1.0)	55 (2.0)
Renal and urinary disorders		
Haematuria	46 (1.7)	102 (3.8)

The denominator to calculate each percentage was the total number of treated subjects within each group.
AE=adverse event; n=number of subjects with AE, N=total number of subjects in respective group.

In Study CV185057, TEAEs were reported in 596 (71.0%) subjects in the apixaban 2.5 mg group, 542 (66.8%) in the apixaban 5 mg, and 606 (73.4%) in the placebo. DVT was reported as a TEAE more commonly in the placebo group (Table 17). In the follow-up period TEAEs were reported in 58 (6.9%) subjects in the apixaban 2.5 mg group, 47 (5.8%) in the apixaban 5 mg, and 52 (6.4%) in the placebo.

Table 17: Summary of the Most Frequently Reported (≥2% in Any Treatment Group) Adverse Events with Onset During the Treatment Period (Treated Subjects)

System Organ Class Preferred Term	Apixaban 2.5 mg (N=840), n (%)	Apixaban 5 mg (N=811), n (%)	Placebo (N=826), n (%)
Total subjects with an event	596 (71.0)	542 (66.8)	606 (73.4)
Infections and infestations			
Bronchitis	25 (3.0)	32 (3.9)	14 (1.7)
Nasopharyngitis	41 (4.9)	31 (3.8)	40 (4.8)
Urinary tract infection	29 (3.5)	31 (3.8)	35 (4.2)
Influenza	18 (2.1)	20 (2.5)	20 (2.4)
Upper respiratory tract infection	18 (2.1)	18 (2.2)	18 (2.2)
Musculoskeletal and connective tissue disorders			
Pain in extremity	44 (5.2)	52 (6.4)	54 (6.5)
Back pain	27 (3.2)	45 (5.5)	24 (2.9)
Arthralgia	32 (3.8)	22 (2.7)	23 (2.8)
Muscle spasms	21 (2.5)	16 (2.0)	13 (1.6)
Osteoarthritis	15 (1.8)	16 (2.0)	18 (2.2)
Gastrointestinal disorders			
Diarrhoea	37 (4.4)	24 (3.0)	24 (2.9)
Nausea	20 (2.4)	18 (2.2)	20 (2.4)
Constipation	18 (2.1)	12 (1.5)	14 (1.7)
Nervous system disorders			
Headache	44 (5.2)	42 (5.2)	42 (5.1)
Dizziness	20 (2.4)	18 (2.2)	15 (1.8)
Respiratory, thoracic and mediastinal disorders			
Epistaxis	13 (1.5)	29 (3.6)	9 (1.1)
Cough	21 (2.5)	21 (2.6)	18 (2.2)
Dyspnoea	18 (2.1)	15 (1.8)	19 (2.3)
Pulmonary embolism	7 (0.8)	4 (0.5)	24 (2.9)
General disorders and administration site conditions			
Oedema peripheral	28 (3.3)	25 (3.1)	34 (4.1)
Fatigue	17 (2.0)	14 (1.7)	11 (1.3)
Vascular disorders			
Hypertension	34 (4.0)	19 (2.3)	14 (1.7)
Deep vein thrombosis	15 (1.8)	17 (2.1)	62 (7.5)
Haematoma	12 (1.4)	16 (2.0)	10 (1.2)
Investigations			
Blood creatine phosphokinase increased	26 (3.1)	20 (2.5)	21 (2.5)
Skin and subcutaneous tissue disorders			
Rash	18 (2.1)	8 (1.0)	12 (1.5)
Renal and urinary disorders			
Haematuria	11 (1.3)	17 (2.1)	9 (1.1)

Source: Table 14.3.1.2.6.3.1.
The denominator to calculate each percentage was the total number of treated subjects within each treatment group.
The AEs are sorted by SOC and PT in descending order of frequency in the apixaban 5 mg, then apixaban 2.5 mg treatment group.
AE=Adverse event; n=Number of subjects with AE; N=Total number of subjects in respective group; PT=Preferred term; SOC=System Organ Class.

8.4.1.2. Other studies

In Study CV185017, TEAEs were reported in 77 (60.2) % subjects in the 5 mg twice daily group, 72 (54.1%) in the 10 mg twice daily, 82 (66.1%) in the 20 mg once daily and 72 (57.1%) in the LMWH/VKA group. Overall in the apixaban groups, the commonest TEAEs were headache, 31 (8.1%) subjects, pain in the extremity, 19 (4.9%) subjects, and diarrhoea, 16 (4.2%) subjects.

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

8.4.2.1. Pivotal studies

In Study CV185056 treatment related TEAEs were reported in 520 (19.4%) subjects in the apixaban group and 815 (30.3%) in the enoxaparin/warfarin. Epistaxis was reported in 63 (2.4%) subjects in the apixaban group and 123 (4.6%) in the enoxaparin/warfarin (Table 18).

Table 18: Summary of the Most Frequently Reported (≥1% in Either Treatment Group) Treatment-Related Adverse Events With Onset During the Treatment Period Study CV185056

System Organ Class Preferred Term	Apixaban N=2676	Enoxaparin/Warfarin N=2689
	n (%)	n (%)
Total subjects with an event	520 (19.4)	815 (30.3)
Gastrointestinal disorders		
Gingival bleeding	23 (0.9)	45 (1.7)
Rectal haemorrhage	16 (0.6)	31 (1.2)
Respiratory, thoracic and mediastinal disorders		
Epistaxis	63 (2.4)	123 (4.6)
Investigations		
Blood creatine phosphokinase increased	16 (0.6)	35 (1.3)
Alanine aminotransferase increased	14 (0.5)	69 (2.6)
Gamma-glutamyltransferase increased	12 (0.4)	29 (1.1)
Liver function test abnormal	4 (0.1)	26 (1.0)
Nervous system disorders		
Headache	25 (0.9)	27 (1.0)
Injury, poisoning and procedural complications		
Contusion	34 (1.3)	72 (2.7)
Reproductive system and breast disorders		
Menorrhagia	33 (1.2)	23 (0.9)
General disorders and administration site conditions		
Injection site haematoma	8 (0.3)	35 (1.3)
Vascular disorders		
Haematoma	20 (0.7)	58 (2.2)
Renal and urinary disorders		
Haematuria	32 (1.2)	83 (3.1)
Eye disorders		
Conjunctival haemorrhage	7 (0.3)	33 (1.2)

Source: Table 14.3.1.2.6.3.4.
The denominator to calculate each percentage was the total number of treated subjects within each treatment group.
Investigator determined relatedness was defined as certain, probable, and possible. AEs with missing relationship were counted as related AEs.
AE=Adverse event; n=Number of subjects with AE; N=Total number of subjects in respective group.

In Study CV185057 treatment related TEAEs were reported in 149 (17.7%) subjects in the apixaban 2.5 mg group, 145 (17.9%) in the apixaban 5 mg, and 127 (14.4%) in the placebo. Epistaxis was reported in 12 (1.4%) subjects in the apixaban 2.5 mg group, 21 (2.6%) in the 5 mg and seven (0.8%) in the placebo (Table 19).

Table 19: Summary of the Most Frequently Reported (≥1% in Any Treatment Group) Treatment-Related Adverse Events With Onset During the Treatment Period (Treated Subjects) Study CV185057

System Organ Class Preferred Term	Apixaban 2.5 mg (N=840), n (%)	Apixaban 5 mg (N=811), n (%)	Placebo (N=826), n (%)
Total subjects with an event (%)	149 (17.7)	145 (17.9)	127 (15.4)
Gastrointestinal disorders			
Gingival bleeding	10 (1.2)	7 (0.9)	3 (0.4)
Diarrhoea	8 (1.0)	5 (0.6)	5 (0.6)
Respiratory, thoracic and mediastinal disorders			
Epistaxis	12 (1.4)	21 (2.6)	7 (0.8)
Investigations			
Blood creatine phosphokinase increased	9 (1.1)	6 (0.7)	8 (1.0)
Alanine aminotransferase increased	8 (1.0)	2 (0.2)	3 (0.4)
Injury, poisoning and procedural complications			
Contusion	6 (0.7)	9 (1.1)	7 (0.8)
Vascular disorders			
Haematoma	9 (1.1)	8 (1.0)	3 (0.4)

Source: Table 14.3.1.2.6.3.4.
The denominator to calculate each percentage was the total number of treated subjects within each treatment group.
The AEs are sorted by SOC and PT in descending order of frequency in the apixaban 5 mg, then apixaban 2.5 mg treatment group.
Investigator determined relatedness was defined as certain, probable, and possible. AEs with missing relationship were counted as related AEs.
AE=Adverse event; n=Number of subjects with AE; N=Total number of subjects in respective group; PT=Preferred term; SOC=System Organ Class.

8.4.2.2. Other studies

In Study CV185017 treatment related TEAEs were reported in 28 (21.9) % subjects in the 5 mg twice daily group, 29 (21.8%) in the 10 mg twice daily, 32 (25.8%) in the 20 mg once daily and 33 (26.2%) in the LMWH/VKA group. The most common treatment related TEAE in the apixaban groups was headache, ten (2.6%) subjects.

8.4.3. Deaths and other serious adverse events

8.4.3.1. Pivotal studies

In Study CV185056 death was reported in 37 (1.4%) subjects in the apixaban group and 44 (1.6%) in the enoxaparin/warfarin. The causes of death were similar for the two treatment groups (Table 20). In Study CV185056 SAEs were reported in 417 (15.6%) subjects in the apixaban group and 410 (15.2%) in the enoxaparin/warfarin. The commonest SAEs were PE, reported in 24 (0.9%) subjects in the apixaban group and 38 (1.4%) in the enoxaparin/warfarin, and DVT, reported in 20 (0.7%) subjects in the apixaban group and 33 (1.2%) in the enoxaparin/warfarin.

