EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

26 June 2014
EMA/478338/2014
Committee for Medicinal Products for Human Use (CHMP)

# Assessment report

## Eliquis

### International non-proprietary name: APIXABAN

### Procedure No. EMEA/H/C/002148/II/0014/G

## Note

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

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# List of abbreviations

| | |
|---|---|
| ACCP | American College of Chest Physicians |
| AE | Adverse event |
| AF | Atrial fibrillation |
| ALS | Amyotrophic lateral sclerosis |
| ALT | Alanine aminotransferase |
| aPTT | Activated partial thromboplastin time |
| ASA | Acetylsalicylic acid |
| AUC | Area under the concentration-time curve |
| AUCinf | Concentration time to infinity curve |
| AXA | Anti-Xa activity |
| BID | Bis in die (twice daily) |
| BMI | Body mass index |
| BMS | Bristol-Myers Squibb |
| CHMP | Committee for Medicinal Products for Human Use |
| CI | Confidence interval |
| CLT | Total body clearance |
| Cmax | Maximum plasma concentration |
| CPMP | Committee for Proprietary Medicinal Products |
| CrCl | Creatinine clearance |
| CRNMB | Clinically relevant non-major bleeding |
| CSR | Clinical study report |
| CUS | Compression ultrasound |
| CV | Cardiovascular |
| CYP | Cytochrome P450 |
| DB | Double-blind |
| DC | Discontinue |
| DSMB | Data Safety Monitoring Board |
| DVT | Deep vein thrombosis |
| EMA | European Medicines Agency |
| E-R | Exposure-response |
| ESC | European Society of Cardiology |
| ESRD | End stage renal disease |
| EU | European Union |
| FDA | Food and Drug Administration |
| FXa | Factor Xa |
| GBS | Guillain-Barre syndrome |
| GCP | Good clinical practice |
| GI | Gastrointestinal |
| H2 | Histamine H2 receptor |
| hr | Hour |
| HR | Hazard ratio |
| ICAC | Independent Central Adjudication Committee |
| ICH | International Conference on Harmonization |
| ICTOM | International Conference of Technology and Operations Management |
| INR | International normalized ratio |
| ISTH | International Society on Thrombosis and Hemostasis |

| | |
|---|---|
| IU | International unit |
| IV | Intravenous |
| IVRS | Interactive voice response system |
| kg | Kilogram |
| L | Litre |
| LFT | Liver function test |
| LMWH | Low molecular weight heparin |
| MB | Major bleeding |
| MedDRA | Medical Dictionary for Regulatory Activities |
| mg | Milligram |
| MI | Myocardial infarction |
| min | Minute |
| mL | Millilitre |
| ng | Nanogram |
| NGT | Nasogastric tube |
| NI | Non-inferiority |
| NICE | National Institute for Clinical Excellence |
| NNH | Number needed to harm |
| NNT | Number needed to treat |
| NOAEL | No observed adverse effect level |
| p | P-value |
| PD | Pharmacodynamic |
| PE | Pulmonary embolism |
| P-gp | P-glycoprotein |
| PK | Pharmacokinetic |
| PLS | Perfusion lung scan |
| PO | Per os (orally) |
| PP | Per protocol |
| PPK | Population pharmacokinetics |
| PT | Preferred term |
| Q12h | Every 12 hours |
| QD | Quaque diem (once daily) |
| RD | Risk difference |
| RHD | Recommended human dose |
| RR | Relative risk |
| SAE | Serious adverse event |
| SAP | Statistical analysis plan |
| SC | Subcutaneous |
| SCE | Summary of Clinical Efficacy |
| SCP | Summary of Clinical Pharmacology Studies |
| SCS | Summary of Clinical Safety |
| SD | Standard deviation |
| SMC | Study management committee |
| SmPC | Summary of Product Characteristics |
| sNDA | Supplemental New Drug Application |
| SPA | Special Protocol Assessment |
| t½ | Half-life |
| TTR | Time in therapeutic range |

| | |
|---|---|
| UFH | Unfractionated heparin |
| ULN | Upper limit of normal |
| US | United States |
| VKA | Vitamin K antagonist |
| VPLS | Ventilation/perfusion lung scintigraphy |
| VTE | Venous thromboembolism |

# 1. Background information on the procedure

## *1.1. Type II variation*

Pursuant to Article 7.2 variations of Commission Regulation (EC) No 1234/2008, Bristol-Myers Squibb /Pfizer EEIG submitted to the European Medicines Agency on 31 October 2013 an application for a group of variations including an extension of indication.

This application concerns the following medicinal product:

| **Medicinal product:** | **International non-proprietary name:** | **Presentations:** |
|---|---|---|
| Eliquis | APIXABAN | See Annex A |

The following variations were requested in the group:

| **Variation(s) requested** | | **Type** |
|---|---|---|
| C.I.6.a | C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one | II |
| B.II.e.5.a.1 | B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes | IAin |

The MAH applied for an extension of the indication for the treatment of deep vein thrombosis and pulmonary embolism and prevention of recurrent DVT and PE in adults. Consequently, the MAH proposed the update of sections 4.1, 4.2, 4.4, 4.5, 4.8 and 5.1 of the SmPC.

The Package Leaflet was proposed to be updated in accordance.

In addition, the MAH applied for a variation to add a new pack size of 28 film coated tablets for Eliquis 5mg strength (SmPC section 6.5). The Package Leaflet and Labelling were proposed to be updated in accordance.

The group of variations proposed amendments to the SmPC, labelling and Package Leaflet.

## *Information on paediatric requirements*

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0235/2013 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0235/2013 was not yet completed as some measures were deferred.

## *Information relating to orphan market exclusivity*

## Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with

authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

### *Scientific advice*

The applicant received Scientific Advice from the CHMP on 13 December 2007 with a follow up advice on 23 September 2010.

The Scientific Advice pertained to clinical aspects of the dossier.

## *1.2. Steps taken for the assessment of the product*

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

Rapporteur: Pieter de Graeff Co-Rapporteur: Robert James Hemmings

| | |
|---|---|
| Submission date: | 31 October 2013 |
| Start of procedure: | 22 November 2013 |
| Rapporteur's preliminary assessment report circulated on: | 16 January 2014 |
| Rapporteur's updated assessment report circulated on: | 14 February 2014 |
| Request for supplementary information and extension of timetable adopted by the CHMP on: | 20 February 2014 |
| PRAC RMP Assessment report endorsed on: | 6 March 2014 |
| MAH's responses submitted to the CHMP on: | 2 April 2014 |
| Joint Rapporteur's updated assessment report circulated on: | 26 May 2014 |
| PRAC Rapporteurs updated assessment report circulated on: | 26 May 2014 |
| PRAC RMP advice and assessment overview adopted by PRAC : | 13 June 2014 |
| Joint Rapporteur's updated assessment report circulated on: | 19 June 2014 |
| CHMP opinion: | 26 June 2014 |

# 2. Scientific discussion

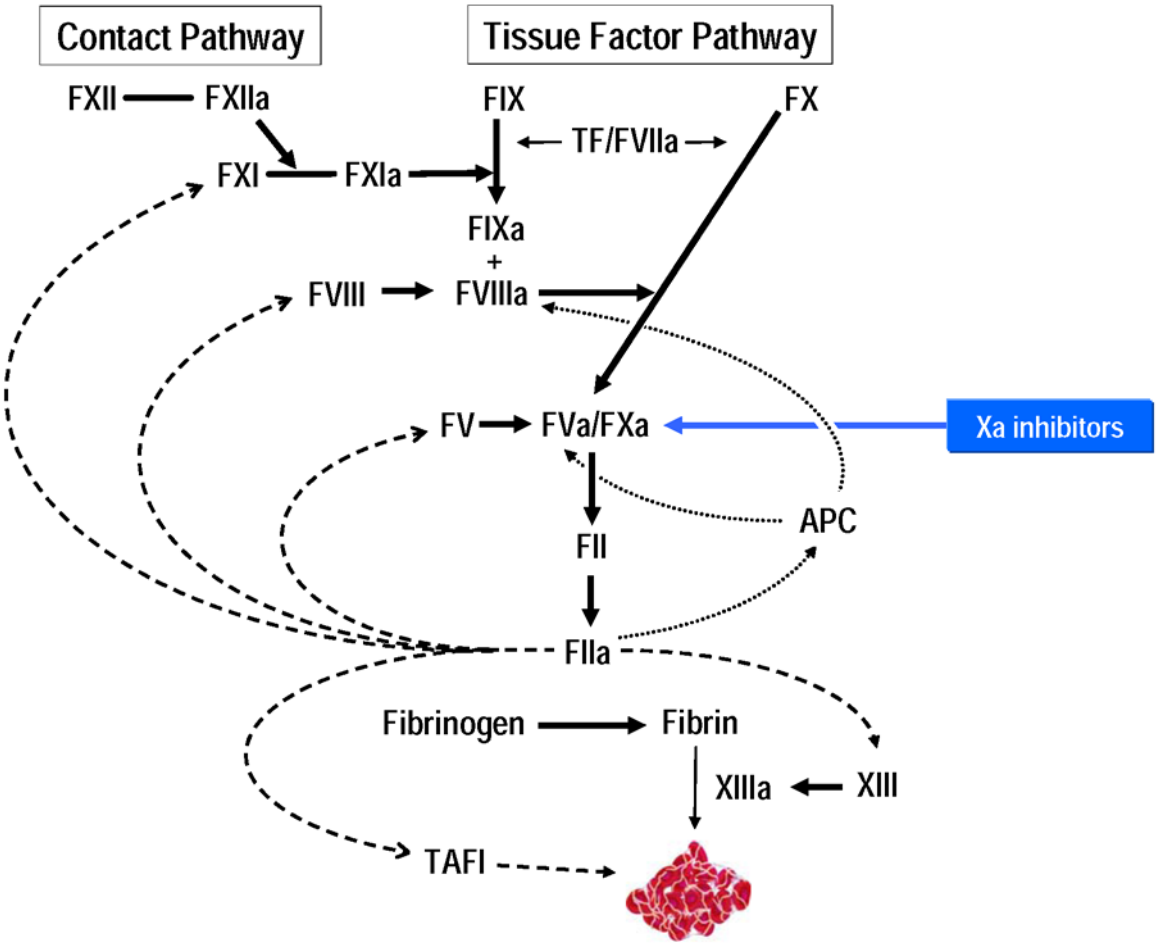
## *2.1. Introduction*

Apixaban is a selective, orally active inhibitor of coagulation factor X [FXa] that is being co-developed by Bristol-Myers Squibb (BMS) and Pfizer as an anticoagulant and antithrombotic agent. Apixaban (also referred to as BMS-562247), is a reversible and highly potent inhibitor of human FXa, with an inhibitor constant (Ki) of 0.08 ± 0.01 nM, and a high degree of selectivity over other coagulation proteases and structurally related enzymes involved in digestion and fibrinolysis.

**Pharmacotherapeutic action**

FXa occupies a pivotal role in the clotting cascade, converting prothrombin to thrombin (FIIa). Thrombin has multiple functions, converting fibrinogen to fibrin, promoting fibrin cross-linking by activating factor XIII, providing positive feedback activation of coagulation by activating factors V, VIII, and XI, activating the protein C anticoagulant pathway, and activating thrombin-activatable fibrinolysis inhibitor (TAFI) to protect the clot from premature degradation (Figure 1). Thrombin is also a powerful platelet agonist, activating platelets and recruiting additional platelets into the platelet-rich thrombus. FXa inhibition decreases conversion of prothrombin to active thrombin, thereby diminishing fibrin formation, and reducing coagulation and platelet activation. Unlike unfractionated heparin (UFH), low-molecular-weight heparin (LMWH), and fondaparinux, each of which acts through an antithrombin (AT)-mediated mechanism, apixaban directly inhibits FXa. Compared with UFH, LMWHs (including enoxaparin) have relatively more effect on inhibiting FXa than FIIa, while the pentasaccharide, fondaparinux, selectively inhibits FXa.

**Figure 1: The haemostatic pathway and site of action of inhibitors of activated factor X (FXa). FXa occupies a central position in the pathway, converting prothrombin (FII) to thrombin (FIIa). Thrombin then converts fibrinogen to fibrin.**




**Approved indications**

Apixaban is currently approved for preventing VTE in adults following elective knee or hip replacement surgery at a dose of 2.5 mg BID in the EU and other countries and for reducing the risk of stroke or systemic embolism in adults with non-valvular AF at a dose of 5 mg BID.

**Problem statement**

The following new indication is proposed by the MAH:

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

The proposed dose regimen is:

- For the treatment of DVT and PE, 10 mg taken orally twice daily for 7 days followed by 5 mg taken orally twice daily.
- In patients requiring treatment for the prevention of recurrent DVT and PE, 2.5 mg taken orally twice daily after at least 6 months of treatment for DVT or PE.

The clinical development program for the treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults included 1 Phase 2 study (CV185017) and 2 Phase 3 studies (CV18506 and CV18507;

**Disease background**

Venous Thromboembolism (VTE) is a common name to denote diseases related to DVT or PE. Thrombosis is a pathological process by which blood clots form within the lumen of arteries, veins, or the chambers of the heart. In the venous circulation, thrombosis in the large veins of the legs, pelvis, or arms is referred to as DVT. The most common anatomical site of a DVT is the venous system of the lower limb. DVT may result in pain and swelling of the affected limbs, but is often asymptomatic. Any episode of DVT, whether symptomatic or not, significantly increases the risk of further VTE, and may lead to a PE or post-thrombotic syndrome that includes venous ulceration, debilitating pain, and intractable oedema.

PE is a clot within the lung vasculature that results from embolisation of a DVT, most often from the proximal veins of the legs. PE may occur together with a DVT or may occur in the absence of symptoms of DVT. Patients with symptomatic DVT also often have silent PE. In DVT treatment studies, it has been demonstrated that the majority of patients with symptomatic proximal DVT, but without symptoms of PE, have perfusion deficits on lung scanning. Thus, DVT and PE are manifestations of the same disease with serious and potential fatal outcomes.

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).

VTE is a common disorder, with literature reports of > 900,000 VTE events annually in the US and > 1 million VTE events annually in France, Germany, Italy, Spain, Sweden and the UK combined. Thus, VTE is a major health problem worldwide, and as the population ages, mortality and morbidity resulting from PE and DVT will increasingly contribute to significant clinical and health-related problems.

VTE may be associated with an identifiable and reversible risk factor, such as surgery, trauma, or prolonged immobilization. These cases are considered to be provoked VTEs, and usually occur within 3 months of the associated risk factor. Unprovoked VTE is associated with no such identifiable risk factors. Many patients with unprovoked VTE are found, subsequent to their diagnosis, to have conditions that result in a higher risk for recurrence, such as active cancer or thrombophilia. 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.

**Current Standard of Care, Available Therapies, and Unmet Medical Need for the Treatment of Venous Thromboembolism**

The present standard of care for treatment of DVT is a 2-stage process. The first involves initiation of treatment parenterally with UFH, LMWH or the pentasaccharide fondaparinux. The second stage, usually begun at the same time as the first, is the initiation of oral dosing with a vitamin K antagonist (VKA). Treatment with UFH or LMWH is continued until therapeutic anticoagulation is achieved with the VKA, as evidenced by an INR above 2.0. At this point parenteral therapy is discontinued and oral therapy with the VKA (target range: 2.0 ≤ INR ≤ 3.0) is continued for a duration that depends upon the clinical setting.

The therapeutic goals in managing patients with VTE are 2-fold: 1) stabilize the thrombus in the acute episode to facilitate its degradation by the endogenous fibrinolytic system, and 2) prevent recurrence or new episodes of VTE.