Table 20: Summary of Serious Adverse Events With Outcome of Death During the Treatment Period (Treated Subjects) Study CV185056

System Organ Class Preferred Term	Apixaban N=2676	Enoxaparin/Warfarin N=2689
	n (%)	n (%)
Total subjects with an event	37 (1.4)	44 (1.6)
Cardiac disorders	10 (0.4)	7 (0.3)
Acute myocardial infarction	3 (0.1)	0
Cardiac arrest	1 (<0.1)	1 (<0.1)
Cardiac failure	1 (<0.1)	2 (<0.1)
Cardio-respiratory arrest	1 (<0.1)	0
Cardiopulmonary failure	1 (<0.1)	0
Myocardial infarction	1 (<0.1)	2 (<0.1)
Pericardial haemorrhage	1 (<0.1)	0
Ventricular fibrillation	1 (<0.1)	0
Cardiogenic shock	0	2 (<0.1)
General disorders and administration site conditions	8 (0.3)	4 (0.1)
Death	4 (0.1)	2 (<0.1)
Multi-organ failure	3 (0.1)	1 (<0.1)
Multi-organ disorder	1 (<0.1)	0
Asthenia	0	1 (<0.1)
Infections and infestations	8 (0.3)	6 (0.2)
Sepsis	2 (<0.1)	3 (0.1)
Infection	1 (<0.1)	0
Lung infection	1 (<0.1)	0
Peritonitis	1 (<0.1)	0
Pneumonia	1 (<0.1)	2 (<0.1)
Septic shock	1 (<0.1)	1 (<0.1)
Urosepsis	1 (<0.1)	0
Purulent pericarditis	0	1 (<0.1)
Respiratory, thoracic and mediastinal disorders	8 (0.3)	10 (0.4)
Pulmonary embolism	4 (0.1)	6 (0.2)
Acute respiratory failure	2 (<0.1)	0
Pneumonia aspiration	1 (<0.1)	0
Respiratory distress	1 (<0.1)	0
Chronic obstructive pulmonary disease	0	1 (<0.1)
Interstitial lung disease	0	1 (<0.1)
Pneumothorax	0	2 (<0.1)
Neoplasms benign, malignant and unspecified (including cysts and polyps)	5 (0.2)	12 (0.4)
Colon cancer	1 (<0.1)	0
Gallbladder cancer	1 (<0.1)	0
Malignant neoplasm progression	1 (<0.1)	1 (<0.1)
Metastatic neoplasm	1 (<0.1)	1 (<0.1)
Neoplasm malignant	1 (<0.1)	0
Adenocarcinoma	0	1 (<0.1)
Cervix carcinoma	0	1 (<0.1)
Gastrointestinal cancer metastatic	0	1 (<0.1)
Lung cancer metastatic	0	1 (<0.1)
Lung neoplasm malignant	0	1 (<0.1)
Oesophageal cancer metastatic	0	1 (<0.1)
Ovarian cancer metastatic	0	1 (<0.1)

Table 20 continued: Summary of Serious Adverse Events With Outcome of Death During the Treatment Period (Treated Subjects) Study CV185056

System Organ Class Preferred Term	Apixaban N=2676	Enoxaparin/Warfarin N=2689
	n (%)	n (%)
Pancreatic carcinoma	0	1 (<0.1)
Pancreatic carcinoma stage IV	0	1 (<0.1)
Small cell lung cancer metastatic	0	1 (<0.1)
Vascular disorders	1 (<0.1)	2 (<0.1)
Arterial thrombosis	1 (<0.1)	0
Aortic rupture	0	1 (<0.1)
Shock haemorrhagic	0	1 (<0.1)
Blood and lymphatic system disorders	0	2 (<0.1)
Anaemia	0	1 (<0.1)
Disseminated intravascular coagulation	0	1 (<0.1)
Gastrointestinal disorders	0	4 (0.1)
Gastrointestinal haemorrhage	0	3 (0.1)
Neutropenic colitis	0	1 (<0.1)
Hepatobiliary disorders	0	2 (<0.1)
Hepatic failure	0	2 (<0.1)
Metabolism and nutrition disorders	0	1 (<0.1)
Failure to thrive	0	1 (<0.1)

Source: Table 14.3.2.2.1.1.
The denominator to calculate each percentage was the total number of treated subjects within each treatment group.
Deaths: included all deaths that occurred from first dose through 30 days after the last dose of blinded study drug.
Subject could have multiple adverse events with outcome of death.
n=Number of subjects with adverse event; N=Total number of subjects in respective group.

In Study CV185057 death was reported for three (0.4%) subjects in the apixaban 2.5 mg group, four (0.5%) in the apixaban 5 mg, and ten (1.2%) in the placebo. Two of the deaths in the placebo group were due to PE (Table 21). SAEs were reported in 112 (13.3%) subjects in the apixaban 2.5 mg group, 107 (13.2%) in the apixaban 5 mg, and 158 (19.1%) in the placebo. DVT as a SAE was reported for three (0.4%) subjects in the apixaban 2.5 mg group, nine (1.1%) in the 5 mg and 40 (4.8%) in the placebo. PE as a SAE was reported for five (0.6%) subjects in the apixaban 2.5 mg group, three (0.3%) in the 5 mg and 20 (2.4%) in the placebo.

Table 21: Summary of Serious Adverse Events With Outcome of Death During the Treatment Period (Treated Subjects) Study CV185057

System Organ Class Preferred Term	Apixaban 2.5 mg (N=840), n (%)	Apixaban 5 mg (N=811), n (%)	Placebo (N=826), n (%)
Total subjects with an event (%)	3 (0.4)	4 (0.5)	10 (1.2)
Cardiac disorders	1 (0.1)	2 (0.2)	3 (0.4)
Cardio-respiratory arrest	0	1 (0.1)	0
Myocardial infarction	0	1 (0.1)	0
Cardiac arrest	1 (0.1)	0	1 (0.1)
Congestive cardiomyopathy	0	0	1 (0.1)
Myocardial ischaemia	0	0	1 (0.1)
General disorders and administration site conditions	1 (0.1)	2 (0.2)	5 (0.6)
Multi-organ failure	0	1 (0.1)	0
Sudden death	0	1 (0.1)	3 (0.4)
General physical health deterioration	1 (0.1)	0	0
Death	0	0	2 (0.2)
Renal and urinary disorders	1 (0.1)	0	0
Renal failure acute	1 (0.1)	0	0
Respiratory, thoracic and mediastinal disorders	0	0	2 (0.2)
Pulmonary embolism	0	0	2 (0.2)

Source: Table 14.3.2.2.1.1.
The denominator to calculate each percentage was the total number of treated subjects within each treatment group.
The AEs are sorted by SOC and PT in descending order of frequency in the apixaban 5 mg, then apixaban 2.5 mg treatment group.
Deaths: included all deaths that occurred from first dose through 30 days after the last dose of blinded study drug.
AE=Adverse event; n=Number of subjects with AE; N=Total number of subjects in respective group; PT=Preferred term; SOC=System Organ Class.

8.4.3.2. Other studies

In Study CV185017 death was reported during the treatment period in two (1.6) % subjects in the 5 mg twice daily group (suicide, brain metastases), none (0.0%) in the 10 mg twice daily, one (0.8%) in the 20 mg once daily (PE) and none (0.0%) in the LMWH/VKA group. An additional five deaths occurred between 31 and 87 days after discontinuation of study treatment. SAEs were reported in 16 (12.5) % subjects in the 5 mg twice daily group, 11 (8.3%) in the 10 mg twice daily, 20 (16.1%) in the 20 mg once daily and 47 (12.2%) in the LMWH/VKA group. The commonest SAE in the apixaban groups was dizziness, reported in three (0.8%) subjects.

8.4.4. Discontinuation due to adverse events

8.4.4.1. Pivotal studies

In Study CV185056 DAE was reported for 162 (6.1%) subjects in the apixaban group and 199 (7.4%) in the enoxaparin/warfarin. No individual AE resulted in discontinuation in ≥ 1% subjects in either treatment group (Table 22).

Table 22: Summary of the Most Frequently Reported Adverse Events Leading to Treatment Discontinuation of >1 Subject in Either Treatment Group (Treated Subjects) Study CV185056

System Organ Class Preferred Term	Apixaban N=2676	Enoxaparin/Warfarin N=2689
	n (%)	n (%)
Total subjects with an event	162 (6.1)	199 (7.4)
Neoplasms benign, malignant and unspecified (including cysts and polyps)		
Adenocarcinoma	2 (<0.1)	0
Bile duct cancer	2 (<0.1)	0
Lung neoplasm malignant	2 (<0.1)	0
Breast cancer	0	2 (<0.1)
Colon cancer metastatic	0	2 (<0.1)
Pancreatic carcinoma	0	2 (<0.1)
Vascular disorders		
Deep vein thrombosis	13 (0.5)	23 (0.9)
Haematoma	2 (<0.1)	6 (0.2)
Post thrombotic syndrome	2 (<0.1)	0
Venous thrombosis	2 (<0.1)	0
Respiratory, thoracic and mediastinal disorders		
Pulmonary embolism	12 (0.4)	15 (0.6)
Gastrointestinal disorders		
Gastrointestinal haemorrhage	5 (0.2)	11 (0.4)
Abdominal pain	2 (<0.1)	1 (<0.1)
Rectal haemorrhage	2 (<0.1)	1 (<0.1)
Nausea	1 (<0.1)	3 (0.1)
Duodenal ulcer haemorrhage	0	2 (<0.1)
Dyspepsia	0	2 (<0.1)
Haematemesis	0	2 (<0.1)
Nervous system disorders		
Cerebral infarction	2 (<0.1)	0
Ischaemic stroke	2 (<0.1)	0
Paraesthesia	2 (<0.1)	0
Dizziness	0	3 (0.1)
Encephalopathy	0	2 (<0.1)
Haemorrhage intracranial	0	2 (<0.1)
Headache	0	3 (0.1)
Subarachnoid haemorrhage	0	2 (<0.1)
Skin and subcutaneous tissue disorders		
Rash	3 (0.1)	0
Rash pruritic	2 (<0.1)	0
Erythema	0	2 (<0.1)
Urticaria	0	2 (<0.1)
Cardiac disorders		
Atrial fibrillation	3 (0.1)	2 (<0.1)
Cardiac failure	3 (0.1)	1 (<0.1)
Acute myocardial infarction	2 (<0.1)	1 (<0.1)
Angina unstable	0	2 (<0.1)
Infections and infestations		
Sepsis	4 (0.1)	1 (<0.1)
Tuberculosis	2 (<0.1)	0
Pneumonia	1 (<0.1)	3 (0.1)

Table 22 continued: Summary of the Most Frequently Reported Adverse Events Leading to Treatment Discontinuation of >1 Subject in Either Treatment Group (Treated Subjects) Study CV185056

System Organ Class Preferred Term	Apixaban N=2676	Enoxaparin/Warfarin N=2689
	n (%)	n (%)
Pulmonary tuberculosis	0	2 (<0.1)
General disorders and administration site conditions		
Death	3 (0.1)	2 (<0.1)
Pyrexia	2 (<0.1)	0
Investigations		
Alanine aminotransferase increased	4 (0.1)	1 (<0.1)
Liver function test abnormal	3 (0.1)	2 (<0.1)
Hepatic enzyme increased	1 (<0.1)	2 (<0.1)
International normalised ratio increased	0	5 (0.2)
Psychiatric disorders		
Anxiety	2 (<0.1)	0
Panic attack	0	2 (<0.1)
Blood and lymphatic system disorders		
Thrombocytopenia	2 (<0.1)	0
Anaemia	1 (<0.1)	3 (0.1)
Renal and urinary disorders		
Haematuria	5 (0.2)	7 (0.3)
Renal failure acute	1 (<0.1)	3 (0.1)
Renal failure	0	2 (<0.1)
Musculoskeletal and connective tissue disorders		
Pain in extremity	2 (<0.1)	0
Injury, poisoning and procedural complications		
Contusion	0	2 (<0.1)
Overdose	0	3 (0.1)
Pregnancy, puerperium and perinatal conditions		
Pregnancy	3 (0.1)	2 (<0.1)
Reproductive system and breast disorders		
Vaginal haemorrhage	2 (<0.1)	0
Metrorrhagia	0	2 (<0.1)
Hepatobiliary disorders		
Hepatic function abnormal	0	2 (<0.1)

Source: Table 14.3.1.1.1.1.

The denominator to calculate each percentage was the total number of treated subjects within each treatment group.

n=Number of subjects with adverse event; N=Total number of subjects in respective group.

In Study CV185057 DAE was reported in 67 (8.0%) subjects in the apixaban 2.5 mg group, 61 (7.5%) in the apixaban 5 mg, and 134 (16.2%) in the placebo. Withdrawal due to DVT was reported for four (0.5%) subjects in the apixaban 2.5 mg group, eight (1.0%) in the 5 mg and 55 (6.7%) in the placebo (Table 23). Withdrawal due to PE was reported for four (0.5%) subjects in the apixaban 2.5 mg group, two (0.2%) in the 5 mg and 19 (2.3%) in the placebo.

Table 23: Summary of the Most Frequently Reported Adverse Events Leading to Treatment Discontinuation of >1 Subject in Any Treatment Group (Treated Subjects) Study CV185057

System Organ Class Preferred Term	Apixaban 2.5 mg (N=840), n (%)	Apixaban 5 mg (N=811), n (%)	Placebo (N=826), n (%)
Total subjects with an event (%)	67 (8.0)	61 (7.5)	134 (16.2)
Gastrointestinal disorders			
Constipation	3 (0.4)	1 (0.1)	0
Diarrhoea	3 (0.4)	1 (0.1)	0
Vascular disorders			
Deep vein thrombosis	4 (0.5)	8 (1.0)	55 (6.7)
Embolism venous	0	0	2 (0.2)
Thrombophlebitis superficial	0	0	2 (0.2)
Venous thrombosis	0	0	3 (0.4)
Nervous system disorders			
Headache	2 (0.2)	5 (0.6)	1 (0.1)
Dizziness	1 (0.1)	2 (0.2)	0
Cerebrovascular accident	0	1 (0.1)	2 (0.2)
Cardiac disorders			
Acute myocardial infarction	1 (0.1)	2 (0.2)	0
Atrial fibrillation	1 (0.1)	2 (0.2)	2 (0.2)
Myocardial infarction	1 (0.1)	2 (0.2)	2 (0.2)
Myocardial ischaemia	0	0	2 (0.2)
Respiratory, thoracic and mediastinal disorders			
Pulmonary embolism	4 (0.5)	2 (0.2)	19 (2.3)
Neoplasms benign, malignant and unspecified (including cysts and polyps)			
Metastatic neoplasm	3 (0.4)	0	0
Musculoskeletal and connective tissue disorders			
Myalgia	2 (0.2)	1 (0.1)	0
Arthralgia	1 (0.1)	1 (0.1)	2 (0.2)
Renal and urinary disorders			
Haematuria	0	3 (0.4)	1 (0.1)
Blood and lymphatic system disorders			
Anaemia	2 (0.2)	1 (0.1)	1 (0.1)
Metabolism and nutrition disorders			
Diabetes mellitus	2 (0.2)	1 (0.1)	0
Pregnancy, puerperium and perinatal conditions			
Pregnancy	2 (0.2)	1 (0.1)	1 (0.1)
General disorders and administration site conditions			
Death	0	0	2 (0.2)
Skin and subcutaneous tissue disorders			
Pruritus	0	0	2 (0.2)

Source: Table 14.3.1.1.1.1.
The denominator to calculate each percentage was the total number of treated subjects within each treatment group.
The AEs are sorted by SOC and PT in descending order of frequency in the apixaban 5 mg, then apixaban 2.5 mg treatment group.
AE=Adverse event; n=Number of subjects with AE; N=Total number of subjects in respective group; PT=Preferred term; SOC=System Organ Class.

8.4.4.2. Other studies

In Study CV185017 DAE was reported in nine (7.0) % subjects in the 5 mg twice daily group, six (4.5%) in the 10 mg twice daily, 11 (8.9%) in the 20 mg once daily and five (4.0%) in the LMWH/VKA group. Vaginal haemorrhage and dizziness were each reported in two (0.5%) subjects in the apixaban groups.

8.5. Laboratory tests

8.5.1. Liver function

8.5.1.1. Pivotal studies

In Study CV185056 AEs relating to elevated liver enzymes were reported in 162 (6.1%) subjects in the apixaban group and 308 (11.5%) in the enoxaparin/warfarin. There were four (0.2%) subjects in the apixaban group and one (< 0.1%) in the enoxaparin/warfarin with ALT or AST > 3xULN and total bilirubin > 2xULN on the same date. For three of the four subjects in the apixaban group the elevations were noted after Day 120 of treatment.

In Study CV185057 TEAEs relating to elevated liver enzymes were reported in 31 (3.7%) subjects in the apixaban 2.5 mg group, 24 (3.0%) in the apixaban 5 mg, and 27 (3.3%) in the placebo (Table 24). Elevation of AST > 3×ULN was reported in five (0.6%) subjects in the apixaban 2.5 mg group, eight (1.0%) in the 5 mg and five (0.6%) in the placebo. Elevation of ALT > 3×ULN was reported in nine (1.1%) subjects in the apixaban 2.5 mg group, five (0.6%) in the 5 mg and nine (1.1%) in the placebo. There was one subject in the apixaban 2.5 mg group and three in the placebo with ALT or AST > 3xULN and total bilirubin > 2xULN on the same date, but the subject in the apixaban 2.5 mg treatment group had comorbidities that included cholangitis, pancreatitis, and cholelithiasis that required cholecystectomy (and therefore did not fulfil the criteria for Hy's Law).