VKAs have a narrow therapeutic window, and so dosing must be individualized, which requires gradual titration to achieve and maintain a therapeutic level. This requires frequent INR monitoring. In addition, VKAs suffer from significant drug-drug and drug-food interactions, which can result in INR levels that fall below or exceed the optimal therapeutic level. As a result, treatment with VKAs requires constant diligence with respect to compliance, INR monitoring, concomitant drug use and diet in order to achieve and maintain a level of anticoagulation that is efficacious and has an acceptable bleeding risk. As such, the complexity of warfarin dosing contributes to it being the medication most commonly implicated in emergency admissions for adverse drug events in patients ≥ 65 years old, based on a survey performed in 58 non-paediatric hospitals in the US. Warfarin-related adverse events (AEs) accounted for approximately one-third of these hospitalizations and it has been estimated that hospitalizations for warfarin-related haemorrhages in the US exceed 20,000 cases annually.

The recently published “concept paper on the need for revision of the guideline on clinical investigation of medicinal products for the treatment of venous thromboembolic disease (CPMP/EWP/563/98)” indicates that the current clinical practice guidelines make a distinction between acute treatment (usually the first 7 days), long-term treatment (from day 7 to 3 months) and extended treatment of VTE (from 3 months to indefinite). VTE events are classified as either unprovoked (or idiopathic) or provoked (secondary to a transient or reversible cause, such as surgery, recent immobilisation or trauma).

Published evidence indicates that in patients with VTE provoked by a transient risk factor such as surgery, the risk of recurrent VTE after 3-6 months of effective anticoagulant therapy is approximately 50% lower compared to patients who had an unprovoked (idiopathic) VTE. This lower risk of recurrence with provoked VTE has resulted in a recommendation by all current treatment guidelines (American College of Chest Physician (ACCP), National Institute for Clinical Excellence (NICE), European Society of Cardiology (ESC)) to discontinue anticoagulation after 3 months of treatment for patients who have a VTE provoked by a transient risk factor and do not have an on-going risk factor for recurrence. However, in patients with unprovoked VTE and a low or moderate risk for bleeding, treatment beyond 3 months is recommended based on an individual patient’s risk for bleeding. The recommended anticoagulant treatment doses are the same for VTE events, regardless of whether the event was provoked or unprovoked. This recommendation is driven by evidence which demonstrated that the cumulative incidence of VTE recurrence in such a population was 11% within 1 year after discontinuing anticoagulant therapy, 29% within 5 years, and 40% within 10 years.

Although current guidelines support extending anticoagulant therapy in patients with unprovoked VTE until the risk of recurrent VTE no longer outweighs the risk of bleeding or until the patient wishes to stop treatment (even if the patient's risk of recurrence outweighs the increase in bleeding), an exact duration is not specified.

## *2.2. Non-clinical aspects*

### 2.2.1. Introduction

*Pharmacology:*

Apixaban inhibits free factor Xa (FXa) as well as thrombus-associated FXa and FXa within the prothrombinase complex. Unlike the indirect inhibitors of FXa, apixaban does not require antithrombin III to inhibit FXa. By inhibiting FXa, apixaban reduces directly tissue factor-induced thrombin generation and indirectly thrombin-mediated platelet aggregation, suggesting that it may prevent and treat both venous as well as arterial thrombosis. The major circulating metabolite of apixaban, O-desmethyl apixaban sulfate, does not significantly inhibit human FXa.

Primary pharmacodynamic data provided in the original MAA showed that in diabetic/obese mice and in a broad range of experimental models of thrombosis in rabbits, rats, and dogs, apixaban demonstrated antithrombotic efficacy at doses that resulted in modest changes in standard coagulation assays. Substantial prevention of both venous and arterial thrombosis was achieved at apixaban doses that produced minor changes in bleeding times, while higher doses resulted in more pronounced increases in clotting times and bleeding times. Apixaban also effectively inhibited the growth of a preformed intravascular thrombus.

Secondary and safety pharmacology data revealed no concern of adverse secondary pharmacodynamic or other adverse effects related to its pharmacological action.

In rabbits, the combination of apixaban with aspirin and/or clopidogrel significantly enhanced antithrombotic activity without excessive increases in bleeding time.

(For more details of the pharmacological studies, see the EPAR of the first MAA (2011)).

*Pharmacokinetics:*

*In vitro* studies with excised segments of rat duodenum, jejunum, ileum and colon, showed that apixaban is absorbed throughout the rat intestinal tract. The permeability coefficient in the jejunum provided evidence for involvement of an intestinal efflux transport mechanism.

A range of *in vitro* studies in monolayers of Caco-2 cells expressing a number of efflux transporters including P-gp and BCRP, porcine kidney-derived cells (LLC-PK1) transfected with P-gp transporters, canine kidney-derived (MDCKII) cells transfected with BCRP transporters, indicated that apixaban is a substrate for both P-gp and BCRP, and it is not transported by MRP or OAT1, OAT3, OATP1B1, OATP1B3 and OATP2B1 transporters. These active transport mechanisms may play a role in the limited bioavailability after oral administration of apixaban. In addition, evidence was found for paracellular transport. At high doses, absorption may also be limited by dissolution rate.

Elimination half-life in rats (2-3 hrs) was shorter than in dogs (5-6 hrs) and chimpanzees. Distribution volume was relatively low in rats (0.31 L/kg), dogs (0.30 L/kg) and chimpanzees (0.17 L/kg). Clearance (rat 4.3 ml/min/kg, dog 0.87 ml/min/kg, chimpanzee 0.30 ml/min/kg) was low (10, 2 and 1% respectively) compared to hepatic blood flow.

In toxicokinetic studies, exposure increased less than dose-proportional. At high doses and in dietary studies exposure hardly increased with increasing dose.

Protein binding differs between the species. The unbound fraction at concentrations of 1-10 µM is about 13% in human vs about 4% in rats and 8% in dogs.

Single dose radiolabel distribution studies in rats showed a wide distribution, with the highest values in excretory organs (liver, kidney, urinary bladder (and contents), bile) and intestinal tract (and contents). Distribution in pregnant rats/foetuses showed significant foetal exposure with foetal plasma levels mostly lower than maternal levels. Pregnant rats showed a high Cmax in mammary gland. Concentrations of apixaban in rat milk exceed those in blood and plasma. The high concentration in milk vs plasma suggested involvement of active transport (possibly BCRP transporter). Elimination half life from rat milk, blood and plasma was similar.

Apixaban is mainly metabolised by CYP3A4/5 with conjugation via SULT1A1, but several other CYP and SULT isozymes are also involved. There were no apixaban metabolites with pharmacological activity. There were no unique human metabolites.

After single oral administration of radiolabelled apixaban to intact male mice, male rats, female rabbits or male dogs, most of the dose was excreted in faeces and most of the remainder of the dose in urine. Bile-duct cannulated rats eliminated part of the dose by the biliary route (about 3% over a 48 hr period after oral gavage). After intravenous infusion intact male rats or female rabbits excreted a larger part into urine. Intravenously treated bile-duct cannulated rats excreted even more into urine (47% in 24 hrs) and also a large part into bile (23% in 24 hrs). Most of the faecally and urinary eliminated material consists of parent compound. A large part of the faecally cleared material was probably unabsorbed apixaban. Secretion of apixaban and metabolites into the intestine was most likely due to excretion via P-glycoprotein.

Apixaban is not an inhibitor or inducer of CYP. Inhibition was only observed at concentrations 25 times the maximal observed human plasma concentrations. Apixaban did not affect the absorption of drugs that are P-glycoprotein substrates. Since apixaban is a substrate for CYP3A4/5, BCRP, and P-glycoprotein, co-administration of drugs that modulate their activities could affect the absorption and disposition of apixaban. However, the relatively low dependence of apixaban on metabolic clearance for its elimination and the multiple pathways available for apixaban elimination (renal and biliary clearance and, possibly, intestinal secretion) suggests that any such effects are likely to be of relatively low magnitude. Since apixaban is a substrate for the P-glycoprotein transporter, its absorption may be affected by P-glycoprotein inhibitors.

With the first line extension application (2012) two *in vitro* studies were provided, showing an inhibiting effect of diltiazem on digoxin efflux in Caco- 2 cells and in porcine kidney-derived LLC-PK1 cell monolayers. Based on these data it was concluded that diltiazem is an inhibitor of P-gp.

In fasted beagle dogs (first MAA), bioavailability of apixaban was reduced (up to 50%) by active charcoal treatment, given 0.25 – 3 hrs after the oral apixaban dose. The highest reduction was found when activated charcoal was administered 3 hrs after the apixaban dose (1 hour before Tmax).

(For more details of the pharmacokinetic studies, see the EPAR of the first MAA (2011)).

*Toxicology:*

In the repeated dose studies, up to 6 months with a recovery phase in rats (doses up to 600 mg/kg/day, AUC up to apixaban up to 30 times human AUC at a dose of 2.5 mg BID) and to 1 year in dogs (doses up to 100 mg/kg/day, AUC up to > 80 times human AUC at a dose of 2.5 mg BID), apixaban showed no significant toxicity. The major observed effects were those on blood coagulation parameters: PT and aPTT and, sometimes, fibrinogen and/or bleeding time. In some studies, minor effects on blood cells and/or on serum K, Na and/or Cl and/or evidence of subclinical haemorrhage was observed. Exposure to the major metabolite O-demethyl apixaban sulfate was not measured in the pivotal long term repeated dose studies. However, based on separate 7-day repeated dose pharmacokinetics studies in rats and dogs, systemic exposure to the metabolite was lower than in humans in the rat study and about similar to that in humans in the dog study. It was concluded that the metabolite was tested in the pivotal studies, but that these studies revealed no exposure margin for the metabolite. Since conjugates are usually not more toxic than the unconjugated compounds, and in addition to the toxicity studies with limited exposure there were data showing the absence of effects of the metabolite in pharmacodynamic and safety pharmacology studies, no further toxicity data were deemed necessary.

No evidence was found of genotoxicity, carcinogenicity or adverse effects at clinical exposure levels on fertility, embryo-foetal development or pre/postnatal development. The original MAA only contained an exploratory juvenile toxicity study, the definitive study was ongoing at that time. With the first application for a line extension (2012) the report of the definitive juvenile toxicity study was provided. No special juvenile toxicity was observed in addition to the effects already known from the studies in adult animals.

(For more details of the toxicological studies, see the EPAR of the first MAA (2011)).

The ERA provided for the first MAA, was amended for the authorisation of the first line extension. It was further amended for the current line extension. For details, see the EPAR of the first MAA and that of the first line extension (2012).

### 2.2.2. Pharmacology

An addendum correction to study 930028749 (effect of apixaban in dog models of thrombosis and hemostasis) was included in the dossier, to correct errors in the reported results, as shown below.

The purpose of this addendum is to correct errors in the results for AV shunt thrombosis model.

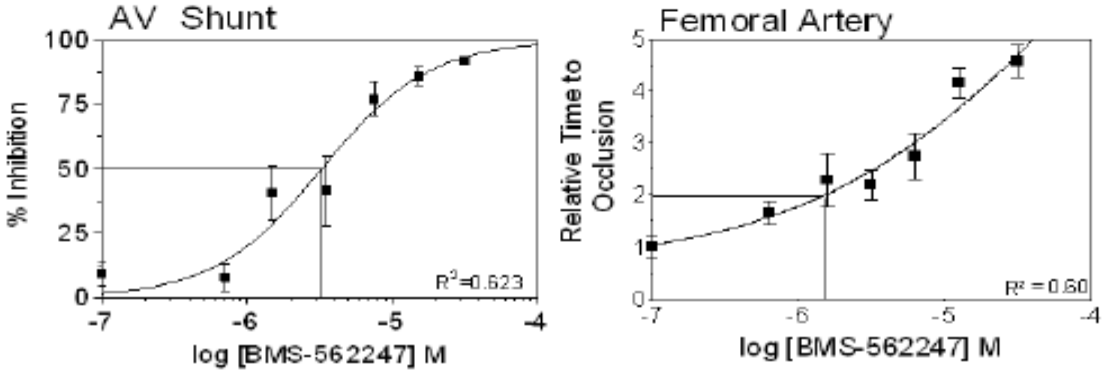
Two values were incorrectly reported in Table 3.1.1. Mean values for Percent inhibition for the vehicle group and the lowest dose of BMS-562247 have been corrected in the revised table below.

**Table 3.1.1: AV Shunt Model**

| Group | n | Clot weight (mg) | | Percent inhibition |
|---|---|---|---|---|
| | | Pre-test | 60' | |
| Vehicle | 14 | 161 ± 22.6 | 182 ± 27.9 | 9 ± 4.3 |
| BMS-562247: 0.14 mg/kg + 0.014 mg/kg/hr | 7 | 95 ± 12.3 | 114 ± 14.2 | 8 ± 5.5 |
| BMS-562247: 0.28 mg/kg + 0.028 mg/kg/hr | 8 | 163 ± 48.2 | 84 ± 15.4 | 41 ± 10.6* |
| BMS-562247: 0.56 mg/kg + 0.056 mg/kg/hr | 8 | 141 ± 28.8 | 74± 17.5 | 42 ± 13.4* |
| BMS-562247: 1.12 mg/kg + 0.112 mg/kg/hr | 8 | 187 ± 13.9 | 44 ± 13.2 | 77 ± 6.7* |
| BMS-562247: 2.24 mg/kg + 0.224 mg/kg/hr | 6 | 198 ± 41.5 | 24 ± 4.8 | 86 ± 3.7* |
| BMS-562247: 4.48 mg/kg + 0.448 mg/kg/hr | 6 | 122 ± 22.1 | 9 ± 0.5 | 92 ± 1.3* |

* $p < 0.05$ for comparison to Vehicle group

Correct values for A-V shunt inhibition are plotted in the revised figure below. The calculated IC50 is 3.3 µM.




The correct IC50 for the AV shunt model of 3.3 µM should occur in the abstract on page 2, in section 3.4 on page 16, and in the conclusions on page 18. The correct free IC50 in the AV shunt model of 290 nM should also occur in the section 3.4 on page 16.

Although the corrections noted above change the quantitative values for the results of the AV shunt thrombosis model, they do not alter the interpretation or conclusions drawn from the results.

**CHMP comment:**

It is agreed that the correction has no implications for the interpretation or conclusions from this study.

***Effect of activated charcoal treatment***

The objective of the new Study 930046725 1.0 was to re-evaluate the effects of activated charcoal administration on pharmacokinetics of apixaban after oral administration to male beagle dogs using a cross-over design with the charcoal administration at different dose levels and time points.

In this study, a five-treatment, 5-period, cross-over design was carried out. After fasted male dogs received apixaban (5 mg/kg, 1 mg/mL in 0.5% Tween 80 in Labrafil suspension) by oral gavage followed by a 10 mL flush of water, one control dog was treated with water while other dogs received activated charcoal as an aqueous suspension at either 250 mg/kg (low dose) at 3 or 5 hours, at 2500 mg/kg (high dose) at 3 hours, or at 250 mg/kg (low dose) at 3 and 5 hours. The treatments were separated by at least 48 hours. Blood (1.0 mL, $K_3$EDTA anticoagulant) at 0.5, 1, 2, 3, 4, 5, 6, 8, 12, 14, 20, and 24 h was collected via venipuncture of a peripheral blood vessel and plasma was prepared by centrifugation.