Table 24: Summary of Adverse Events Related to Elevation in LFTs With Onset During the Treatment Period (Treated Subjects) Study CV185057

Standardized MedDRA Query Preferred Term	Apixaban 2.5 mg (N=840), n (%)	Apixaban 5 mg (N=811), n (%)	Placebo (N=826), n (%)
Total subjects with an event	31 (3.7)	24 (3.0)	27 (3.3)
Liver related investigations, signs and symptoms	30 (3.6)	20 (2.5)	23 (2.8)
Gamma-glutamyltransferase increased	9 (1.1)	12 (1.5)	4 (0.5)
Alanine aminotransferase increased	13 (1.5)	4 (0.5)	10 (1.2)
Hepatic enzyme increased	1 (0.1)	4 (0.5)	3 (0.4)
Aspartate aminotransferase increased	6 (0.7)	3 (0.4)	6 (0.7)
Liver function test abnormal	4 (0.5)	2 (0.2)	1 (0.1)
Blood alkaline phosphatase increased	3 (0.4)	1 (0.1)	0
Hepatic pain	0	1 (0.1)	0
Hypertransaminasaemia	0	1 (0.1)	0
Blood bilirubin increased	2 (0.2)	0	1 (0.1)
Hepatomegaly	1 (0.1)	0	1 (0.1)
Hyperbilirubinaemia	1 (0.1)	0	0
Ascites	0	0	1 (0.1)
Hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions[a]	3 (0.4)	4 (0.5)	2 (0.2)
Hepatic steatosis	3 (0.4)	2 (0.2)	1 (0.1)
Drug-induced liver injury	0	2 (0.2)	0
Ascites	0	0	1 (0.1)
Cholestasis and jaundice of hepatic origin	1 (0.1)	2 (0.2)	0
Drug-induced liver injury	0	2 (0.2)	0
Hyperbilirubinaemia	1 (0.1)	0	0
Hepatitis, non-infectious	1 (0.1)	1 (0.1)	1 (0.1)
Hepatitis toxic	1 (0.1)	1 (0.1)	0
Hepatitis	0	0	1 (0.1)
Liver neoplasms, benign (including cysts and polyps)	0	0	2 (0.2)
Hepatic cyst	0	0	2 (0.2)

Source: Table 14.3.1.2.6.1.1.
The denominator to calculate each percentage was the total number of treated subjects within each treatment group.
The same PT could have been displayed within more than 1 SMQ.
The AEs are sorted by SMQ and PT in descending order of frequency in the apixaban 5 mg, then apixaban 2.5 mg treatment group.
AE=Adverse event; LFTs=Liver function tests; MedDRA=Medical Dictionary for Regulatory Activities
n=Number of subjects with AE; N=Total number of subjects in respective group; PT=Preferred term;
SMQ=Standardized MedDRA Query.

8.5.1.2. Other studies

In Study CV185017 no subject in any treatment group had a concomitant elevation of total bilirubin> 2xULN and ALT> 3xULN. Elevated bilirubin was reported in eight (2.2%) subjects in the apixaban groups and two (1.7%) in the LMWH/VKA. Elevation of ALT or AST > 3xULN was reported for five (1.3%) subjects in the apixaban groups and two (1.6%) in the LMWH/VKA.

8.5.2. Kidney function

In Study CV185017, marked elevation in serum creatinine (> 1.5xULN) was reported in 2 (1.6%) subjects in the apixaban 5 mg group, one (0.8%) in the 10 mg group, 2 (1.7%) in the 20 mg group, and 2 (1.7%) in the LMWH/VKA group.

In Study CV185056, marked elevation in serum creatinine was reported in 47 (1.8%) subjects in the apixaban group and 37 (1.4%) in the enoxaparin/warfarin.

In Study CV185057, marked elevation in serum creatinine was reported in 7 (0.8%) subjects in the apixaban 2.5 mg group, 13 (1.6%) in the 5 mg, and 11 (1.3%) in the placebo.

8.5.3. Other clinical chemistry

8.5.3.1. Pivotal studies

In Study CV185056, there were 20 (0.8%) subjects in the apixaban group and 24 (0.9%) in the enoxaparin/warfarin with CK elevated > 5xULN during the treatment period.

In Study CV185057 elevated CK was reported in five (0.6%) subjects in the apixaban 2.5 mg group, ten (1.3%) in the apixaban 5 mg, and nine (1.1%) in the placebo.

8.5.4. Haematology

8.5.4.1. Pivotal studies

In Study CV185056 there were 22 (0.8%) subjects in the apixaban group and 9 (0.3%) in the enoxaparin/warfarin with platelet counts decreased to < $100x10^9$/L during the treatment period.

In Study CV185057 platelet counts decreased to < $100x10^9$/L was reported in eleven (1.3%) subjects in the apixaban 2.5 mg group, four (0.5%) in the apixaban 5 mg, and six (0.7%) in the placebo.

8.5.4.2. Other studies

In Study CV185017 low haemoglobin (> 2 g/dL decrease from pre-treatment values or Hb ≤ 8.0 g/dL) was reported in seven (2.3%) subjects in the apixaban groups and five (4.8%) in the LMWH/VKA. In the opinion of the evaluator this does not appear to represent a pattern.

8.6. Post-marketing experience

8.6.1. Post-marketing data

No post-marketing data were included in the submission.

8.6.2. Risk management plan

The important identified risks are:

- VTE prevention, AF
- VTE Treatment, and Prevention of Recurrent VTE: bleeding
- VTE prevention : transient elevation of liver tests
- GI Bleeding in those ≥ 80 years for AF

- Ocular bleeding in those ≥ 80 years for AF

The important potential risks are:

- AF, VTE Treatment, and Prevention of Recurrent VTE: Liver Injury

Important missing information is:

- Management of severe bleeding
- Use in the Very Elderly (≥ 75 years) for VTE prophylaxis
- Overdose / Coagulation monitoring
- Paediatrics
- Pregnant or lactating women
- Severe hepatic impairment
- Severe renal impairment
- Black/African American population
- Hip fracture surgery, AF with valvular disease, patients with prosthetic heart valve, and haemodynamically unstable PE patients
- Non-Caucasian and non-Asian ethnicity

An additional safety concern is off-label use.

8.7. Safety issues with the potential for major regulatory impact

8.7.1. Bleeding related adverse events

In Study CV185017 bleeding AEs were reported in 15 (11.7) % subjects in the 5 mg twice daily group, 17 (12.8%) in the 10 mg twice daily, 13 (10.5%) in the 20 mg once daily and 24 (19.0%) in the LMWH/VKA group. Adjudicated bleeding events were reported in 14 (10.9) % subjects in the 5 mg twice daily group, 17 (12.8%) in the 10 mg twice daily, 13 (10.5%) in the 20 mg once daily and 20 (15.9%) in the LMWH/VKA group. Adjudicated major bleeding events were reported in one (0.8) % subjects in the 5 mg twice daily group, none (0.0%) in the 10 mg twice daily, one (0.8%) in the 20 mg once daily and none (0.0%) in the LMWH/VKA group. There was one major bleeding episode in the 5 mg group (bloody pleural effusion), one in the 20 mg (intracerebral bleed) and none in the LMWH/VKA. There were no reports of intraocular haemorrhage. Major bleeding or CRNMB was reported in 11 (8.6) % subjects in the 5 mg twice daily group, six (4.5%) in the 10 mg twice daily, nine (7.3%) in the 20 mg once daily and 10 (7.9%) in the LMWH/VKA group. The event rate (95% CI) for major bleeding or CRNMB was 8.6 (4.4 to 14.9) % for 5 mg twice daily, 4.5 (1.7 to 9.6) % for 10 mg twice daily, 7.3 (3.4 to 13.3) % for 20 mg once daily and 7.9 (3.9 to 14.1) % for LMWH/VKA. The most common bleeding related AEs were haematuria, haematoma and epistaxis.

In Study CV185056 bleeding AEs were reported in 415 (15.5%) subjects in the apixaban group and 695 (25.8%) in the enoxaparin/warfarin. The commonest bleeding related AEs were: epistaxis 77 (2.9%) subjects in the apixaban group and 146 (5.4%) in the enoxaparin/warfarin; contusion, 49 (1.8%) subjects in the apixaban group and 97 (3.6%) in the enoxaparin/warfarin; haematuria, 46 (1.7%) subjects in the apixaban group and 106 (3.9%) in the enoxaparin/warfarin; menorrhagia 38 (1.4%) subjects in the apixaban group and 30 (1.1%) in the enoxaparin/warfarin; and haematoma 35 (1.3%) subjects in the apixaban group and 76 (2.8%) in the enoxaparin/warfarin). Superiority was achieved for apixaban over standard enoxaparin/warfarin treatment in adjudicated major bleeding: RR (95% CI) 0.3070 (0.1728 to 0.5452) $p < 0.0001$. There were three subjects with intracranial bleeds in the apixaban group

and six in the enoxaparin/warfarin. There were no subjects with intraocular bleeds in the apixaban group and two in the enoxaparin/warfarin. There were six subjects with gastrointestinal bleeds in the apixaban group and 17 in the enoxaparin/warfarin.

In Study CV185057 bleeding AEs were reported in 99 (11.8%) subjects in the apixaban 2.5 mg group, 124 (15.3%) in the apixaban 5 mg, and 78 (9.4%) in the placebo. The commonest bleeding AE was epistaxis: 13 (1.5%) subjects in the apixaban 2.5 mg group, 29 (3.6%) in the 5 mg and eight (1.0%) in the placebo. Gastrointestinal bleeds were reported in 22 (2.6%) subjects in the apixaban 2.5 mg group, 29 (3.6%) in the 5 mg and 13 (1.6%) in the placebo. There were no reports of intracranial haemorrhage. There were two reports of intraocular haemorrhage in the apixaban 2.5 mg group, none in the 5 mg and one in the placebo. In the follow-up period bleeding TEAEs were reported in six (0.7%) subjects in the apixaban 2.5 mg group, six (0.7%) in the apixaban 5 mg, and nine (1.1%) in the placebo.

8.7.2. Neurological and cardiovascular events of special interest

In Study CV185056 neurological AEs were reported in 70 (2.6%) subjects in the apixaban group and 85 (3.2%) in the enoxaparin/warfarin. The most commonly reported neurological AE was paraesthesia, reported in 20 (0.7%) subjects in the apixaban group and 40 (1.5%) in the enoxaparin/warfarin. Other events of special interest were uncommon and there was no significant increase in relative risk for any of the events.

In Study CV185057 neurological TEAEs were reported in 23 (3.0%) subjects in the apixaban 2.5 mg group, 21 (2.6%) in the apixaban 5 mg, and 26 (3.1%) in the placebo. There was no increase in the risk of thrombotic events or thrombocytopenia with apixaban.