**Table 3:** **Apixaban pharmacokinetics and % AUC reduction in male dogs after oral administration of apixaban (5 mg/kg) following oral treatment with activated charcoal (N = 5)**

| PK Parameters | Charcoal administration post apixaban dose | | | | |
|---|---|---|---|---|---|
| | No Charcoal | Low Charcoal, 3 h | High Charcoal, 3 h | Low Charcoal, 5 h | Low Charcoal, 3&5 h |
| AUC0-24 (µg•h/mL) | 97.0 ± 23.6 (0%) | 82.0 ± 10.5 (15.5%) | 52.6 ± 4.7 (45.7%) | 90.3 ± 19.7 (6.9%) | 76.1 ± 8.3 (21.5%) |
| Cmax (µg/mL) | 10.8 ± 1.92 | 10.9 ± 1.21 | 9.96 ± 1.49 | 11.1 ± 2.57 | 11.0 ± 0.90 |
| Tmax (h) | 4.5 ± 1.3 | 2.8 ± 0.5 | 2.6 ± 0.5 | 3.5 ± 0.7 | 3.2 ± 0.8 |
| C24 (µg/mL) | 0.29 ± 0.13 | 0.29± 0.13 | 0.07 ± 0.06 | 0.24 ± 0.11 | 0.18 ± 0.14 |
| MRT (h) | 7.71 ± 0.51 | 6.81 ± 0.81 | 4.82 ± 0.60 | 6.71 ± 0.87 | 6.25 ± 0.76 |
| T1/2 (h) | 3.17 ± 0.59 | 4.13 ± 1.00 | 3.01 ± 0.57 | 3.34 ± 0.56 | 3.15 ± 0.55 |
| CL/F (mL/h/kg) | 47.4 ± 8.58 | 60.4 ± 7.5 | 95.0 ± 9.4 | 57.3 ± 15.2 | 65.6 ± 8.04 |
| Vs/F (L/kg) | 0.379 ± 0.09 | 0.41 ± 0.06 | 0.45 ± 0.03 | 0.38 ± 0.08 | 0.41 ± 0.04 |

No charcoal = 5 mg/kg apixaban in 0.5% Tween 80 in Labrafil

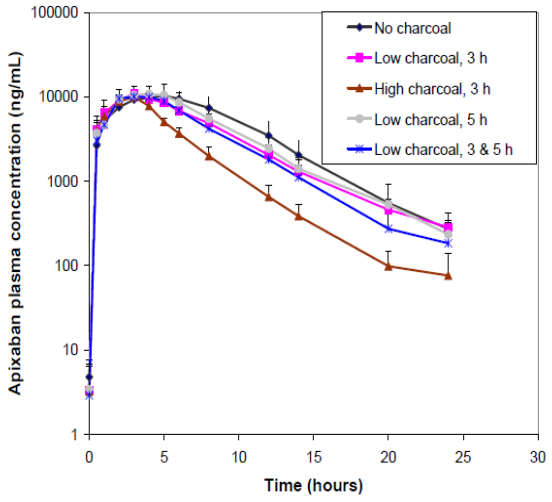
Low charcoal, 3 h = 5 mg/kg apixaban followed by 250 mg/kg (1.2 mL/kg) dose of charcoal 3 h postdose

High charcoal, 3 h = 5 mg/kg apixaban followed by 2500 mg/kg (1.2 mL/kg) dose of charcoal 3 hour postdose

Low charcoal, 5 h = 5 mg/kg apixaban followed by 250 mg/kg (1.2 mL/kg) dose of charcoal 5 hours postdose

Low charcoal, 3 & 5 h = 5 mg/kg apixaban followed by 250 mg/kg (1.2 mL/kg) dose of charcoal 3 and then 5 hours postdose

**Figure 3:** **Apixaban exposures in log scale in male dogs (n = 5) following oral administration ( 5 mg/kg) without and with oral doses of activated charcoal**




Activated charcoal treatments decreased apixaban $AUC_{0\text{-}24h}$ values by 15.5, 45.7, 6.9, and 21.5%, respectively, when administered at low dose 3 h, high dose 3 h, low dose 5 h , and low dose 3 and 5 h post apixaban dose. A dose of 2500 mg/kg activated charcoal significantly increased the clearance, and significantly reduced the AUC, MRT and C24, when administered three hours after apixaban ($p < 0.05$). The low dose (250 mg/kg) did not statistically significantly decrease exposure. Activated charcoal did not have statistically significant effects on the half-life, the maximum plasma concentration, the time to reach peak concentration, mean residence time, or the volume of distribution.

**CHMP comments:**

For information: In the original MAA dossier, a study on the effect of activated charcoal treatment on apixaban pharmacokinetics in dogs was submitted. It was shown that in fasted Beagle dogs, bioavailability of apixaban could be decreased up to 50% by active charcoal treatment at a dose of 250 mg/kg, 0.25 – 3 hrs after the oral apixaban dose. The highest reduction was found when activated charcoal was administered 3 hrs after the apixaban dose (1 hour before Tmax).

The new study showed that at a sufficiently high dose, activated charcoal can reduce exposure to apixaban. In this study, however the effect of 250 mg/kg was very limited, whereas the higher dose

of 2500 mg/kg had a clear, but still modest effect. The presumable mechanism is inhibition of absorption and reabsorption (after secretion into the intestine by biliary excretion and secretion by active transporters, see below). It is not clear how this effect should be extrapolated to the clinical situation. However, section 4.9 of the current SmPC contains treatment advice based on clinical data, therefore these dog data contribute no relevant new information regarding current advice in the SmPC.

***Effect of haemodialysis in dogs***

Study 930046779 1.0 examined effects of hemodialysis on circulating concentrations of apixaban (BMS-562247) following oral and intravenous dosing in male dogs.

The objective of this study was to determine the effect of hemodialysis on circulating concentrations of apixaban (BMS-562247) after oral or intravenous administration to fasted male beagle dogs (8-12 kg body weight at start of study). Groups I, II, III, and IV dogs (n = 4) received sequential treatments with apixaban in order to measure the impact of dialysis on oral PK, intravenous PK, intravenous PK with hemodialysis, and oral PK with hemodialysis, respectively. The treatments were separated by at least 48 hours. The doses were 5 mg/kg, 1 mg/mL in 0.5% Tween 80 in Labrafil suspension by oral gavage followed by a 10 mL flush of water for PO, and 1 mg/kg, 1 mg/mL in 35% 2-hydroxypropyl-beta-cyclodextrin in 10 mM phosphate, pH 7.0 by bolus injection followed by 0.5 mL flush of 0.9% NaCl for IV. For groups III and IV, dialysis started approximately 5 min after apixaban dose at 50 mL/min blood flow and 300 mL/min dialysate flow in the opposite direction. Blood was collected from a port immediately before the dialysis filter at 0.166, 0.25, 0.5, 1, 2, 3, 4, 8, 12, 16, and 24 h and at 0.166, 0.25, 0.5, 1, 2, and 3 h from the port immediately after the dialysis filter.

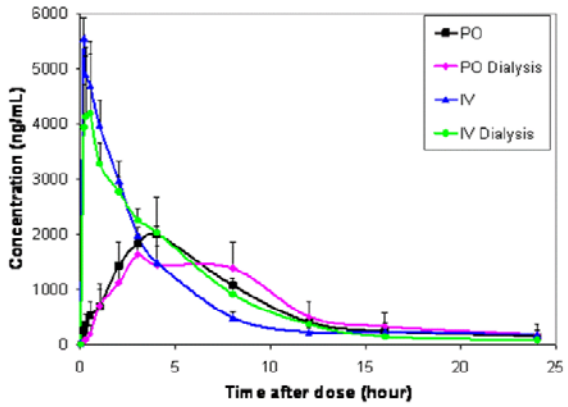
**Table 1:** **Apixaban concentrations and amounts in dialysate following oral and IV administration with and without hemodialysis in male dogs (n=4, mean ± SD)**

| | Time or animal number | IV | PO |
|---|---|---|---|
| Concentration (ng/mL) | 0-1 h | 43.8 ± 9.7 | 13.4 ± 11.4 |
| | 1-2 h | 29.1 ± 8.7 | 41.1 ± 12.5 |
| | 2-3 h | 20.7 ± 3.8 | 60.1 ± 13.0 |
| | 3-4 h | 16.9 ± 3.4 | 60.1 ± 9.3 |
| Amount recovered during 0-4 h (µg) | # 201 | 2284 | 3244 |
| | # 202 | 1704 | 2106 |
| | # 203 | 2349 | 3083 |
| | # 204 | 1611 | 3179 |
| Total amount recovered (µg) | | 1987 ± 461 | 2902 ± 535 |

**Table 2:** Pharmacokinetics of apixaban following oral and IV administration with and without hemodialysis in male dogs (n=4, mean ± SD)

| PK Parameters | PO | PO Dialysis | IV | IV Dialysis |
|---|---|---|---|---|
| Cmax (µg/mL) | 10.3 ± 0.39 | 9.05 ± 1.69 | 5.64 ± 0.27 | 4.29 ± 1.26 |
| Tmax (h) | 3.75 | 3.25 | 0.25 | 0.35 |
| AUC0-4 (µg•h/mL) | 25.3 ± 3.9 | 20.3 ± 6.3 | 12.3 ± 0.5 | 11.5 ± 1.5 |
| AUC0-24 (µg•h/mL) | 82.3 ± 8.6 | 83.2 ± 21.3 | 19.3 ± 2.2 | 20.9 ± 2.5 |
| T1/2 (h) | 5.3 ± 3.9 | 5.9 ± 2.4 | 4.3 ± 0.8 | 3.9 ± 0.5 |
| $CL_P$ (mL/h/kg) | | | | 47.3 ± 6.5 |
| $CL_{Dialysis}$ (mL/h/kg) | | | | 17.2 ± 4.0 |
| Vs (L/kg) | | | 0.31 ± 0.04 | 0.26 ± 0.04 |

**Figure 4:** Plasma apixaban concentration - time profile following oral and IV administration (dose adjusted to 1 mg/kg) with and without hemodialysis in male dogs (n=4)




Hemodialysis reduced apixaban concentrations including $C_{max}$ values during dialysis although overall AUC of apixaban was not greatly reduced. There was a concentration drop of apixaban after the dialysis filter for the majority of samples. The 4-hour dialysis removed approximately 20 and 6% of doses for IV and PO dosing, respectively. The hemodialysis clearance (17.3 mL/min/kg) was approximately three times the apixaban renal clearance in dogs.

The MAH concluded that the results suggested that hemodialysis reduced apixaban concentrations. Therefore, hemodialysis could reduce bleeding risk from potential apixaban overdose and should be useful to remove apixaban for renal impaired patients. Dose adjustment might be needed for patients under dialysis due to removal of apixaban by hemodialysis.

**CHMP comments:**

The effect of hemodialysis in dogs was rather limited. Based on these data, it is not clear whether in case of a high overdose or if a patient needs enhanced elimination in other emergency situations (e.g. bleeding due to accident or e.g. unexpected operative procedures) exposure can be sufficiently reduced by dialysis. However, considering the new proposed text for section 4.9 (see below), there is already clinical data and therefore extrapolation of the dog data is not needed. Apparently, dialysis was not highly effective at therapeutic doses in humans either.

According to new proposed text in section 4.9 of the SmPC*: "Haemodialysis decreased apixaban AUC by 14% in subjects with end- stage renal disease (ESRD), when a single dose of apixaban 5 mg was administered orally. Therefore, haemodialysis is unlikely to be an effective means of managing apixaban overdose."*

Non clinical data suggest that dose adjustment might be needed for patients under dialysis due to removal of apixaban by hemodialysis. According to section 4.2 of the SmPC, apixaban is not recommended in patients undergoing dialysis, because there is no clinical experience.

The above proposal is considered acceptable.

***Excretion and enterohepatic/enteroenteric recirculation***

The excretion and enterohepatic recirculation of apixaban were investigated in male bile-duct cannulated (BDC) rats (wild type (WT) or P-gp or BCRP knock-out (KO)) and in male dogs (BDC and intact) following a single IV dose of 2 mg/kg or 1 mg/kg $^{14}$C-apixaban, respectively (studies BMS-r1759; NCPK3). The excretion pattern (expressed as radioactivity) and pharmacokinetic parameters in these animals are presented in the following two tables.

**Excretion pattern of apixaban in WT, P-gp KO and BCRP KO BDC rats and in BDC and intact dogs**

| Species | Route | Dose (mg/kg) | Collection period (hr) | % of dose | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | Urine | Faeces | Bile | GI tract | Cage rinse | Total |
| WT BDC rat | IV | 2 | 0-48 | 51 | 24 | 11 | 0.7 | 1.2 | ~87 |
| WT BDC rat [a] | IV | 2 | 0-48 | 53 | 15 | 15 | 0.5 | 4.9 | ~88 |
| WT BDC rat [b] | IV | 2 | 0-48 | 43 | 31 | 16 | 1.7 | 1.1 | ~92 |
| P-gp KO BDC rat | IV | 2 | 0-48 | 46 | 26 | 14 | 0.2 | 2.5 | ~89 |
| P-gp KO BDC rat [b] | IV | 2 | 0-48 | 44 | 28 | 11 | 0.3 | 3.2 | ~88 |
| BCRP KO BDC rat | IV | 2 | 0-48 | 37 | 35 | 13 | 0.06 | 1.7 | ~86 |
| BCRP KO BDC rat [b] | IV | 2 | 0-48 | 29 | 42 | 15 | 0.4 | 3.0 | ~89 |
| BDC dog | IV | 1 | 0-72 | 16 | 46 | 21 | - | - | ~83 |
| BDC dog [b] | IV | 1 | 0-72 | 12 | 69 | 17 | - | - | ~98 |
| intact dog | IV | 1 | 0-72 | 9.9 | 51 | - | - | - | ~61 |

a concomitant administration of the P-gp and BCRP inhibitor elacridar
b concomitant intraduodenal administration of 250 mg/kg active charcoal 30 min before and 5, 90 and 180 min after administration of apixaban

Intravenous Dose to BDC rats (2 mg/kg) (n =3)

| | WT Control | WT GF-120918 | WT Charcoal | P-gp-KO | BCRP-KO |
|---|---|---|---|---|---|
| $AUC_{0-\infty}$ (µg·h/mL) | 1.41±0.23 | 2.84±0.76 | 1.02±0.02 | 2.04±0.09 | 2.34±0.68 |
| $C_{max}$ (µg/mL) | 2.26±0.25 | 1.97±0.32 | 1.64±0.27 | 2.16±0.29 | 2.37±0.11 |
| $C_8$ (ng/mL) | 4.5±1.6 | 46.1±38.8 | 2.8±0.1 | 8.6±3.9 | 19.5±7.4 |
| $T_{1/2}$ (h) | 1.2±0.6 | 2.8±0.5 | 0.8±0.2 | 1.1±0.3 | 2.1±1.4 |
| CL (L/h/kg) | 1.4±0.6 | 0.7±0.2 | 2.0±0.1 | 0.8±0.2 | 0.9±0.3 |
| Vs (L/kg) | 0.9±0.1 | 1.6±0.3 | 1.2±0.2 | 0.7±0.1 | 1.8±1.2 |
| MRT (h) | 0.6±0.1 | 1.7±0.4 | 0.6±0.1 | 0.8±0.3 | 1.4±0.5 |
| $C_{max}/C_8$ | 502 | 43 | 586 | 274 | 121 |

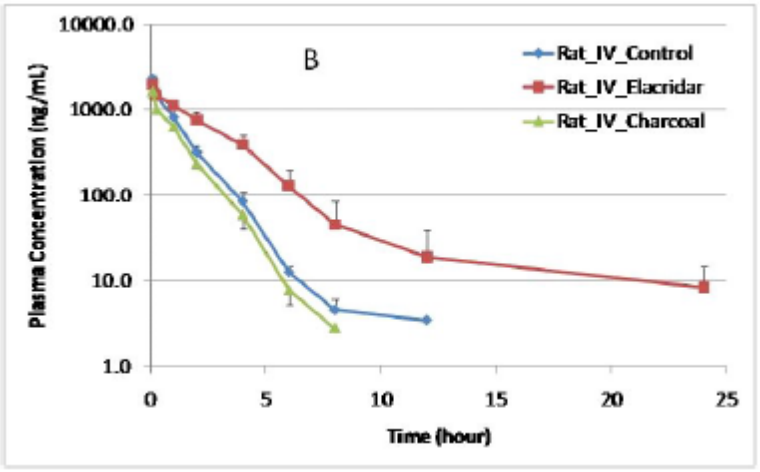
In WT BDC rats, drug-related total radioactivity was almost completely excreted into urine, bile, and faeces within 48 hours post-dose. It appears that urinary excretion is the major route of elimination for this compound in rats. Because the study was conducted in BDC rats, and the dose was administered IV, any radioactivity found in faeces is likely to be attributed to active secretion of the compound and its metabolites in the intestine. When the P-gp/BCRP inhibitor elacridar was administered along with $^{14}$C-apixaban, the excretion of apixaban was slightly increased in urine and bile, but decreased in faeces. The apixaban $AUC_{0-\infty}$ increased by 100% compared to control WT rats. When active charcoal was administered to WT BDC rats, it appears to have increased the radioactivity elimination, especially in faeces. Apixaban exposure (AUC) decreased slightly. This suggests that the charcoal is able to facilitate the excretion of radioactive material via the faecal route.