8.8. Other safety issues

8.8.1. Safety in special populations

Although not addressed in the clinical trials, breast feeding may be an issue as the milk: plasma ratio in rats is 30 and apixaban is known to be a substrate of BCRP. Breast fed infants are already at risk of Vitamin K deficiency and haemorrhagic disease of the newborn. Hence, in the opinion of the evaluator, apixaban may pose a risk to breast fed infants.

8.8.2. Overdose

In overdose, therapeutic or otherwise, there is no specific treatment to counter the effects of apixaban. There is insufficient experience from overdose in the clinical trials to be able to predict risk.

8.9. Evaluator's overall conclusions on clinical safety

Apixaban has a similar adverse effects profile to enoxaparin/warfarin but appears to have a decreased risk of bleeding related AEs with the dose regimen intended for the proposed new indications. Overall, in Study CV185056, TEAEs were reported in 1795 (67.1%) subjects in the apixaban group and 1923 (71.5%) in the enoxaparin/warfarin. Death was reported in 37 (1.4%) subjects in the apixaban group and 44 (1.6%) in the enoxaparin/warfarin. SAEs were reported in 417 (15.6%) subjects in the apixaban group and 410 (15.2%) in the enoxaparin/warfarin.

In comparison with placebo, when used for prevention of recurrent DVT and PE, apixaban had a similar overall rate of AEs in comparison with placebo, but there were more bleeding related AEs with apixaban and more VTE with placebo. In Study CV185057 TEAEs were reported in 596 (71.0%) subjects in the apixaban 2.5 mg group, 542 (66.8%) in the apixaban 5 mg, and 606 (73.4%) in the placebo. Death was reported for three (0.4%) subjects in the apixaban 2.5 mg group, four (0.5%) in the apixaban 5 mg, and ten (1.2%) in the placebo. SAEs were reported in 112 (13.3%) subjects in the apixaban 2.5 mg group, 107 (13.2%) in the apixaban 5 mg, and 158 (19.1%) in the placebo. DVT was reported as a SAE for three (0.4%) subjects in the apixaban 2.5

mg group, nine (1.1%) in the 5 mg and 40 (4.8%) in the placebo; and PE was reported as a SAE for five (0.6%) subjects in the apixaban 2.5 mg group, three (0.3%) in the 5 mg and 20 (2.4%) in the placebo.

Bleeding related AEs occurred at a lesser frequency with apixaban, using the dosing regimen intended for treatment of DVT and pulmonary embolism PE, in comparison with enoxaparin/warfarin. In Study CV185056, bleeding AEs were reported in 415 (15.5%) subjects in the apixaban group and 695 (25.8%) in the enoxaparin/warfarin. Superiority was achieved for apixaban over standard enoxaparin/warfarin treatment in adjudicated major bleeding: RR (95% CI) 0.3070 (0.1728 to 0.5452) $p < 0.0001$.

There was clearly an increased risk of bleeding related AEs in comparison with placebo, but this risk was less than the increased risk of VTE in the placebo group.

In the opinion of the evaluator, the pattern of bleeding related adverse events is consistent with that observed with the currently approved indications for apixaban.

The sponsor has stated in the PI that no dose adjustment is required in the elderly. This statement is supported by the data.

9. First round benefit-risk assessment

9.1. First round assessment of benefits

9.1.1. Benefits for treatment DVT and PE

Non-inferiority was demonstrated for apixaban in comparison with conventional treatment according to the predefined criteria. There were 59 events (symptomatic, recurrent VTE [nonfatal DVT or nonfatal PE] or VTE-related death) in the apixaban population and 71 in the enoxaparin/warfarin. The RR (95% CI) for the primary efficacy outcome measure in the per-protocol population was 0.6611 (0.4243 to 1.0301) with the upper 95% CI being < 1.8 (the criterion for non-inferiority). In the primary efficacy population the RR (95% CI) was 0.8390 (0.2965 to 1.1802), and the risk difference (95% CI) was - 0.0044 (- 0.0128 to 0.0040). The secondary outcome measures were also supportive for similar efficacy of apixaban and conventional treatment.

9.1.2. Benefits for prevention of recurrent DVT and PE

Both apixaban treatment regimens were superior to placebo with no apparent difference in efficacy between the apixaban doses. There were 19 events (symptomatic, recurrent VTE [nonfatal DVT or nonfatal PE] or all-cause death) in the apixaban 2.5 mg group, 14 in the 5 mg and 77 in the placebo. In addition, there were 13 imputed events in the apixaban 2.5 mg group, 20 in the 5 mg and 19 in the placebo. The RR (95% CI) compared to placebo for apixaban 2.5 mg was 0.3283 (0.2225 to 0.4844) and for apixaban 5 mg was 0.3615 (0.2475 to 0.5281). The Risk difference (95% CI) compared to placebo was - 0.0779 (- 0.1032 to - 0.0526) for apixaban 2.5 mg and - 0.0740 (- 0.0997 to - 0.0482) for apixaban 5 mg. All these hypothesis tests were significant to $p < 0.0001$. The secondary efficacy outcome measures were also supportive of superiority.

The sponsor has chosen the lower dose regimen to be recommended in clinical practice. In the opinion of the evaluator this is appropriate as it minimises exposure to apixaban without compromising efficacy.

9.2. First round assessment of risks

When used for the treatment of DVT and PE apixaban has a similar adverse effects profile to enoxaparin/warfarin but appears to have a decreased risk of bleeding related AEs with the dose regimen intended for the proposed new indications. Overall, in Study CV185056, TEAEs were reported in 1795 (67.1%) subjects in the apixaban group and 1923 (71.5%) in the enoxaparin/warfarin. Death was reported in 37 (1.4%) subjects in the apixaban group and 44 (1.6%) in the enoxaparin/warfarin. SAEs were reported in 417 (15.6%) subjects in the apixaban group and 410 (15.2%) in the enoxaparin/warfarin.

In comparison with placebo, when used for prevention of recurrent DVT and PE, apixaban had a similar overall rate of AEs in comparison with placebo, but there were more bleeding related AEs with apixaban and more VTE with placebo. In Study CV185057 TEAEs were reported in 596 (71.0%) subjects in the apixaban 2.5 mg group, 542 (66.8%) in the apixaban 5 mg, and 606 (73.4%) in the placebo. Death was reported for three (0.4%) subjects in the apixaban 2.5 mg group, four (0.5%) in the apixaban 5 mg, and ten (1.2%) in the placebo. SAEs were reported in 112 (13.3%) subjects in the apixaban 2.5 mg group, 107 (13.2%) in the apixaban 5 mg, and 158 (19.1%) in the placebo. DVT was reported as a SAE for three (0.4%) subjects in the apixaban 2.5 mg group, nine (1.1%) in the 5 mg and 40 (4.8%) in the placebo; and PE was reported as a SAE for five (0.6%) subjects in the apixaban 2.5 mg group, three (0.3%) in the 5 mg and 20 (2.4%) in the placebo.

The previously identified risks with apixaban are bleeding related AEs and potentially hepatic AEs. Other than these risks, the profile of AEs indicated by the PI and from Study CV185057 is similar to that of placebo (Table 25).

Table 25: Summary of the Most Frequently Reported (≥2% in Any Treatment Group) Adverse Events With Onset During the Treatment Period (Treated Subjects) Study CV185057

System Organ Class Preferred Term	Apixaban 2.5 mg (N=840), n (%)	Apixaban 5 mg (N=811), n (%)	Placebo (N=826), n (%)
Total subjects with an event	596 (71.0)	542 (66.8)	606 (73.4)
Infections and infestations			
Bronchitis	25 (3.0)	32 (3.9)	14 (1.7)
Nasopharyngitis	41 (4.9)	31 (3.8)	40 (4.8)
Urinary tract infection	29 (3.5)	31 (3.8)	35 (4.2)
Influenza	18 (2.1)	20 (2.5)	20 (2.4)
Upper respiratory tract infection	18 (2.1)	18 (2.2)	18 (2.2)
Musculoskeletal and connective tissue disorders			
Pain in extremity	44 (5.2)	52 (6.4)	54 (6.5)
Back pain	27 (3.2)	45 (5.5)	24 (2.9)
Arthralgia	32 (3.8)	22 (2.7)	23 (2.8)
Muscle spasms	21 (2.5)	16 (2.0)	13 (1.6)
Osteoarthritis	15 (1.8)	16 (2.0)	18 (2.2)
Gastrointestinal disorders			
Diarrhoea	37 (4.4)	24 (3.0)	24 (2.9)
Nausea	20 (2.4)	18 (2.2)	20 (2.4)
Constipation	18 (2.1)	12 (1.5)	14 (1.7)
Nervous system disorders			
Headache	44 (5.2)	42 (5.2)	42 (5.1)
Dizziness	20 (2.4)	18 (2.2)	15 (1.8)
Respiratory, thoracic and mediastinal disorders			
Epistaxis	13 (1.5)	29 (3.6)	9 (1.1)
Cough	21 (2.5)	21 (2.6)	18 (2.2)
Dyspnoea	18 (2.1)	15 (1.8)	19 (2.3)
Pulmonary embolism	7 (0.8)	4 (0.5)	24 (2.9)
General disorders and administration site conditions			
Oedema peripheral	28 (3.3)	25 (3.1)	34 (4.1)
Fatigue	17 (2.0)	14 (1.7)	11 (1.3)
Vascular disorders			
Hypertension	34 (4.0)	19 (2.3)	14 (1.7)
Deep vein thrombosis	15 (1.8)	17 (2.1)	62 (7.5)
Haematoma	12 (1.4)	16 (2.0)	10 (1.2)
Investigations			
Blood creatine phosphokinase increased	26 (3.1)	20 (2.5)	21 (2.5)
Skin and subcutaneous tissue disorders			
Rash	18 (2.1)	8 (1.0)	12 (1.5)
Renal and urinary disorders			
Haematuria	11 (1.3)	17 (2.1)	9 (1.1)

Source: Table 14.3.1.2.6.3.1.
The denominator to calculate each percentage was the total number of treated subjects within each treatment group.
The AEs are sorted by SOC and PT in descending order of frequency in the apixaban 5 mg, then apixaban 2.5 mg treatment group.
AE=Adverse event; n=Number of subjects with AE; N=Total number of subjects in respective group; PT=Preferred term; SOC=System Organ Class.

With regard the proposed new indications:

- Bleeding related AEs occurred at a lesser frequency with apixaban, using the dosing regimen intended for treatment of DVT and pulmonary embolism PE, in comparison with enoxaparin/warfarin. In Study CV185056 bleeding AEs were reported in 415 (15.5%) subjects in the apixaban group and 695 (25.8%) in the enoxaparin/warfarin. Superiority

was achieved for apixaban over standard enoxaparin/warfarin treatment in adjudicated major bleeding: RR (95% CI) 0.3070 (0.1728 to 0.5452) p < 0.0001.

- When used for the prevention of recurrent DVT and PE, there was clearly an increased risk of bleeding related AEs in comparison with placebo, but this risk was less than the increased risk of VTE in the placebo group.

The risks of intracranial, gastrointestinal and intraocular bleeds appear to be similar to that identified in the RMP.

Elevation of liver enzymes and hepatic AEs appear to occur at a lesser rate than for warfarin. However, it is not clear whether these AEs are more common with apixaban than with placebo. In the opinion of the evaluator, it is appropriate that liver injury should remain an Important Potential Risk in the RMP.

Although not identified in the clinical data, issues that may arise in clinical practice include lack of practical laboratory methods for monitoring effect, lack of an antidote to reverse effect in an emergency, lack of guidelines for switching to alternative treatments, and the potential for decreased adherence to a twice daily dosing regimen compared to a once daily regimen.

9.3. First round assessment of benefit-risk balance

The benefit-risk balance of Eliquis (apixaban), given the proposed usage, is favourable. For the treatment of DVT and PE, apixaban has similar efficacy to enoxaparin/warfarin but a lower risk of bleeding related AEs. For the prevention of recurrent DVT and PE, the reduction in DVT, PE and all-cause death with apixaban more than compensates for the increased risk of bleeding related AEs. The extended treatment of recurrent VTE is justified by the reduction in risk of DVT and PE in the treated population.

10. First round recommendation regarding authorisation

The evaluator has no objection to the approval of Eliquis (abixaban) for the following additional indications:

> *Eliquis is indicated for the treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE).*
>
> *Eliquis is indicated for the prevention of recurrent DVT and PE.*

However, there are some subgroups of patients not included in the pivotal studies, to whom the results could not be extrapolated and consideration should be given to excluding these patients from treatment with apixaban. These patients include: haemodynamically unstable patients, patients with massive PE, patients with multiple DVT/PE or patients with an underlying pro-coagulant disorder.

11. Clinical questions

11.1. Pharmacokinetics

With regard to the effect of food on the bioavailability of the 5 mg tablet demonstrated in Study CV185111, does the sponsor have any additional information that demonstrates no effect of food on the bioavailability of this formulation?

11.2. Pharmacodynamics

Please provide summary tabulations for the results of aPTT from Study CV185073. The tabulations should include mean, median, SD, minimum, maximum, for Day 1, Day 6 and for change from baseline for each of the study groups.

11.3. Efficacy

Were the formulations of apixaban and comparator used in the pivotal studies the same as those available in Australia?

What proportion of patients in Study CV185057 with DVT also had a PE?

Please clarify, and list, the symptoms used to define symptomatic DVT and PE.

Please explain why apixaban should not undergo routine, initial or intermittent laboratory monitoring either by plasma concentration monitoring or by using anticoagulation assays such as anti-factor Xa for the proposed indications or populations:

- Discuss if there are any special circumstances/populations where laboratory monitoring could be beneficial, for example, the peri-operative setting, acute coronary syndrome (where interventions such as PCI or the administration of thrombolytic agents are under consideration), in the event of bleeding or recurrent thrombosis, elderly patients, deteriorating hepatic or renal function, when parenteral anticoagulants are considered, concomitant use of potentially interacting medications, in the event of overdose or to assess possible poor compliance?
- Discuss whether new patients or patients switching to apixaban could benefit from laboratory monitoring.
- Discuss whether any changes to the Product Information are proposed as a result of the above?

Has there been any modelling or analysis of apixaban plasma concentrations or anticoagulation assay results in the proposed indications or populations to:

- Investigate the potential role for any laboratory monitoring?
- Investigate a potentially improved efficacy and/or safety profile for apixaban, or dose adjustment?
- If there has been any modelling or analysis undertaken for the above questions, please submit the reports to the TGA.

Have there been any discussions with the FDA, EMA or Health Canada regarding laboratory monitoring of apixaban in relation to the new indications proposed?

Are there any clinical trials completed, underway or being proposed or discussed for apixaban that include laboratory monitoring as part of the study design, for example, trials that compare monitored apixaban with unmonitored apixaban or with warfarin?

Is the sponsor proposing to include further information in the Product Information for apixaban regarding plasma concentrations, or anticoagulant activity that may be associated with an increased risk of bleeding, or regarding a therapeutic range, or any form of laboratory monitoring in relation to the proposed indications?

11.4. Safety

In Study CV185056 did any of the four subjects in the apixaban group with ALT or AST > 3xULN and total bilirubin > 2xULN on the same date fulfil the criteria for Hy's Law? What other medical

conditions or concomitant treatments would have explained these abnormalities in these individual subjects?

Please provide an update on the progress of the drug development program for the antidote.

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

12.1. Clinical question 1 - Pharmacokinetics

With regard to the effect of food on the bioavailability of the 5 mg tablet demonstrated in Study CV185111, does the sponsor have any additional information that demonstrates no effect of food on the bioavailability of this formulation?

12.1.1. Sponsor's response

The sponsor has investigated the effect of food on bioavailability in the following studies:

- Study SV185008 investigated the effect of a high fat, high calorie meal on the absorption of 2 x 5 mg phase II formulation tablets and found the 90% CIs for the fed/fasted ratios for C_{max}, AUC_{inf} and AUC_{0-t} to be within the bounds of 80% to 125%.
- Study B0661019 investigated the effect of a high fat, high calorie meal on the absorption of a 5 mg commercial tablet and found a 20% decrease in AUC_{inf} and a 15% decrease in C_{max}, with the 90% CIs for the fed/fasted ratios for C_{max}, AUC_{inf} and AUC_{0-t} outside the bounds of 80% to 125%. The sponsor does not consider this decrease in bioavailability to be clinically significant.
- Study CV185292 investigates the effect of crushing tablets and mixing with apple sauce on 2 x 5 mg tablets. The geometric mean ratio of AUC_{inf} and C_{max} for crushed tablets with apple sauce versus whole tablets was 83.6% (90% CI: 79.8%, 87.5%) and 78.9% (90% CI: 74.2%, 84.0%) and the lower bound of the CIs fell below the pre-specified bioequivalence interval. The sponsor does not consider this decrease in bioavailability to be clinically significant.

12.1.2. Evaluator's comments

The sponsor's response is acceptable. There appears to be a decrease in bioavailability with food of approximately 20%. The dose finding study and the pivotal trials did not specify whether apixaban should be taken fasted or fed, and the final dosing advice is based upon these studies. The population PK/PD study also suggests a 20% decrease in exposure would not be expected to have a clinically significant effect. However, in the opinion of the evaluator, the sponsor should perform simulation studies, based upon the population PK/PD analysis, to explore the effects of the 20% decrease in bioavailability.

12.2. Clinical question 2 - Pharmacodynamics

Please provide summary tabulations for the results of aPTT from Study CV185073. The tabulations should include mean, median, SD, minimum, maximum, for Day 1, Day 6 and for change from baseline for each of the study groups.

12.2.1. Sponsor's response

The sponsor has drawn attention to the location of these data in the report for Study CV185073 (Table 26). There were no between group differences, or within group changes, in aPTT during the study.

Table 26: Scheduled Laboratory Values and Changes from Baseline Summary. Population: Safety

HEMATOLOGY. Partial Thromboplastin Time (PTT) (sec)

Treatment	Visit	n#	Mean	SD	Median	Min. Max	Change from Baseline			
							Mean	SD	Median	Min. Max
TRT A Apixaban	BASELINE (DAY -1)	43	27.2	2.05	27	23, 32				
	DAY 6	43	27.4	1.91	28	23, 31	0.3	0.93	0	-2, 2
TRT B Prasugrel	BASELINE (DAY -1)	44	27.5	1.91	27	24, 31				
	DAY 6	44	27.3	1.93	27	23, 31	-0.1	1.11	0	-3, 2
TRT C Apixaban + Prasugrel	BASELINE (DAY -1)	53	27.4	1.83	27	24, 31				
	DAY 6	53	27.6	1.89	27	23, 32	0.3	0.86	0	-1, 2

12.2.2. Evaluator's comments

The sponsor's response is acceptable and has resolved the issue.

12.3. Clinical question 3 - Efficacy

Were the formulations of apixaban and comparator used in the pivotal studies the same as those available in Australia?