In P-gp KO BDC rats, drug-related radioactivity was almost *completely* excreted with a comparable excretion pattern as in WT BDC rats. The excretion pattern did not significantly alter in the presence of active charcoal. In BCRP KO BDC rats, drug-related radioactivity was also almost completely excreted within 48 hours, but the excretion pattern differed from that in WT BDC rats. The excretion via faeces in the BCRP KO BDC rat was elevated, which is opposite to what is expected. When activated charcoal

was administered along with $^{14}$C-apixaban, the excretion via faeces increased. The apixaban $AUC_{0-\infty}$ increased by 45 and 66%, respectively, in P-gp KO and BCRP KO rats compared to WT rats.

These data in rats clearly demonstrate that inhibition of intestinal efflux transporters decreases the systemic clearance of apixaban leading to the reduced intestinal excretion and active charcoal increased the systemic clearance leading to the increased intestinal excretion because of disrupted apixaban re-absorption.

**Apixaban plasma concentration-time profiles in BDC rats (n=3) following a 2 mg/kg IV dose of [$^{14}$C]apixaban with and without oral administration of activated charcoal and elacridar**




In BDC dogs (excretion pattern and pharmacokinetic results, see two following tables), ~46% of the dose was recovered in faeces, indicating the drug was directly excreted into the gut and eliminated via faeces. Upon treatment with active charcoal, the faecal recovery was increased to ~70% in BDC dogs. However, as total recovery was also greater in BDC dogs that received active charcoal compared to BDC dogs not receiving active charcoal, this may interfere with the results. In addition, apixaban AUC was reduced by ~19-39% and apparent systemic clearance of apixaban was increased by ~20-60%. The increased faecal elimination observed in BDC dogs treated with activated charcoal suggests that active charcoal prevents re-absorption of apixaban thereby resulting in increases of intestinal excretion through interruption of entero-hepatic recirculation.

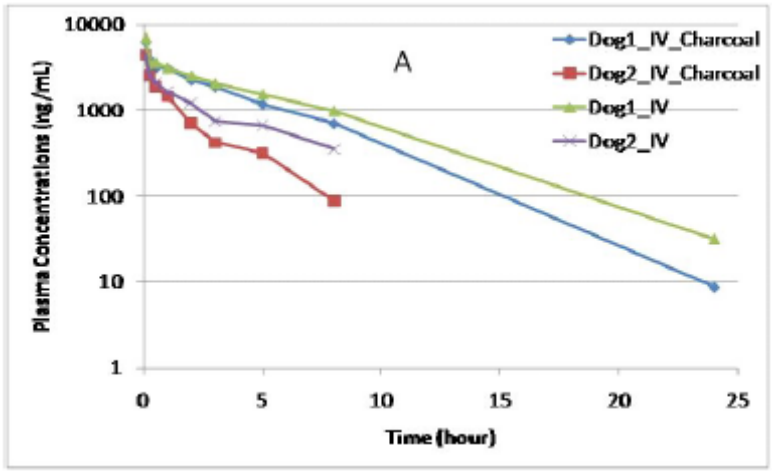
**Percent recovery of radioactivity following a single IV dose of [$^{14}$C]apixaban to male intact and bile duct-cannulated Beagle dogs**

| Compound and Dose Route | Animals | Urine | Bile | Feces | Total |
|---|---|---|---|---|---|
| | Dog | | 0-72 h collections | | |
| [$^{14}$C]Apixaban (IV) | BDC, n=2 | 13.5, 19.1 | 29.4, 12.4 | 42.7, 48.6 | 85.6, 80.1 |
| [$^{14}$C]Apixaban (IV) and Charcoal | BDC, n=2 | 16.3, 8.1 | 20.5, 13.1 | 62.7, 74.4 | 99.5, 95.6 |
| [$^{14}$C]Apixaban (IV) | Intact, n=3 | 9.9 ± 7.9 | NA | 50.8 ± 8.3 | 60.7 ± 10.6 |

**Table 2:** **Pharmacokinetic parameters of male bile duct-cannulated Beagle dogs following IV dose of [$^{14}$C]apixaban with and without oral administration of activated charcoal**

| | IV Dose to BDC dogs (n=2) (1 mg/kg) | |
|---|---|---|
| | Control | AC |
| $AUC_{0-\infty}$ (µg•h/mL) | 24.8, 9.30 | 20.1, 5.60 |
| $C_{max}$ (µg/mL) | 6.97, 4.43 | 6.23, 4.33 |
| $C_8$ (µg/mL) | 0.98, 0.35 | 0.68, 0.09 |
| $T_{1/2}$ (h) | 3.5, 2.9 | 3.2, 1.8 |
| CL (mL/h/kg) | 40, 110 | 50, 180 |
| Vs (L/kg) | 0.2, 0.4 | 0.2, 0.4 |
| MRT (h) | 4.7, 2.6 | 4.3, 1.9 |
| $C_{max}/C_8$ | 7, 13 | 9, 48 |

**Apixaban plasma concentration-time profiles in BDC dogs (n=2) following a 1 mg/kg IV dose of [$^{14}$C]apixaban with and without oral administration of activated charcoal and elacridar**




The contributions of P-gp and BCRP in governing apixaban disposition were also examined after oral doses in rats. Apixaban exposure (AUC) increased by 100% in the P-gp KO rats, and by 300% in the BCRP KO rats compared with WT rats, predominately through an increase in $C_{max}$. The concomitant administration of the P-gp/BCRP inhibitor elacridar increased apixaban exposures (AUC) by nearly 400% in WT rats. See table 3 below for the pharmacokinetic parameters.

**Table 3:** **Pharmacokinetic parameters of apixaban following a single oral dose of apixaban or IV dose of [$^{14}$C]apixaban to male bile duct-cannulated SD rats (WT = wild-type; P-gp-KO = P-gp-KO; BCRP-KO = BCRP-KO) with or without oral administration of activated charcoal**

| | Oral Dose to intact rats (4 mg/kg) (n = 3) | | | |
|---|---|---|---|---|
| | WT Control | P-gp-KO | BCRP-KO | WT GF-120918 |
| $AUC_{0-\infty}$ (µg·h/mL) | 1.39±0.36 | 3.34±0.37 | 5.71±1.45 | 6.57±1.87 |
| $C_{max}$ (µg/mL) | 0.42±0.08 | 0.94±0.11 | 1.92±0.77 | 2.87±0.80 |
| $C_{10}$ (ng/mL) | 27.8±6.4 | 60.9±28.4 | 64.1±11.3 | 30.6±16.3 |
| $T_{1/2}$ (h) | 3.3±1.7 | 3.8±0.4 | 2.5±0.6 | 1.6±0.3 |
| CL/F (L/h/kg) | 1.5±0.4 | 0.6±0.1 | 0.4±0.1 | 0.3±0.1 |
| Vs/F (L/kg) | 5.8±1.1 | 2.4±0.7 | 1.1±0.2 | 0.7±0.2 |
| MRT (h) | 3.8±0.3 | 3.8±1.0 | 2.9±0.2 | 2.1±0.2 |
| $C_{max}$/ C10 | 15 | 15 | 29 | 93 |

### Metabolite profile in excreta

The metabolite profile in excreta in WT, P-gp KO and BCRP KO rats after IV dosing is presented in the table shown below (study BMS-R1759). Unchanged apixaban was the most prominent drug-related component in urine and accounted for more than 91% of total urine radioactivity in all 3 groups of animals. In addition, a number of metabolites were observed in trace quantities. In contrast to urine, unchanged apixaban was found along with other significant drug-related components (metabolites) in bile of rats from all 3 groups. Several metabolites were observed to be present in high levels. However, it must be noted that the elimination of total radioactivity via biliary route for this compound was <15% of total dose for all 3 groups. Similar to urine, unchanged apixaban was the most predominant drug-related component present in faeces, while M475a, M475b and M445 were observed as minor metabolites in all groups of animals. The metabolites were not identified, however M475a and b were proposed to be formed by hydroxylation, M445 by desmethylation, M473 by hydroxylation-dehydrogenation, and M487 was believed to be dihydroxylated M445 or dioxo analogue of apixaban.

**Metabolite profile in the excreta of WT, P-gp KO and BCRP KO rats in % of dose**

| | Urine* | | | Bile | | | Faeces | | |
|---|---|---|---|---|---|---|---|---|---|
| | WT | P-gp KO | BCRP KO | WT | P-gp KO | BCRP KO | WT | P-gp KO | BCRP KO |
| apixaban | 49.1 | 45.7 | 35.4 | 2.2 | 4.9 | 2.3 | 17.8 | 20.3 | 30.4 |
| M487 | - | - | - | 3.3 | 3.3 | 4.9 | - | - | - |
| M475a | 0.6 | 0.6 | 0.9 | 0.3 | 0.5 | 0.5 | 1.8 | 2.1 | 1.8 |
| M445 | 0.5 | 0.8 | 0.8 | 2.9 | 2.5 | 2.2 | 4.0 | 2.6 | 1.8 |
| M475b | 0.7 | 1.2 | 1.2 | 0.9 | 1.7 | 1.5 | 0.4 | 0.6 | 0.8 |
| M473 | - | 0.5 | 0.5 | 0.6 | 0.8 | 0.6 | - | - | - |
| unknown | - | - | - | 0.6 | 0.4 | 0.9 | - | - | - |
| Total | 50.9 | 48.8 | 38.8 | 10.8 | 14.1 | 12.9 | 24.0 | 25.6 | 34.8 |

*Urinary data are including cage wash

In dogs, unchanged [$^{14}$C]apixaban accounted for >95, 83, 67, and 81% of total radioactivity in plasma, urine, bile and feces. In IV dosed rats, unchanged [$^{14}$C]apixaban accounted for 96.4, 93.7, 91.2% in urine, 20.7, 34.8, and 18% in bile, 74, 79.6, and 87.2% in feces of wild-type, P-gp-KO, and BCRP-KO rats, respectively. (study NCPK3).

### CHMP comments:

Besides renal excretion, apixaban is directly excreted into the intestine and eliminated via faeces in

both rat and dog. Also in humans, apixaban has multiple routes of elimination including metabolism, renal excretion, biliary excretion and direct secretion into the intestine. Transporters involved are P-gp and BCRP with BCRP playing a larger role than P-gp as indicated by decreased faecal elimination and higher systemic exposures when these transporters are inhibited. In conclusion, these data suggest that if apixaban is concomitantly administered with especially BCRP inhibitors, direct secretion into the intestine will be inhibited. Thus, this could lead to possible drug-drug interactions by diminishing one of the elimination routes. Active charcoal may increase faecal excretion and decrease systemic exposure to apixaban by interference in both initial absorption and in the entero-enteric recirculation although the effects are not very large.

***P-gp inhibition***

The potential of apixaban (BMS-562247) to inhibit P-glycoprotein (P-gp)-mediated digoxin efflux was evaluated in a Caco-2 inhibition assay (study 930050578). No inhibition of digoxin efflux was observed up to a maximum concentration of 62 µM apixaban.

At clinically relevant concentrations, apixaban is not an inhibitor of P-gp.

| | ***Formula*** | ***Value*** |
|---|---|---|
| *apixaban (10 mg BID)* | | |
| *Intestinal concentration* | *0.1 × dose/250 mL* | *8.7 µM (4 µg/mL)* |
| *Systemic concentration* | *50 × $C_{max,unbound}$* | *5.2 µM (2.4 µg/mL)* |

***Preclinical and clinical assessments of a major human circulating metabolite of apixaban, apixaban O-demethyl sulfate (M1)***

In Report 930043709 1.0 the major human circulating metabolite M1 is discussed. Following oral administration of a single 20 mg dose of [$^{14}$C]apixaban, the major circulating component in plasma was the parent compound in humans . A major circulating metabolite, O-demethyl apixaban sulfate (M1), represented approximately 25% of the estimated parent AUC (approximately 20% of total drug-related materials). The document summarises the available pharmacokinetic and toxicological information provided for this metabolite as provided in the initial MAA. Safety of the exposure to this metabolite at an apixaban dose of 2.5 mg/kg twice daily is discussed.

**CHMP comment:**

- Report 930043709 is dated 29 April 2010, i.e. it was written after the submission of the first MAA assessment, but before the authorisation of Eliquis in 2011. It does not add relevant new information to the assessment of the first MAA. In particular it does not discuss to which extent the exposure to M1 at the higher dose of 10 mg twice daily is covered by the already provided documentation.
- Since no new toxicological data has been provided with regard to M1 and because even at a dose of 2.5 mg twice daily exposure of the relevant non-clinical species was only marginally covered by the existing data package, it must be concluded that the available non-clinical studies don't cover the exposure to M1 at the increased dose recommended for the line extension.
- In the original MAA the following conclusions were drawn in the Day 150 JAR (Question 3):

"Exposure in the 52 week dog study may have been about 1 – 2 times human exposure (i.e. twice daily 2.5 mg, the recommended dose in the initial MAA). In the 2 year rat carcinogenicity study exposure was 0.36 µg.h/mL in males and 0.22 µg.h/mL in females vs 0.37 µg.h/mL in humans, so exposure in rats was ≤ humans (at a dose of twice daily 2.5 mg)." and:

"Overall it is concluded that O-desmethyl apixaban sulfate is not pharmacologically active and showed no significant activity in *in vitro* cardiovascular safety studies, but exposure at the highest dose levels in the repeated dose studies is not high enough to justify any margin of exposure for the toxicity studies. Since conjugates are usually not more toxic than the unconjugated compounds, and in addition to the toxicity studies with limited exposure there are some results from pharmacodynamic and safety pharmacology studies, no further toxicity data are requested."