12.3.1. Sponsor's response

The formulations of apixaban used in the pivotal studies were not the same as those available in Australia. The formulations have the same core composition but are different in 'appearance, non-functional film-coat composition, colour, shape and label storage statement'. The sponsor argues that the formulations would have comparable in vivo performance. The sponsor has not answered the question with regard to the comparator formulations.

12.3.2. Evaluator's comments

The sponsor's response is acceptable, and has resolved the issues, with regard the formulations of apixaban. The sponsor's response is not acceptable with regard the comparator formulations. The sponsor should clarify the formulations of comparator used in the pivotal studies.

12.4. Clinical question 4 - Efficacy

What proportion of patients in Study CV185057 with DVT also had a PE?

12.4.1. Sponsors response

In Study CV185057 there were 52 (6.2%) subjects in the apixaban 2.5 mg group, 62 (7.6%) in the apixaban 5 mg and 49 (5.9%) in the placebo with DVT and PE. There was one (0.1%) subject in the apixaban 2.5 mg group, one (0.1%) in the apixaban 5 mg and two (0.2%) in the placebo with recurrent DVT and PE.

12.4.2. Evaluator's comments

The sponsor's response is acceptable, and has resolved the issue. The proportions are similar for each of the groups.

12.5. Clinical question 5 - Efficacy

Please clarify, and list, the symptoms used to define symptomatic DVT and PE.

12.5.1. Sponsor's response

The sponsor has responded that 'A specific list of symptoms was not provided to the investigators as the clinical symptoms of VTE are very variable at presentation. This was considered the best approach, as providing specific symptoms could potentially influence the investigators clinical evaluation of the subjects.' The sponsor used an adjudication committee consisting of 'experts experienced in the conduct of VTE treatment trials and assessments of endpoints in such trials' to determine the diagnosis of symptomatic DVT or PE. However, the sponsor also refers to 'pre-specified criteria for diagnosis of symptomatic DVT or PE'.

12.5.2. Evaluator's comments

The sponsor's response is not acceptable. It appears from the sponsor's response that although there were pre-specified criteria for defining the diagnosis of symptomatic DVT or PE, these criteria have not been provided in the response. The sponsor should provide this information to the TGA.

12.6. Clinical question 6 – Efficacy

Please explain why apixaban should not undergo routine, initial or intermittent laboratory monitoring either by plasma concentration monitoring or by using anticoagulation assays such as anti-factor Xa for the proposed indications or populations:

- Discuss if there are any special circumstances/populations where laboratory monitoring could be beneficial, for example, the peri-operative setting, acute coronary syndrome (where interventions such as PCI or the administration of thrombolytic agents are under consideration), in the event of bleeding or recurrent thrombosis, elderly patients, deteriorating hepatic or renal function, when parenteral anticoagulants are considered, concomitant use of potentially interacting medications, in the event of overdose or to assess possible poor compliance?
- Discuss whether new patients or patients switching to apixaban could benefit from laboratory monitoring.
- Discuss whether any changes to the Product Information are proposed as a result of the above?

12.6.1. Sponsor's response

The sponsor investigated the use of apixaban plasma concentrations and anti-FXa activity during the development program for apixaban and did not find that these measures had predictive utility for either efficacy or safety. The sponsor contends that '*Thus, there is no evidence that adjusting doses of apixaban using routine, initial or intermittent laboratory monitoring of apixaban plasma drug concentrations or anti-FXa activity levels would improve the efficacy/safety profile of apixaban for VTE treatment patients.*' However, the sponsor does state that anti-FXa assays may be useful in exceptional cases such as overdose or emergency surgery'. The sponsor states that in the clinical trials apixaban was commenced without monitoring and still had superior efficacy to enoxaparin/warfarin.

12.6.2. Evaluator's comments

The sponsor's response is acceptable. For laboratory monitoring to be useful the laboratory test should have good predictive ability for either efficacy or safety. The population PK/PD analysis (Study PMAR-00312) did not establish a relationship between apixaban exposure and either efficacy or safety outcome measures. However, in the opinion of the evaluator, laboratory tests with good predictive ability would be useful to clinicians and beneficial to patients. Hence, the sponsor should be encouraged to develop, or facilitate the development, of such tests.

12.7. Clinical question 7 – Efficacy

Has there been any modelling or analysis of apixaban plasma concentrations or anticoagulation assay results in the proposed indications or populations to:

- Investigate the potential role for any laboratory monitoring?
- Investigate a potentially improved efficacy and/or safety profile for apixaban, or dose adjustment?
- If there has been any modelling or analysis undertaken for the above questions, please submit the reports to the TGA.

12.7.1. Sponsor's response

The sponsor has conducted a population PK/PD study (Study PMAR-00312) that explored the relationship between apixaban plasma concentration and efficacy and safety outcomes. These analyses used a logistic regression approach. The analysis was limited by the small numbers of events. The sponsor, in summary, states '*the data demonstrated a wide overlap in apixaban exposure and anti-FXa activity values for those who did and did not experience safety or efficacy events. No discernible threshold levels could be identified that would predict better or worse safety or efficacy outcomes for individual patients*'.

12.7.2. Evaluator's comments

The sponsor's response is acceptable. However, the modelling approach used by the sponsor is not the optimal approach to determining the utility of a diagnostic test. A more appropriate approach would be to use receiver operating characteristic plots, and to determine specificity and sensitivity for the most appropriate threshold levels (Fischer et. al. 2003). A ROC analysis would provide better information to determine the utility of laboratory tests in guiding management.

12.8. Clinical question 8 – Efficacy

Please discuss if there is a therapeutic range for apixaban that could be defined for the proposed indications or populations?

12.8.1. Sponsor's response

The sponsor refers to their response to Question 7. The sponsor has not defined a therapeutic range for apixaban.

12.8.2. Evaluator's comments

The sponsor's response is acceptable. In the opinion of the evaluator there are insufficient data to be able to establish a therapeutic range for apixaban. There were few outcome events in Study PMAR-0032: 34 efficacy outcome events and 33 safety outcome events (Table 27). Although a ROC analysis has not been performed, the paucity of outcome events would limit the ability of such an analysis to identify a therapeutic range. However, the sponsor should be encouraged to perform an exploratory ROC analysis.

Table 27: Number of Safety and Efficacy Events in the ER Analysis Dataset PMAR-0032

	CV185017/056 Studies	CV185057 Study
Number of subjects with PK	522	178
Index event DVT/PE	409 / 113	93/ 85
Safety Endpoint	25	8
MB event	1	0
CRNMB event	24	8
Efficacy Endpoint	23	11
DVT event	13	8
PE event	15	3
VTE-related death	0	0

12.9. Clinical question 9 – Efficacy

Have there been any discussions with the FDA, EMA or Health Canada regarding laboratory monitoring of apixaban in relation to the new indications proposed?

12.9.1. Sponsor's response

'In relation to the new indications proposed '*treatment of DVT and PE and prevention of recurrent DVT and PE*' there have been no discussions with FDA, EMA or Health Canada regarding laboratory monitoring of apixaban.'

However, the sponsor has provided the following correspondence with the EMA and Health Canada authorities with regard the use of laboratory monitoring with apixaban:

- EU VTEp MAA - Day 120 Response to Clinical Question 17: This is a communication to the EMA from the sponsor with regard to the use of the Rotachrom anti-Xa test. The sponsor reports that this test has appropriate characteristics and correlates with apixaban plasma concentrations, but there is no clinical experience to guide its use in decision making.
- EU VTEp MAA -Day 180 Response to Clinical Question 3: This is a communication with the EMA with regard laboratory monitoring. The sponsor states '*While the Applicant has found the Rotachrom assay to be suitable for research purposes without modification, the assay would require further evaluation to meet the necessary laboratory standards prior to its use for clinical purposes.*' The sponsor also discusses that there is not a clear relationship between anti-factor Xa and either efficacy or safety.
- EU VTEp MAA -Day 180 Response to Clinical Question 4: This is a communication with the CHMP with regard to bleeding related AEs in the APPRAISE-2 study and whether monitoring would have a role in preventing such events. The sponsor has responded that the anti-factor Xa assay would not have been useful in monitoring pharmacodynamic interactions with antiplatelet agents.
- EU NVAF – Day 180 Response to Clinical Question 4: This is a communication with the EMA with regard to the commercial availability of the Rotachrom anti-Xa test. The sponsor reports that the Rotachrom anti-Xa test is commercially available and also the STA-Liquid anti-Xa product, that uses the same technology, is also commercially available.
- EU NVAF – Day 180 Response to RMP Question 17: This is a communication with the EMA with regard to the RMP. The sponsor states that plans to develop an appropriate assay for apixaban are included in the RMP.
- Health Canada Responses NVAF: This is a communication with Health Canada in response to a question with regard to whether there are clinical circumstances where the sponsor would recommend using the monitoring of anti-factor Xa to inform therapeutic decisions.

The sponsor responds to Health Canada that '*there are insufficient data to define a therapeutic range for anti-FXa activity*'.

12.9.2. Evaluator's comment

The sponsor's response is acceptable. There is a shared concern between regulatory agencies that a method for monitoring apixaban effect should be developed. The sponsor has provided similar responses to the EMA, Health Canada and to the TGA.

12.10. Clinical question 10 - Efficacy

Are there any clinical trials completed, underway or being proposed or discussed for apixaban that include laboratory monitoring as part of the study design, for example, trials that compare monitored apixaban with unmonitored apixaban or with warfarin?

12.10.1. Sponsor's response

'*There are no clinical trials completed, underway or proposed which include laboratory monitoring of apixaban as part of the study design, or compare monitored apixaban with unmonitored apixaban or with warfarin*.'

12.10.2. Evaluator's comments

The sponsor has satisfactorily answered the question. However, although monitoring of anti-factor Xa to guide treatment has been identified as needing development by the TGA, EMA and Health Canada, the sponsor does not appear to be currently evaluating laboratory monitoring in clinical trials.

12.11. Clinical question 11- Efficacy

Is the sponsor proposing to include further information in the Product Information for apixaban regarding plasma concentrations, or anticoagulant activity that may be associated with an increased risk of bleeding, or regarding a therapeutic range, or any form of laboratory monitoring in relation to the proposed indications?

12.11.1. Sponsor's response

The sponsor refers to the response to Question 7. The sponsor does not propose to include further information in the PI with regard to laboratory monitoring or therapeutic range.

12.11.2. Evaluator's comments

The sponsor's response is acceptable. In the opinion of the evaluator there are insufficient data to be able to recommend monitoring or a therapeutic range. However, the development of appropriate laboratory monitoring and the identification of a therapeutic range may offer benefits to patients treated with apixaban.

12.12. Question A – Safety

In Study CV185056 did any of the four subjects in the apixaban group with ALT or AST > 3xULN and total bilirubin > 2xULN on the same date fulfil the criteria for Hy's Law? What other medical conditions or concomitant treatments would have explained these abnormalities in these individual subjects?

12.12.1. Sponsor's response

With regard to these four subjects, three had clear alternative explanations for the biochemical abnormalities:

- One subject had pancreatic cancer with obstruction of the common bile duct [information redacted]
- One subject had cholangiocarcinoma [information redacted]
- One subject had metastatic liver cancer and obstructive jaundice [information redacted]

The remaining subject had LFT elevations at the final visit and had a past history of gall stones and cholecystectomy [information redacted]. After ceasing study treatment on Day 170, the LFT elevations resolved within 5 weeks with no sequelae (Table 28). The patient narrative includes the statements: '*Prior to study unblinding, this case was reviewed by the Applicants' independent Hepatology Consultant Panel. The hepatologist consultants' considered the relationship to blinded study drug (apixaban) was probably related*'.

Table 28: Liver Function Tests from PID 434-248 (last dose of study drug was taken on Day 170)

Day	Alanine Aminotransferase Reference range: 6-37 U/L[a] Upper limits of normal : 37[b]	Aspartate Aminotransferase Reference range: 10-36 U/L[a] Upper limits of normal : 36[b]	Total Bilirubin Reference range: 0.2-1.2 mg/dL[a] Upper limits of normal: 21[b]	Direct Bilirubin Reference range: 0-0.3 mg/dL[a] Upper limits of normal: 5[b]
Day 1	32 U/L[a]	18 U/L[a]	1.2 mg/dL[a]	0.3 mg/dL
Day 167	259 U/L[a]	113 U/L[a]	4 mg/dL[a] 68[b]	2.3 mg/dL[a] 39[b]
Day 173	281 U/L[a]	129 U/L[a]	2.6 mg/dL[a]	1.7 mg/dL[a]
Day 177	343 U/L[a] 343[b]	161 U/L[a] 161[b]	2.8 mg/dL[a]	1.6 mg/dL[a]
Day 189	156 U/L[a]	71 U/L[a]	1.9 mg/dL[a]	0.8 mg/dL[a]
Day 204	34 U/L[a]	24 U/L[a]	1.1 mg/dL[a]	0.4 mg/dL[a]

[a] Values are from the central laboratory.

[b] Values are from the local laboratory. Units were not provided.

12.12.2. Evaluator's comments

The sponsor's response is acceptable. One subject fulfilled the criteria for Hy's law. Although the biochemical abnormalities resolved following cessation of study treatment the case fulfils the criteria for drug induced liver injury. The RMP lists transient elevation of liver enzymes as an important identified risk but only for VTE prevention. In the opinion of the evaluator, transient elevation of liver enzymes should be listed as an important identified risk for all indications of apixaban.

12.13. Question B – Safety

Please provide an update on the progress of the drug development program for the antidote.

12.13.1. Sponsor's response

The sponsor is not developing an antidote independently. The sponsor '*has entered into a clinical collaboration agreement with Portola Pharmaceuticals to study PRT4445 (andexanet), a universal FXa inhibitor antidote, and apixaban in Phase III clinical studies*'. A Phase II study indicates andexanet can reverse the effects of apixaban. Phase III studies in healthy volunteers are ongoing.

In addition, a study of prothrombin complex concentrates in reversing the effects of apixaban is ongoing.

12.13.2. Evaluator's comments

The sponsor has satisfactorily answered the question.

12.14. Page 39 of CER – Breast feeding

In the opinion of the evaluator, breast feeding should be included in the contraindications.

In the opinion of the evaluator, there should be a warning not to take apixaban if breast feeding.

12.14.1. Sponsor's response

The sponsor is not of the opinion that breast feeding should be a contraindication and considers that there is sufficient warning with regard breast feeding in the PI.

12.14.2. Evaluator's comments

The sponsor's response is not acceptable. The sponsor has not addressed the issues raised. These issues are:

- The milk: plasma ratio of apixaban in rats is 30 and apixaban is known to be a substrate of BCRP.
- Breast fed infants are already at risk of Vitamin K deficiency and haemorrhagic disease of the newborn.

Hence the available data indicate that apixaban may pose a risk to breast fed infants. The current warnings in the PI only reflect the level of risk usually associated with any new chemical entity. There is reason for considering apixaban to have a higher level of risk and this should be communicated in the PI.

12.15. Page 39 of CER – Strong inducers

The clinical aspects of the draft Product Information are not entirely satisfactory. In the Section of the PI headed 'Interactions With Other Medicines' the following statements have been inserted: '*For the treatment of DVT and PE, concomitant therapy with strong inducers of both CYP3A4 and P-gp is not recommended. For the prevention of recurrent DVT and PE, strong inducers of both CYP3A4 and P-gp should be co-administered with caution*'. The evaluator considers that there is the same risk of interaction for both indications and that the following warning should apply: '*For the treatment of DVT and PE and for the prevention of recurrent DVT and PE, concomitant therapy with strong inducers of both CYP3A4 and P-gp is not recommended*'.

12.15.1. Sponsor's response

The sponsor contends that concomitant therapy with strong inducers of both CYP and P-gp should be designated 'use with caution' rather than 'not recommended' for the indication of prevention of recurrent DVT and PE. The argument supporting this is: the population of patients being treated for the prevention for recurrent DVT and PE is '*at clinical equipoise and 2.5 mg BD may still be effective and safe with concomitant strong inducers of CYP3A4 and P-gp compared to placebo*'.

12.15.2. Evaluator's comments

The sponsor's response is not acceptable. If the population of subjects being treated for recurrent DVT and PE were in clinical equipoise (that is, insufficient data to determine whether the patient should receive treatment or not) then there would also be insufficient data to approve apixaban for that indication. In the opinion of the evaluator this is not the case. The available data also indicate that strong inducers of CYP3A4 and P-gp would be expected to significantly reduce the efficacy of apixaban. Hence, in the opinion of the evaluator the following

warning should apply: '*For the treatment of DVT and PE and for the prevention of recurrent DVT and PE, concomitant therapy with strong inducers of both CYP3A4 and P-gp is not recommended*'.

12.15.3. Erratum provided by the sponsor

The sponsor has provided lists of erratum, and explanations of their significance, for the pivotal studies, the ISE and the ISS. In the opinion of the evaluator, these errata do not materially change any of the conclusions from the data.

13. Second round benefit-risk assessment

13.1. Second round assessment of benefits

After consideration of the responses to clinical questions, the benefits of apixaban in the proposed usage are unchanged from those identified in the First round evaluation.

13.2. Second round assessment of risks

After consideration of the responses to clinical questions, the risks of apixaban in the proposed usage, in addition to those identified in the First round assessment of risk, are: drug induced liver injury. The S31 data included one case of drug induced liver injury. In the opinion of the evaluator, transient elevation of liver enzymes should be listed as an important identified risk for all indications of apixaban. It is also appropriate that liver injury remains an Important Potential Risk.

13.3. Second round assessment of benefit-risk balance

The risk-benefit balance remains the same as that stated in First round evaluation. The benefit-risk balance of Eliquis (apixaban), given the proposed usage, is favourable. For the treatment of DVT and PE, apixaban has similar efficacy to enoxaparin/warfarin but a lower risk of bleeding related AEs. For the prevention of recurrent DVT and PE, the reduction in DVT, PE and all-cause death with apixaban more than compensates for the increased risk of bleeding related AEs. The extended treatment of recurrent VTE is justified by the reduction in risk of DVT and PE in the treated population.

14. Second round recommendation regarding authorisation

The evaluator has no objection to the approval of Eliquis (apixaban) for the following additional indications:

> *Eliquis is indicated for the treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE).*
>
> *Eliquis is indicated for the prevention of recurrent DVT and PE.*

However, there are some subgroups of patients not included in the pivotal studies, to whom the results could not be extrapolated, and consideration should be given to excluding these patients from treatment with apixaban. These patients include: haemodynamically unstable patients, patients with massive PE, patients with multiple DVT/PE or patients with an underlying pro-coagulant disorder.

15. References

Dignan R, Keech AC, Gebski VJ, Mann KP, Hughes CF; Warfarin SMART Investigators. Is home warfarin self-management effective? Results of the randomised Self-Management of Anticoagulation Research Trial. Int J Cardiol. 2013 Oct 15;168(6):5378-84.

Fischer JE, Bachmann LM, Jaeschke R. A readers guide to the interpretation of diagnostic test properties: clinical example of sepsis. Intensive Care Medicine. 2003; 29: 1043-1051

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