- Since the recommended dose of 20 mg/day for the new indication of the current line extension is 4 times higher than the dose assessed in the initial MAA AR, exposure in the non-clinical studies does not cover the clinical exposure in patients (1.5 µg.h/mL at 10 mg twice daily vs 0.37 µg.h/mL at the lower dose of twice daily 2.5 mg). It is concluded that the non-clinical dossier provides very limited information regarding safety of exposure to this metabolite, due to much lower exposure in the toxicity studies as compared to patients. Nevertheless, considering the existing clinical experience with doses up to 20 mg/day, it is not deemed necessary to ask for new studies testing the toxicity of M1.

### 2.2.3. Toxicology

No new toxicity data were provided.

The nonclinical overview for the current line extension provides the following information regarding human exposure at the increased recommended dose:

At the recommended human dose (RHD) of 20 mg for the 1-week lead-in period, human exposure values for apixaban are 0.36 µg/mL for the highest observed plasma concentration (Cmax) and 5.5 µg.h/mL for the area under the plasma concentration-time curve (AUC). At the RHD of 10 mg for chronic treatment, human exposure values for apixaban are 0.21 µg/mL for Cmax and 3.1 µg.h/mL for AUC. For the major human circulating metabolite of apixaban (O-desmethyl apixaban sulfate), which has no meaningful FXa inhibitory activity, the Cmax values are 0.0449 µg/mL and 0.0718 µg/mL and the AUC values are 0.94 µg.h/mL and 1.5 µg.h/mL at the RHD of 10 and 20 mg, respectively, for VTE Tx. The source for these apixaban and O-desmethyl apixaban sulphate exposure values is clinical pharmacology study CV185046. Based on the short circulating half-life of apixaban in humans, plasma apixaban levels are expected to reach a new, lower steady state within a few days of switching from the lead-in dose of 20 mg to the long-term dose of 10 mg. Therefore, unless specified otherwise, apixaban or O-desmethyl apixaban sulphate exposure multiples (Cmax or AUC, as appropriate) are relative to the human values (ie, animal exposure value ÷ human exposure value) at the RHD of 10 mg for chronic VTE Tx. Margins relative to the lead-in RHD of 20 mg are only shown for potentially acute effects, such as hemorrhage.

The following exposure table was derived from a similar table in the Day 80 AR, however with the new human exposure included:

**Species comparison of AUC values and multiples compared to humans**

| Species | Study (sampling time) | Dose (mg/kg) | AUC (µg.h/ml) | | | | AUC multiples based on the human AUC at 10 mg BID (Bold multiples : NOAEL) | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | Apixaban | | O-Desmethyl Apixaban Sulfate | | Apixaban | | O-Desmethyl apixaban sulfate | |
| | | | M | F | M | F | M | F | M | F |
| Human (AUC0-24) | | 2.5 BID | 1.2 | | 0.25 (but 0.37 according to Day 120 response) | | | | | |
| | | 10 BID | 5.5 | | 1.5 | | | | | |
| Mouse | 105 wk (wk 26) | 150 | 2.8 | 5.2 | | | 0.5 | 0.9 | | |
| | | 500 | 5.1 | 10.4 | | | 0.9 | 1.9 | | |
| | | 1500(M)/ 3000 (F) | 7.3 | 16.4 | | | 1.3 | 3.0 | | |
| Rat | 6 month (Wk 26) | 50 | 16.6 | 26.4 | | | 3.0 | 4.8 | | |
| | | 200 | 21.6 | 27.2 | | | 3.9 | 4.9 | | |
| | | 600 | 35.5 | 34.4 | | | ***6.5*** | ***6.3*** | | |
| Rat | 104 wk (Wk 26) | 50 | 13.4 | 22 | 0.24 | | 2.4 | 4.0 | 0.16 | |
| | | 200 | 20.3 | 32.3 | 0.28 | 0.22 | 3.7 | 5.9 | 0.19 | 0.15 |
| | | 600 | 20.3 | 35.5 | 0.36 | 0.22 | 3.7 | 6.5 | 0.24 | 0.15 |
| Dog | 12 month (wk 52) | 10 | 71.8 | 40.8 | | | 13.0 | 7.4 | | |
| | | 30 | 92.2 | 96.5 | | | 16.8 | 17.5 | | |
| | | 100 | 99.4 | 137 | | | ***18.1*** | ***24.9*** | | |
| Rat fertility/early embryonic development | Day 15 | 50 | 12.8 | 23.5 | | | 2.3 | 4.3 | | |
| | | 200 | 24.4 | 22.8 | | | 4.4 | 4.1 | | |
| | | 600 | 27.6 | 36.3 | | | ***5.0*** | ***6.6*** | | |
| Pregnant mice | GD15 | 600 | | 10.1 | | | | 1.8 | | |
| | | 900 | | 14.9 | | | | 2.7 | | |
| | | 1500 | | 17.1 | | | | ***3.1*** | | |
| Pregnant rat | GD15 | 3000 | | 36.4 | | | | ***6.6*** | | |
| Lactating rat | Pre-and Post-natal study (LD4) | 25 | | 11.7 | | | | 2.1 | | |
| | | 200 | | 43.4 | | | | 7.9 | | |
| | | 1000 | | 47.5 | | | | ***8.6*** | | |
| Pregnant rabbit | GD19 | 1500 | | 0.036 | | | | 0.007 | | |

**CHMP comments**

At the higher dose of twice daily 10 mg, exposure margins based on the pivotal repeated dose toxicity studies are still of reasonable magnitude. However, it is noted that if the species difference in plasma protein binding at high plasma concentrations (1-10 µM = 0.46 – 4.6 µg/ml) is taken into account, these factors decrease with a factor 2-4, and sensitivity of the non-clinical species for the pharmacodynamics effect of apixaban may be lower: the *in vitro* affinity of apixaban for rat and dog factor Xa (Ki : rat 1.4 nM, dog 1.8 nM) is about a factor 20 lower compared to human factor Xa (Ki : 0.08nM). However, the protein binding in humans is lower at lower concentrations: Cmax at the 10 mg twice daily dose Cmax is 0.36 µg/ml. In human serum, *in vitro* protein binding was 87% at 0.46 µg/mL, while protein binding in serum taken from humans following apixaban administration (apixaban concentrations of 0.034 to 0.11 µg/mL) was ~93%.

In the initial AR the main toxicity was described as following :

"In the repeated dose studies, up to 6 months with a recovery phase in rats (doses up to 600 mg/kg/day, AUC up to apixaban up to 30 times human AUC at a dose of 2.5 mg BID) and to 1 year in dogs (doses up to 100 mg/kg/day, AUC up to > 80 times human AUC at a dose of 2.5 mg BID), apixaban showed no significant toxicity. The major observed effects were those on blood coagulation parameters: PT and aPTT and, sometimes, fibrinogen and/or bleeding time. In some studies, minor effects on blood cells and/or on serum K, Na and/or Cl and/or evidence of subclinical haemorrhage were observed."

Therefore, the toxicity can be fully explained by the pharmacodynamic action of apixaban. Considering the above information, it is concluded that at reasonable exposure no other safety risks were identified than those which are related to the intended pharmacological effect. Considering the possible species differences in sensitivity for the pharmacological effect, safety aspects related to this effect should preferably be assessed based on the clinical data. Further data regarding toxicity of apixaban are not deemed necessary.

## 2.2.4 Ecotoxicity / environmental risk assessment

A full ERA has already been presented and evaluated for Eliquis 2.5 mg tablets in the initial MAA procedure. At that time a complete dossier was submitted, meeting the requirements of the EMA guideline on ERA. The ERA concluded that no risk to the environment was anticipated following the use of Eliquis 2.5 mg tablets. The active ingredient apixaban is not PBT, nor vPvB. In a subsequent line extension procedure, the same, complete ERA dossier was submitted. Due to the added indication and increased dose, the environmental exposure was expected to increase. Now, the same ERA dossier was resubmitted for the current line extension application, again resulting in an additional indication and increase of dose. The applicant has submitted a revised ERA, which will be evaluated with respect to the PEC calculations and the result of the revised risk quotients.

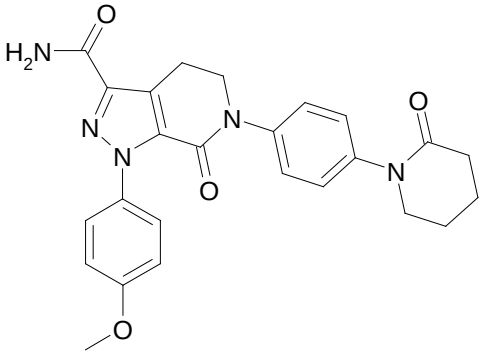
All endpoints resulting from the ERA can be found in the table with environmental endpoints, which is to be published in the EPAR upon finalisation of the authorisation process.

### *Identity of the active substance*

Identitiy of apixaban.

| | |
|---|---|
| Common name | apixaban |
| Synonyms | BMS-562247, DPC-AG0023 |
| Chemical name | 4,5,6,7-Tetrahydro-1-(4-methoxyphenyl)-7-oxo-6-[4-(2-oxo-1-piperidinyl)phenyl]-1H-pyrazolo[3,4,-c]pyridine-3-carboxamide |
| CAS nr. | 503612-47-3 |
| Empirical formula | C25H25N5O4 |
| Molecular weight | 459.5 g $mol^{-1}$ |

**Structural formula of apixaban.**



- **Phase I**

***Calculation of $PEC_{surface\ water}$***

The applicant has submitted an ERA based on the EMEA/CHMP/SWP/4447/00 guideline (EMEA, 2006) and the Questions and Answers document on ERA EMA/CHMP/SWP/44609/2010 (EMA, 2011).

$$PEC_{\text{SURFACE WATER}} = \frac{DOSEai \cdot F_{pen}}{WASTEW_{inhab} \cdot DILUTION}$$

| | | |
|---|---|---|
| *DOSE*ai = | 20 | (mg patient$^{-1}$ d$^{-1}$) |
| $F_{pen}$ = | 0.01 | (patient inh$^{-1}$) |
| *WASTEW*inhab = | 200 | (L inh$^{-1}$ d$^{-1}$) |
| *DILUTION* = | 10 | (–) |

***Refinement of $F_{pen}$***

The resulting $PEC_{surface\ water}$ using the default $F_{pen}$ is 0.10 µg L$^{-1}$. Applicant has performed a Phase IIA assessment, resulting in conservative prevalence figures (equal to or rounded up from highest estimate in six different EU countries) of 1.0% (rounded up from 0.44%) for prevention of VTE in patients undergoing hip or knee replacement surgery (indication 1, initial MAA), of 1.0% (highest estimated value) for prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation (indication 2, first line extension) and of 1.0% (rounded up from 0.37%) for treatment/prevention of VTE (indication 3, second = current line extension) and assuming administration to the entire population covered by the prevalence values.

The applicant presented data on metabolism in humans to establish a fraction of excreted, unchanged active of 0.57. The applicant does not further address the environmental risk of the remaining fraction (metabolites). Since metabolite testing is not a requirement, the remainder of the ERA will be performed without using data on metabolism, following a total residue approach.

The $PEC_{sw}$ values for the three indications, without correction for metabolism, are:

- Indication 1 (*DOSE*ai = 5): 2.5 10$^{-5}$ mg/L
- Indication 2 (*DOSE*ai = 10): 5.0 10$^{-5}$ mg/L

- Indication 3 (*DOSE*ai = 20): 1.0 $10^{-4}$ mg/L

The sum of these $PEC_{sw}$ values is 17.5 $10^{-5}$ mg/L = 0.175 µg/L.

## • Phase II, Tier A

The $PEC_{surface\ water}$ is 0.175 µg/L µg $L^{-1}$.

***Risk characterisation***

| Environmental compartment | PEC µg/L | PNEC µg/L | PEC/PNEC | Trigger value | Conclusion |
|---|---|---|---|---|---|
| STP | 0.175 | >100,000 | $1.8x10^{-6}$ | 0.1 | no risk |
| Surface water | 0.175 | 360 | $4.9\times10^{-4}$ | 1 | no risk |
| Groundwater | 0.044 | 960 | $4.6\times10^{-5}$ | 1 | no risk |

**CHMP comments**

$PEC_{surface\ water}$ exceeds the action limit, thus warranting a Phase IIA assessment, which was performed by the applicant. Based on the outcome of the Phase II A assessment it is concluded that no risks for the STP, surface water and groundwater are anticipated following the use of apixaban.

## • Phase II Tier B

The simulation study in water/sediment systems (OECD 308) triggered a risk assessment for the sediment compartment.

***PEC calculation for sediment and soil***

$PEC_{sediment}$ is calculated using equilibrium partitioning and REACH (EUSES) equations using characteristics for suspended matter (sediment). EUSES standard suspended matter contains 10% organic carbon. A $K_{oc}$ of 12.2 L $kg^{-1}$ is used.

Using $PEC_{surface\ water}$ = 0.175 µg $L^{-1}$, $PEC_{sediment}$ = 0.844 µg $kg_{dw}^{-1}$ (10% o.c.).

In the toxicity study with *C. riparius*, the NOEC could not be determined as no effects were observed at all concentrations tested. The result of the study is therefore presented as NOEC ≥ 100 mg $kg_{dw}^{-1}$. This slightly deviates from the first assessment (MAA) where the result was presented as NOEC = 100 mg $kg_{dw}^{-1}$.

Moreover, the test result was obtained in sediment with 2.4% organic carbon. Hence, the result is NOEC ≥ 417 mg $kg_{dw}^{-1}$ for sediment with 10% organic carbon. Normalisation to 10% organic carbon is performed since the $PEC_{sediment}$ calculated above is also valid for sediment with 10% organic carbon.

Applying an assessment factor of 100, the $PNEC_{sediment}$ is ≥ 4.17 mg $kg_{dw}^{-1}$. The PEC/PNEC ratio for sediment is thus 0.844/≥4170 =.≤ $2.0x10^{-4}$.

**CHMP comments**

The applicant performed the $PEC_{sediment}$ calculation correctly, but departed from a different $PEC_{surface\ water}$ and presented the wet weight $PEC_{sediment}$. Furthermore, the $PNEC_{sediment}$ of the applicant was not normalised to sediment with 10% organic carbon. Applying these corrections results in a risk quotient well below 1. In conclusion, no risk for the sediment compartment is anticipated.

The dossier is considered complete with respect to environmental fate and toxicity studies. No further test data are required.

- **Conclusion**

Apixaban (BMS-562247), CAS nr. 503612-47-3, is a selective, reversible inhibitor of the coagulation factor Xa (FXa). Its log $K_{ow}$ is 1.2 (shake flask), water solubility 38-60 mg/L at 25°C and its $K_{oc}$ 12.2 L/kg (HPLC method; log $K_{oc}$ = 1.09). Apixaban is not readily biodegradable. In a water/sediment simulation study (OECD 308), half life values of 31.5-41.7 d were found for the water phase and 100-182 d for the whole system, all determined at 20±2°C.

*Summary of toxicity data*

Inhibition of activated sludge respiration: EC50 > 1000 mg/L and hence NOEC > 1000 mg/L. Aquatic species: green alga *P. subcapitata*, 3 d NOEC 3.6 mg/L (growth rate); crustacean *D. magna*, 21 d NOEC 9.6 mg/L (reproduction); fish *P. Promelas*, 32 d NOEC ≥ 10 mg/L (E.L.S. test, hatching success, percentage of embryos producing live normal larvae at hatch, survival at test termination, and larval growth (total length and dry weight)). Sediment dwelling organism, midge *C. riparius*, 28 d NOEC 417 mg/kg$_{dw}$ (emergence and development rate; result normalised to 10% o.c.).

Using a conservative refined $F_{pen}$ of 0.01, combining for each indication, the different recommended doses for the three indications and without correction for treatment regime and metabolism,the sum of the PEC$_{surface\ water}$ values of the three indications was 0.175 µg/L.

No risk following the use of apixaban was anticipated for the sewage treatment plant, surface water, groundwater and sediment.

PBT assessment

Apixaban does not meet the screening criterion for B, since log $K_{ow}$ is < 4.5. Based on the OECD 308 study and the resulting whole system halflife values of 100-182 at 20°C, the P criterion is met. Based on the aquatic toxicity data submitted, the substance is not T. In conclusion, apixaban is not PBT, nor vPvB.

The updated data submitted in this application do not lead to a significant increase in environmental exposure further to the use of apixaban. Apixaban is not expected to pose a risk to the environment.

In conclusion, an update of the section 6.6 of the SmPC is introduced : “Any unused medicinal product or waste material should be disposed of in accordance with local requirements.”

### ***EPAR summary table***

| | | | |
|---|---|---|---|
| **Substance (INN/Invented Name):** apixaban | | | |
| **CAS-number (if available):** 503612-47-3 | | | |
| ***PBT screening*** | | Result | **Conclusion** |
| *Bioaccumulation potential*- log $K_{ow}$ | OECD107 | 1.2 | not B |
| ***PBT-assessment*** | | | |
| **Parameter** | **Result relevant for conclusion** | | **Conclusion** |
| Bioaccumulation | log $K_{ow}$ | 1.2 | not B |
| | BCF | not triggered | |
| Persistence | ready biodegradability | not readily biodegradable | |
| | DT50$_{water}$ | 31.5-41.7 d at 20°C | |
| | DT50$_{whole\ system}$ | 100-182 d at 20°C | P |
| Toxicity | NOEC or CMR | > 1 mg/L, not CMR | not T |
| **PBT-statement :** | apixaban is not considered not PBT nor vPvB | | |
| ***Phase I*** | | | |
| ***Calculation*** | **Value** | **Unit** | **Conclusion** |

| | | | | | |
|---|---|---|---|---|---|
| $PEC_{surface\ water}$ (refined $F_{pen}$) | 0.175 | µg/L | | | > 0.01 threshold |
| Other concerns (e.g. chemical class) | | | | | N |
| ***Phase II Physical-chemical properties and fate*** | | | | | |
| **Study type** | **Test protocol** | **Results** | | | **Remarks** |
| Adsorption-Desorption | OECD 121 | $K_{oc}$ = 12.2 L/kg | | | |
| Ready Biodegradability Test | OECD 301 | not readily biodegradable | | | |
| Aerobic and Anaerobic Transformation in Aquatic Sediment systems | OECD 308 | $DT_{50,\ water}$ = 31.5-41.7 d<br>$DT_{50,\ whole\ system}$ = 100-182 d<br>% shifting to sediment =40.2-52.0 | | | determined at 20±2°C |
| ***Phase IIa Effect studies*** | | | | | |
| **Study type** | **Test protocol** | **Endpoint** | **value** | **Unit** | **Remarks** |
| Algae, Growth Inhibition Test/ *Pseudokirchneriella subcapitata* | OECD 201 | NOEC | $3.6 \times 10^3$ | µg/L | |
| *Daphnia* sp. Reproduction Test | OECD 211 | NOEC | $9.6 \times 10^3$ | µg/L | |
| Fish, Early Life Stage Toxicity Test/ *Pimephales promelas* | OECD 210 | NOEC | $\geq 10 \times 10^3$ | µg/L | |
| Activated Sludge, Respiration Inhibition Test | OECD 209 | NOEC<br>EC50 | $>1.0 \times 10^6$<br>$>1.0 \times 10^6$ | µg/L | |
| ***Phase IIb Studies*** | | | | | |
| Sediment dwelling organism / *C. riparius* | OECD 218 | NOEC | ≥ 100 | $mg/kg_{dw}$ | organic carbon content of sediment 2.4% |

## 2.2.5 Discussion on non-clinical aspects

The company provided updated non-clinical overview, and updated written and tabulated pharmacology, pharmacokinetics and toxicology summaries.

A correction of a pharmacodynamics study was provided. This had no implications for previously drawn conclusions.

There are no new toxicological data and no further data are deemed necessary, although it is noted that exposure margins of the major metabolite (M1) are very low.

New pharmacokinetic studies were provided. These studies provided evidence of entero-hepatic and entero-enteric recirculation in dogs and rats, likely due to biliary excretion and active intestinal excretion/uptake processes mediated by P-gp and BCRP transporters.

Studies with active charcoal in rats and dogs showed that this treatment reduces systemic exposure to a limited degree, presumably by preventing intestinal reabsorption. Although it is not certain how the observed limited effects on systemic exposure should be extrapolated to patients, the advice that the administration of activated charcoal may be useful in the management of apixaban overdose or accidental ingestion (based on clinical studies in healthy subjects) was previously included in section 4.9 of the SmPC".

Therefore, no further information regarding extrapolation to clinical practice is deemed necessary.

A study regarding the effect of hemodialysis on systemic exposure in dogs was also provided. The results showed a limited decrease of systemic exposure. Based on the results, it is concluded that dose adjustment might be needed for patients under dialysis due to removal of apixaban by hemodialysis. However, according to section 4.2 of the SmPC, apixaban is not recommended in patients undergoing dialysis, because there is no clinical experience.

### 2.2.6 Conclusion on the non-clinical aspects

Additional data in dogs were provided on reduction of systemic exposure by haemodialysis, showing only a very limited effect of haemodialysis. Additional data in dogs and rats show that active charcoal treatment may lower systemic exposure to a limited degree.

Furthermore data were provided regarding the role of Pgp and BCRP transporters in intestinal secretion c.q. reabsorption. From the initially provided dossier (MAA) it was already known that these transporters play a role in these processes and that enterohepatic and enteroenteric recirculation occur. In addition, a study was provided on inhibition by apixaban of Pgp. No inhibition was found up to a high concentration. This confirms the conclusion already drawn on the basis of the initial MAA that apixaban is not an inhibitor of Pgp.

No additional non-clinical data are requested.

## *2.3. Clinical aspects*

### 2.3.1. Introduction

GCP

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

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

- Tabular overview of clinical studies

The clinical pharmacology profile of apixaban has been characterized based on the results of 35 clinical pharmacology studies as well as population pharmacokinetic (PPK) and exploratory exposure response (E-R) analyses in the VTE treatment patient population that incorporated data from Phase 1, 2, and 3 studies. Details can be found in Module 2.7.2 Summary of Clinical Pharmacology Studies.

The apixaban clinical pharmacology program was designed to evaluate the PK, PD, and initial safety and tolerability profile over a broad dose range and included subjects with characteristics representative of the intended apixaban patient populations.

### 2.3.2 Pharmacokinetics

In this application, the company has submitted five new Pharmacokinetic studies and a population PK study.

- **Study B0661019** this study investigated the food effect on the commercial tablets (1 x 5 mg tablet, which is the highest available strength).This study was conducted on request of the Health Authorities.
- **Study CV185073** drug-drug interaction study with apixaban and prasugrel.
- **Study CV185071 (PF-04652577)** A Randomized, Open-Label, Single Dose, Four Way Cross-Over Bioavailability Study comparing Three Modified Release Formulations of Apixaban Tablets to Apixaban Immediate Release Tablets in Healthy Volunteers
- **Study CV185091** Study of Apixaban Oral Solution Bioavailability When Administered Through a Nasogastric Tube in Healthy Subjects

- **Study CV185111** Bioavailability of Apixaban Oral Solution Administered Through a Nasogastric Tube in the Presence of Boost Plus® and Apixaban Administered as Crushed Tablet Through a Nasogastric Tube Relative to Apixaban Oral Solution in Healthy Subjects
- **Population PK study PMAR-00312**

A more detailed description of study B0661019 and CV185073 and the population PK study PMAR-00312 are given below. The studies CV185071, CV185091 and CV185111 are not further discussed in this report as the formulations that were investigated are not relevant for this application.

#### *2.3.1.1. Study B0661019*

| | |
|---|---|
| Study title | An Open Label, Randomized, 2-Period Crossover Study Evaluating Single Dose Food Effect on Apixaban Commercial Image Tablets in Healthy Subjects |
| Study number | Protocol B0661019 |
| Clinical study period | September 2011 and 17 October 2011 |
| Date Study Report | 01 December 2011 |

The food effect study was an open label, randomized, 2-sequence, 2-period, crossover study evaluating food effect on single dose of the 5 mg apixaban commercial tablet in 22 healthy adult male and female subjects. The effect of a standard high-fat, high-calorie meal was evaluated.

The PK parameters $AUC_{inf}$, $AUC_{last}$, $C_{max}$, $T_{max}$ and $t_{half}$ were summarized descriptively by treatment, and the log transformed $AUC_{inf}$, $AUC_{last}$, $C_{max}$ of apixaban with and without food were statistically compared.

The PK results of the study are summarized in table PK01.

**Table PK01Statistical Summary of Treatment Comparisons**

| Parameter (units) | Adjusted Geometric Mean | | Ratio (Test/Reference) of Adjusted Means[a] | 90% CI for Ratio |
|---|---|---|---|---|
| | Fed (N=22) | Fasted (N=22) | | |
| $AUC_{inf}$ (ng·h/mL) | 982.3[b] | 1229 | 79.93% | (75.19%, 84.97%) |
| $AUC_{last}$ (ng·h/mL) | 948.2[b] | 1200 | 79.03% | (74.12%, 84.25%) |
| $C_{max}$ (ng/mL) | 103.2 | 121.3 | 85.13% | (79.32%, 91.35%) |

Subject 10011017 in Period 2 (Fed period), PK data for $AUC_{inf}$ and $AUC_{last}$ have been excluded from this analysis.
Abbreviations: CI=confidence interval, Test: Fed, Reference: Fasted
a. The ratios (and 90% CIs) are expressed as percentages.
b. N=21

Based on this study the MAH concludes that the observed decrease in apixaban exposure in the fed condition (approximately a 20% decrease in AUC and 15% decrease in $C_{max}$) compared to the fasted condition is not considered clinically significant and therefore no dose adjustment is recommended.

#### *2.3.1.2. Study CV185073*

| | |
|---|---|
| Study title | RANDOMIZED, OPEN-LABEL APIXABAN AND PRASUGREL DRUG INTERACTION STUDY IN HEALTHY SUBJECTS |

| | |
|---|---|
| Study number | CV185073 |
| Clinical study period | September 2011 and 17 October 2011 |
| Date Study Report | 21 May 2010 - 21 Sep 2010 |

This drug-interaction study was a randomized, open-label, 3-period, 3-treatment, crossover, multiple-dose study in healthy subjects which was designed to assess the effect of prasugrel on the PK of apixaban when coadministered and the effect of apixaban on the PK of the active prasugrel metabolite, R-138727 when coadministered. Furthermore the interaction was evaluated with relation to the pharmacodynamics of prasugel (ADP-induced platelet aggregation) and apixaban (anti-FXa) and the safety of the three treatments was also monitored.

The following treatments were administered:

- Treatment A: 5 mg Apixaban orally, twice daily (BID) on Days 1-4
- Treatment B: 60 mg Prasugrel orally on Day 1 followed by 10 mg Prasugrel orally, once daily (QD) on Days 2-4
- Treatment C: 5 mg Apixaban orally, BID on Days 1-4 and 60 mg Prasugrel orally on Day 1 followed by 10 mg Prasugrel orally, QD on Days 2-4

A total of 36 subjects had evaluable PK data. The PK parameters $AUC_{TAU}$, $C_{max}$, $T_{max}$ and $t_{half}$ of apixaban and the active prasugrel metabolite R-138727were summarized descriptively and the different treatments were statistically compared with regard to the $C_{max}$ and AUC The main PK results of this study are presented in table PK02 and PK03 and the main pharmacodynamic results in figure PK01 and PK02

Apixaban exposure was equivalent when administered alone and when coadministered with prasugrel; the 90% CIs for apixaban $C_{max}$ and $AUC_{TAU}$ geometric least squares (LS) mean ratios were wholly contained within the predefined no effect interval of 0.8 - 1.25.

**Table PK 02 Statistical summary of primary pharmacokinetic parameters of Apixaban**

**Summary Statistics of Apixaban**

| | Geometric LS Means | | Geometric LS Mean Ratio | 90% CI | |
|---|---|---|---|---|---|
| Parameter | Treatment A | Treatment C | (Trt C/Trt A) | Lower | Upper |
| Cmax (ng/mL) | 179.67 | 187.84 | 1.045 | 0.975 | 1.122 |
| AUC(TAU) (ng*h/mL) | 1226.57 | 1276.89 | 1.041 | 0.979 | 1.107 |

Treatment A: 5 mg Apixaban orally, twice daily (BID) on Days 1-4

Treatment C: 5 mg Apixaban orally, BID on Days 1-4 and 60 mg Prasugrel orally on Day 1 followed by 10 mg Prasugrel orally, once daily (QD) on Days 2-4

LS = Least Squares; Trt = Treatment; CI = Confidence Interval

The total exposure to the active prasugrel metabolite R-138727 was not affected but a small decrease of the maximum concentration was observed. According to the applicant the difference in R-138727 $C_{max}$ values between the treatments is not likely to be of clinical significance based on the lack of PD interactions.

**Table PK03 Statistical summary of primary pharmacokinetic parameters of R-138727**

**Summary Statistics of R-138727**

| Parameter | Geometric LS Means | | Geometric LS Mean Ratio (Trt C/Trt B) | 90% CI | |
|---|---|---|---|---|---|
| | Treatment B | Treatment C | | Lower | Upper |
| Cmax (ng/mL) | 239.79 | 212.11 | 0.885 | 0.789 | 0.991 |
| AUC(TAU) (ng*h/mL) | 246.11 | 240.65 | 0.978 | 0.940 | 1.017 |

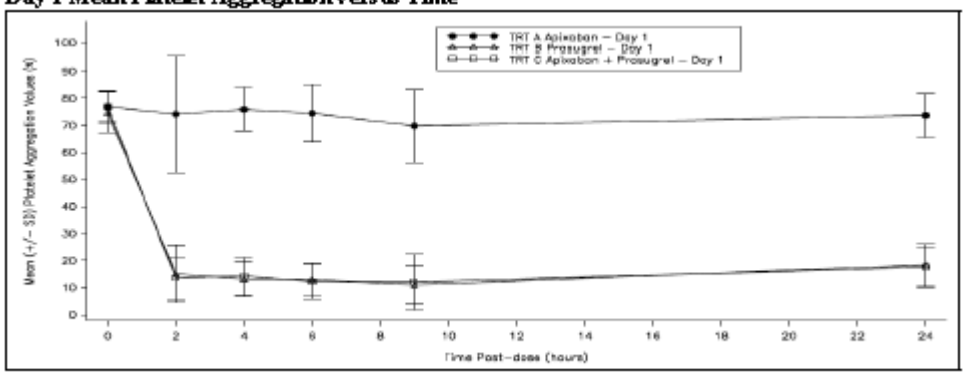
Treatment B: 60 mg Prasugrel orally on Day 1 followed by 10 mg Prasugrel orally once daily (QD) on Days 2-4
Treatment C: 5 mg Apixaban orally, twice daily (BID) on Days 1-4 and 60 mg Prasugrel orally on Day 1 followed by 10 mg Prasugrel orally QD on Days 2-4
LS = Least Squares; Trt = Treatment; CI = Confidence Interval

The MAH concluded that apixaban had a negligible effect on ADP-induced platelet aggregation. There was an apparent decrease in ADP-induced platelet aggregation at the 9-hour time point following apixaban administration (Treatment A) on Day 4 only; however, platelet aggregation returned to baseline by the 24-hour time point. The reason for this decrease at 9 h is unknown.

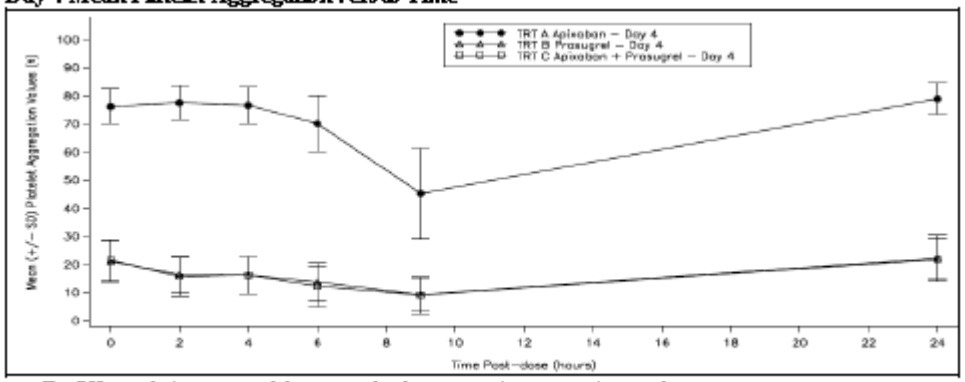
Prasugrel alone resulted in a decrease in ADP-induced platelet aggregation on Day 1 that was maintained through Day 4, consistent with prasugrel's mechanism of action; the presence of apixaban did not influence this effect.

**Figure PK01 ADP-induced platelet aggregation**

**Day 1 Mean Platelet Aggregation versus Time[a]**



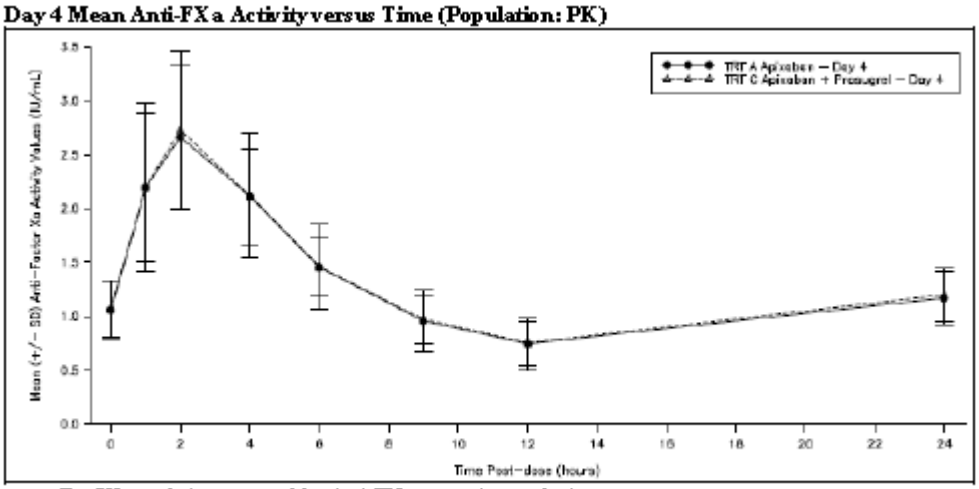

**Day 4 Mean Platelet Aggregation versus Time[a]**




a The PK population was used for mean platelet aggregation versus time analyses.
TRT = Treatment

According to the MAH the mean anti-FXa activity versus time profile on Day 4, when apixaban was administered alone, was similar to that of apixaban administered with prasugrel, as shown in the figure below. In addition, when apixaban was administered alone, the resulting apixaban plasma concentrations had a linear relationship with the corresponding anti-FXa values. This relationship did not seem to change when apixaban was coadministered with prasugrel. All subjects receiving prasugrel alone (Treatment B) had anti-FXa activity values under the detectable limit (<0.1 IU/mL).

**Figure PK02 anti-FXa Activity**




a The PK population was used for Anti-FXa versus time analysis.
TRT = Treatment

### *2.3.1.3. Population Pharmacokinetic Analysis PMAR-00312*

| | | |
|---|---|---|
| Study title | Population Pharmacokinetic and Exploratory Exposure-Response Analyses of Apixaban for the Treatment of Deep Vein Thrombosis (DVT) and Pulmonary Embolism (PE) and for the Prevention of Recurrent DVT and PE. | |
| Study report | 16 August 2013 | |
| Studies included in population study | CV185002A | CV185059 |
| | CV185013 | CV185074 |
| | CV185018 | CV185017 |
| | CV185022 | CV185056 (B0661001) |
| | CV185046 | CV185057 (B0661002) |
| | CV185058 | |

Objectives

The objectives of these pharmacometric analyses are:

1. To describe the pharmacokinetics of apixaban in venous thromboembolism (VTE) treatment subjects using a population pharmacokinetic (PPK) approach.
2. To estimate the impact of physiological and demographic factors that may affect apixaban pharmacokinetics in VTE treatment subjects. This investigation primarily focused on estimating covariate effects including sex, age, renal function, race, body weight, time of administration (diurnal variation), concomitant medication, and patient status, if any, on interindividual differences in the pharmacokinetics of apixaban.
3. To characterize the relationship between apixaban plasma concentration and anti-Xa activity (AXA) in VTE treatment subjects.

4. To explore the relationship between apixaban exposure and safety and efficacy endpoints in VTE treatment subjects. The safety endpoint was an adjudicated composite of major bleeding (MB) or clinically relevant non-major bleeding (CRNMB) and the efficacy endpoint was an adjudicated composite of symptomatic VTE (non-fatal DVT or non-fatal PE) or VTE-related death.

Study Design and methodology

Data from 11 clinical studies (8 Phase 1, one Phase 2, and two Phase 3 studies) were included in the analyses. The study design, study population, and timing of blood samples varied among the 11 clinical studies. The PPK final analysis included 8323 PK observations from 970 subjects. The PK-AXA analysis was based on data from five Phase 1 studies as well as the Phase 2 and two Phase 3 VTE treatment clinical trials. The final AXA analysis included 3139 AXA observations from 795 subjects. The MAH provided an adequate description of the demographics of the studied population. The exploratory safety and efficacy analyses were based on the composite bleeding endpoint (MB or CRNMB) and efficacy event data (VTE or VTE-related death) from the Phase 2 and Phase 3 VTE treatment clinical trials.

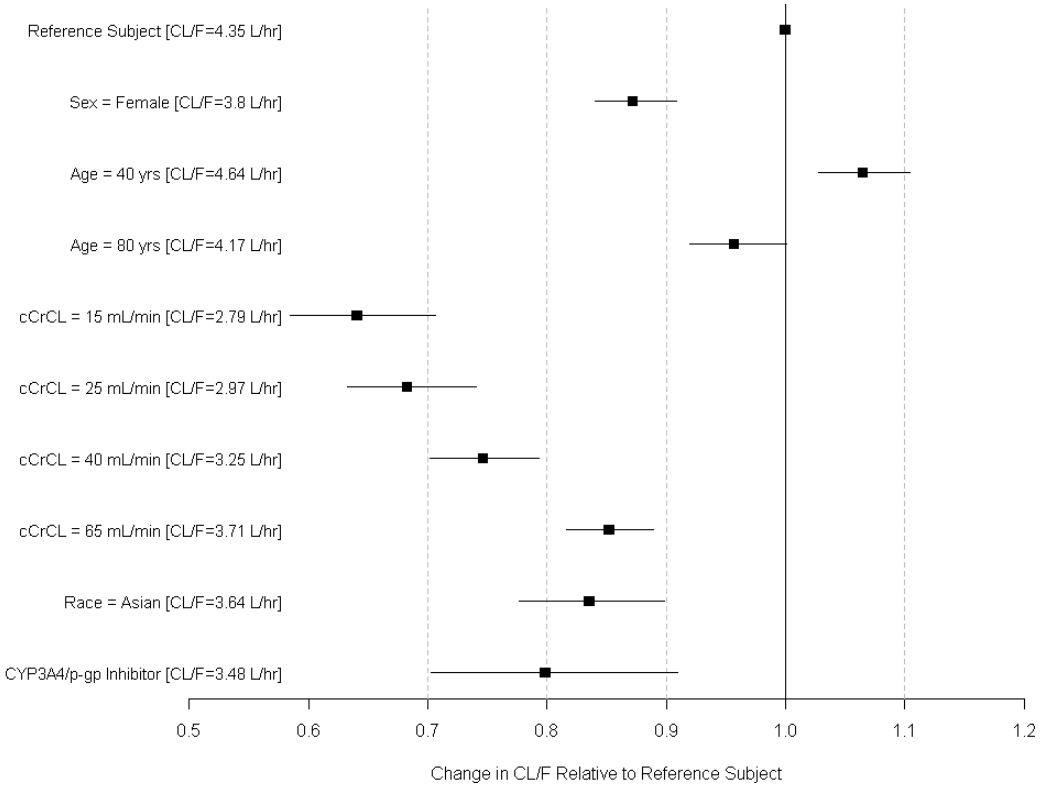
The popution model used was based on PPK models developed previously in VTEp and AF populations, a two-compartment pharmacokinetic model was applied to fit the observed data in terms of the following parameters: apparent oral clearance (CL/F; L/hr), apparent inter-compartmental clearance (Q/F; L/hr), apparent volume of distribution (central = Vc/F and peripheral = Vp/F; L), and first-order absorption rate constant (ka; hr-1). The covariates that were evaluated were: Dosing time (diurnal variation), Age, Sex , Body weight , Asian race , Patient status and Concomitant medication (strong or moderate inhibitors of CYP3A4/P-gp).

Results

Apixaban pharmacokinetics were adequately described with a 2-compartment model with first-order absorption and first-order elimination. Covariate effects on CL/F are illustrated in Figure PK03 as a ratio of the typical model predicted CL/F relative to that for the reference VTE treatment subject. The 90% confidence interval of a ratio was generated by 1000 non-parametric bootstrapping sets of population parameter values using the final PPK model.

The covariates that were determined to be predictive of apixaban apparent CL/F included renal function, age, sex, Asian race, and concomitant administration of strong or moderate CYP3A4/p-gp inhibitors as a combined concomitant medication category.

**Figure PK03 Illustration of Covariate Effects on CL/F**

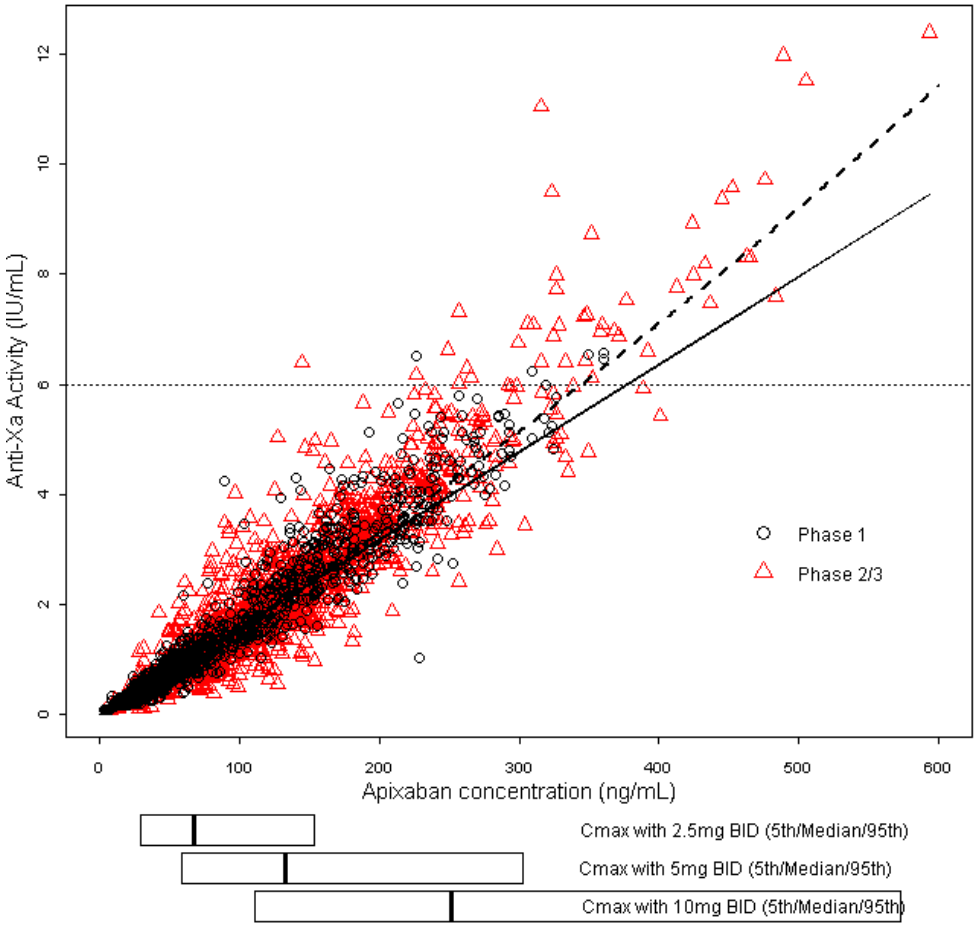



*Solid squares represent the ratio of the typical predicted CL/F relative to the reference subject. The black line represents the 90% confidence interval of the ratio. The reference subject in the VTE treatment population is defined as a male patient who is non-Asian, 60 years of age, and has a body weight of 85 kg and cCrCL = 100 mL/min, and did not receive a concomitant strong or moderate CYP3A4/p-gp inhibitor.*

The MAH concludes that the predicted change in apixaban exposure was generally of a similar magnitude as that observed in the dedicated Phase 1 studies. Given the limited impact on apixaban exposure, no dose adjustment for apixaban is required based on these factors alone, however, caution is warranted when multiple factors that could affect apixaban exposure are present. The impact of strong inhibitors of both CYP3A4 and P-gp could not be adequately evaluated in this PPK analysis, given limited concomitant use in the Phase 2 and 3 studies. The results of the covariate analysis therefore largely reflect the effect of moderate CYP3A4/P-gp inhibitors.

The MAH has evaluated the relationship between apixaban exposure and Anti-Xa activity a linear model and a quadratic model. Although previous evaluations showed consistently that a linear model adequately describes the relationship between apixaban concentration and AXA in the therapeutic dose range after administration of 2.5 and 5mg BID. However for the VTE treatment indication there seems to be a trend for a more than dose proportional increase at higher apixaban concentrations as is illustrated by the better fit of the quadratic model (figure PK04). For the VTE treatment indication in the first days a higher dose is administered (10mg BID) and this results in higher concentrations of Apixaban.

**Figure PK04. Apixaban Plasma Concentration vs AXA in LMWH Units in VTE Treatment (all data)**




*The solid line is the linear regression line [0.0159*CP] while the dotted line is the quadratic regression line [0.0152*CP+0.064*(CP/100)2], where CP is an apixaban concentration (ng/mL) The boxes below represent a 90% prediction interval for predicted maximum concentrations for apixaban 2.5, 5, and 10 mg BID at steady-state, with the vertical line representing a median value, based on the VTE treatment final population PK model.*

The event rate relationships for the composite bleeding endpoint (MB or CRNMB), as well as for the efficacy endpoint (VTE or VTE-related death), were explored, but could not be characterized due to the small number of events.

Previous Population PK studies

In the original marketing authorisation application another population PK study was conducted. There is no overlap between the patients that were included the population PK study PMAR-00312 and this study . This new population study included the PK data of 4 phase II and III trials (Study CV185010,CV185047, 185035 and 185027), all patients included were treated for the prevention of VTE.

Based on the initial population PK analyses it is concluded that the results of the clinical pharmacokinetic trials can be translated to the target population as the population PK data were consistent with findings from the clinical pharmacology studies. Of the covariates included in the final

model (age, gender, body weight, surgery, hematocrit, and renal function) only severe renal impairment and the combination of female gender, age > 75 years, creatinine clearance (CLcr) < 30 mL/min, and weight < 50 kg were predicted to increase apixaban exposure by approximately 58% and 64%, respectively. The predicted effect of most other covariates on apixaban exposure was < 25%.

## 2.3.3. Pharmacodynamics

No new pharmacodynamic data are submitted in relation to the requested indication.

## 2.3.4. Discussion and Conclusions on clinical pharmacology

**Pharmacokinetics**

Food Effect

In the original marketing authorization application of apixaban, one food effect study was conducted (study CV185008). In this study, the food effect of a single dose of 10 mg apixaban (2x5 mg Phase 2 tablets) was investigated in 22 healthy subjects comparing the PK of apixaban administered in fasted state or following a high-fat meal. When apixaban was administered shortly after a high-fat meal, apixaban geometric mean ratio (fed/fasted) for Cmax, AUCinf and AUC0-T were 110%, 104% and 105%. Based on this study it was concluded that a high-fat, high-caloric meal does not affect the PK of apixaban. As a result of this outcome, subsequent Phase 2 and 3 studies allowed administration of apixaban without regards to meal intake.

In the new food effect study B0661019, a slightly greater food effect was found (15-20% decrease in exposure), but this slightly greater effect is again not considered clinically relevant by the CHMP. Therefore, it is agreed that no adaptation of the SmPC section 5.2 nor 4.2 is needed based on this study.

Interaction with prasugrel

No clinically relevant interaction between prasugrel and apixaban was found in Study CV185073. Therefore, the proposed SmPC section 4.5 changes with regard to concomitant use of prasugrel can be accepted.

Population PK study

The results of the population PK study are in line with with the results of the clinical pharmacology trials. The company compared the results of the three population studies in the different patient populations and it can be concluded that the population PK data are consistent between the studies.

Upon request form CHMP, the company provided a more detailed description of the demographics of the population that was included in the population PK study. The findings of the population PK study are in line with the previously reported data from the clinical pharmacology trials according to which the exposure to apixaban is increased in patients with renal dysfunction. Based on the available data it can be concluded that the exposure to apixaban is expected to be 40- 60% higher in patients with severe renal dysfunction, although the number of subjects with severe renal impairment was low. The updated information with regards to renal impairment is discussed later in this report.

The covariate evaluation in the current VTE treatment PPK analyses is consistent with the Phase 1 observations. A decrease of the apixaban clearance was mainly observed in subjects with a decreased renal function, although the number of subjects was low. This observation is line with the results of the phase I study CV185018 that was submitted as a part of the original application dossier. Study

CV185018 evaluated the apixaban PK in patients with renal impairment. Subjects with mild(N=10), moderate(N=7), and severe (N=7) renal disfunction had 16%, 29% and 38% higher AUCs (INF), respectively, compared to subjects with normal renal function. Based on all available data it can be concluded that the exposure to apixaban is expected to be 40- 60% higher in patients with severe renal dysfunction. The impact of the disease status was sufficiently studied in the PK analysis performed for each indication. Due the fact that the VTEtx patients were relatively young and healthy the PK of apixaban for these patients was comparable to the results of the healthy volunteers , no difference was observed with regards to CLT/F compared to healthy subjects.

The company evaluated apixaban exposure and Anti-Xa activity (Figure PK04) and based on the presented data can be concluded that quadratic model seems to predict the relationship between exposure and the Anti-Xa activity better, especially for higher concentrations apixaban. The MAH was therefore asked to further adapt the table in which the predicted Apixaban Steady State Exposure and AXA in VTE Treatment Population is presented in section 5.1 of the SmPC.

Because the apixaban PK is similar between the previously investigated populations and patients that are treated for DVT and PE it is agreed that there is no need to adapt section 5.2 of the SmPC (Pharmacokinetic properties).

Interaction with inhibitors and inducers of CYP3A4 and Pgp

The company has not submitted any new data with regard to the concomitant use of inhibitors and inducers of CYP3A4 and Pgp. For all indications the concomitant use of systemic treatment with strong inhibitors of both CYP3A4 and P-gp is not recommended.The potential for decreased efficacy in the presence of concomitant strong inducers of both CYP3A4 and P-gp is likely to have greater clinical significance in the treatment of VTE population than for the VTEp and NVAF indications.

Therefore it is acceptable that the SmPC text with regards to this interaction is different between indications. In conclusion a warning is introduced in section 4.4 and corresponding information in section 4.5 to mention that in case of concomittant treatment with CYP 3A4 and Pgp strong inducers, apixaban should not be used since efficacy may be compromised for the treatment of DVT or PE (see section 2.4 Clinical efficacy).

Interaction with grapefruit juice

No dose recommendations or additional recommendations are required for the concomitant consumption of grapefruit juice. Grapefruit juice (when consumed in usual dietary volumes) should be considered as a moderate inhibitor of CYP3A4 and for other moderate inhibitor of CYP3A4 no clinically relevant interaction with apixaban has been found. Therefore no interaction with grapefruit juice is expected to occur.

## *2.4. Clinical efficacy*

### 2.4.1. Dose ranging study

At the time of initiation of dose-response study CV185017, there were no completed Phase 2 studies with apixaban. The available preclinical and clinical pharmacokinetic data for apixaban supported the selected dose range of apixaban (5 mg BID, 10 mg BID and 20 mg QD) for treating subjects presenting with acute symptomatic DVT, as described in the study protocol.

***Study Design***

Study CV185017 was a Phase 2, multicenter, randomized, parallel-group study to assess the efficacy and safety of **5 mg BID** apixaban (130 subjects randomized), **10 mg BID** apixaban (134 subjects randomized), and **20 mg QD** apixaban (128 subjects randomized) versus LMWH or fondaparinux plus VKA (128 subjects randomized) in treating subjects with acute symptomatic DVT. The apixaban treatments were double-blind; the LMWH or fondaparinux plus VKA was open-label. There was a 12 week treatment period and a 30 day follow-up period.

The primary efficacy endpoint was the composite of adjudicated symptomatic recurrent VTE or deterioration of the thrombotic burden as assessed by repeat compression ultrasound (CUS) and perfusion lung scan (PLS). CUS of the legs and PLS were to be performed within 36 hours of randomization and at 12 weeks. The ICAC reviewed and adjudicated all suspected thromboembolic events, deaths, baseline and repeat CUS and PLS, and all episodes of suspected bleeding.

The primary safety endpoint was the composite of adjudicated MB/CRNMB. Safety was assessed via the review of all reported adverse events (AEs), serious adverse events (SAEs) and laboratory test results.

***Study Results***

There were no differences in baseline disease characteristics between the apixaban treatment groups and the LMWH/VKA comparator group that were considered to have an impact on the overall outcome of the study. The incidence of previous VTE was similar between the apixaban and comparator groups (approximately 25%).

**Primary Endpoint Events** were infrequent across all treatment groups (4.7% for all apixaban groups combined; 4.2% comparator). The differences in event rates between the apixaban and the LMWH/VKA treatment groups were not statistically significant (95% CIs for the difference included zero). The lowest incidence (2.6%) of recurrent VTE/deterioration across all treatment groups was in the apixaban 20 mg QD group (Table E1).

**Table E1. Result of the primary endpoint (Recurrent VTE / deterioration) in Study CV185017**

| | **Apixaban** | | | | |
|---|---|---|---|---|---|
| | **5 mg BID N=117** | **10 mg BID N=125** | **20 mg QD N=116** | **All N=358** | **LMWH/ VKA N=118** |
| Total events | 7 | 7 | 3 | 17 | 5 |
| Event rate [95% CI] | 6.0% [2.4, 11.9] | 5.6% [2.3, 11.2] | 2.6% (0.5, 7.4] | 4.7% [2.8, 7.5] | 4.2% [1.4, 9.6] |
| Event rate difference [95% CI] | 1.7% [-4.4, 8.2] | 1.4% [-4.6, 7.5] | -1.7% [-7.3, 3.6] | -- | -- |

**Bleeding rates** based on all adjudicated bleeds during the treatment period were lower in each of the apixaban treatment groups than in the comparator group. Incidences of bleeding-related AEs were also lower in all apixaban groups compared to the LMWH/VKA group (Table E2).

**Table E2. Summary of Adjudicated Bleeding Endpoints During the Treatment Period - Treated Subjects, Study CV185017**

| | Apixaban 5 mg BID N = 128 | Apixaban 10 mg BID N = 133 | Apixaban 20 mg QD N = 124 | Any Apixaban N = 385 | LMWH/VKA N = 126 |
|---|---|---|---|---|---|
| Major Bleeding, n | 1 | 0 | 1 | 2 | 0 |
| Event rate[1] | 0.0078 | 0.0000 | 0.0081 | 0.0052 | 0.0000 |
| CRNM bleeding, n | 10 | 6 | 8 | 24 | 10 |
| Event rate[1] | 0.0781 | 0.0451 | 0.0645 | 0.0623 | 0.0794 |
| Trivial bleeding, n | 7 | 11 | 4 | 22 | 10 |
| Event rate[1] | 0.0547 | 0.0827 | 0.0323 | 0.0571 | 0.0794 |

CRNM = clinically relevant non-major bleeding, BID = twice daily

***Recommended Apixaban Doses for the Treatment and Prevention of Recurrent VTE***

The recommended dose of Eliquis for the treatment of acute DVT and PE is 10 mg twice daily for the first 7 days followed by 5 mg twice daily.

The recommended dose of Eliquis for the prevention of recurrent DVT and PE, following completion of at least 6 months of treatment for DVT or PE, is 2.5 mg twice daily.

***Discussion on the dose selection***

The exact doses for the phase 3 studies were not tested in this trial. In study CV185017, the efficacy of the 20 mg once daily dose regimen was numerically superior to the regimens 5 mg BID and 10 mg BID. Bleeding rates (assessed as combination of MB and CRNMB or as trivial bleedings) were better in all apixaban groups when compared to LMWH/VKA, but 20 mg QD appeared to be associated with most bleedings among the apixaban groups. A once-daily dosing regimen would be preferable from a convenience standpoint. However, it appears that bleedings are less frequent with the dose divided in two halves over the day. This is also the approved dose regimen in other indications.

Based on comparison to approved treatment regimens with other products (e.g. LMWH) and the approved regimen for apixaban in atrial fibrillation indication, the Applicant chose a BID regimen with a higher dose during the first week of treatment for further development when risk for thromboembolism is at its highest. This reasoning is supported and considered acceptable by the CHMP. This dose of 10 mg BID is the highest investigated in the apixaban clinical program and has not been approved for any other indication yet.

The proposed dose for treatment of VTE including prevention of recurrence is 5 mg BID for 6 months after the index event; if after that period continued prophylaxis is required, a lower dose of 2.5 mg BID was shown equally effective as discussed below. Thus, it might be questioned if the dose could have been reduced earlier than 6 months from 5 mg BID to 2.5 mg BID. However, based on the small difference in safety profile between both dosages and the large effort it would require to investigate this in a clinical trial, the currently proposed posology is considered acceptable by the CHMP. The SmPC section 4.2 has been amended accordingly.

For extended VTE prophylaxis, the dose is again primarily based on extrapolation of data from other products and other indications. It was decided to test both doses to phase 3 development program, which both proved effective with (small) differences, mainly in safety, as shown later.

Considering that dose adaptations are required in certain patient groups in the SPAF indication, e.g. patients with exclusive criteria of severe renal impairment, or patients with ≥2 risk factors, e.g. age ≥

80 years, body weight ≤ 60 kg, or serum creatinine ≥ 1.5 mg/dl (133 micromole/l), applying no dose adjustments for these same groups in the current program required additional discussion with the CHMP. This was particularly important for the first 7 days of treatment when a dose of 10 mg BID is administered. To address this issue, the applicant explained the differences between management of SPAF and VTEt necessitating different dose recommendations. A dose of 10 mg BID is used in the first week of VTEt to ensure maximal efficacy for dissolving the clot and prevention of extension. In this population, available exposure data in patients with severe renal impairment (n=29) in relation to efficacy and safety are not helpful due to the small number of bleeding events (MB = 1) but shows a higher risk of major bleeding of 1.18 (95% CI 0.13, 10.98) for apixaban vs. enoxaparin/warfarin. To improve interpretation of the results, the MAH submitted pooled data of moderate and severe renal impairment patients. For the whole treatment period, efficacy and safety results are in line with those of patients with mild renal impairment, in which no dose adaptations are recommended. Specific results for the first 9 days to address safety of the highest dose include very limited events precluding any robust conclusions. However, a higher bleeding tendency can not be excluded. Still, it was agreed with the applicant that the B/R of non-investigated dose reductions is not known and accordingly cannot be advised. Comparable results were presented for patients with a combination of risk factors (age, weight or renal impairment) who constituted around 100 patients in AMPLIFY. The presented data do not indicate any increased risk compared to the general cohort. In conclusion, available data are reassuring but can not robustly exclude a bleeding risk due to the limited patients numbers. Theoretical dose adaptations can not be advised either. The agreed SmPC wording clearly reflects the limitation of the clinical trial data and the associated risks above described.

## 2.4.2. Main study(ies)

### *2.4.2.1. Background information*

Efficacy and safety for the proposed indication have been demonstrated in 2 completed pivotal Phase 3 studies (CV185056, AMPLIFY and CV185057, AMPLIFY EXT) and the aforementioned completed supportive Phase 2 study (CV185017).

CV185056 (AMPLIFY) was a randomized, active controlled, parallel-group, double-blind, triple-dummy study in subjects with acute symptomatic proximal DVT or acute symptomatic PE. Randomization was stratified by the type of disease (symptomatic proximal DVT only or symptomatic PE with or without DVT) at baseline. If a subject had both symptomatic proximal DVT and symptomatic PE, the subject was stratified to the symptomatic PE group. Subjects were randomized (1:1 ratio) using a central interactive voice response system (IVRS) and received study treatments for 6 months. Subjects in Group 1 received enoxaparin injections, warfarin tablets, and placebo apixaban tablets. Subjects in Group 2 received placebo enoxaparin injections, placebo warfarin tablets, and apixaban tablets. Total participation in the study for each subject was approximately 7 months (6 months on study treatment followed by a 30-day observation period). Subjects who met eligibility criteria assessed at screening and/or baseline were randomized and dispensed study drug on Day 1. Subjects were requested to return to the study site at Weeks 2, 4, 8, 12, 16, 20, and 24 for study specific activities.

CV185057 (Amplify-Ext) was a randomized, parallel-group, double-blind, placebo-controlled study in subjects with symptomatic proximal DVT or symptomatic PE. Randomization was stratified by the type of disease treated (symptomatic proximal DVT only or symptomatic PE with or without DVT) and by the type of previous treatment (enoxaparin/warfarin in Study CV185056 [AMPLIFY], or standard anti-coagulant therapy outside of Study CV185056 [AMPLIFY]). If a subject had both symptomatic DVT and symptomatic PE, the subject was stratified to the symptomatic PE group. After completing approximately 6 to 12 months of anticoagulant therapy for the treatment of the index event, eligible

subjects were randomized at a 1:1:1 ratio to receive 1 of 3 oral treatments twice daily (BID): apixaban 2.5 mg, apixaban 5 mg, or placebo. Total participation in the study for each subject was approximately 13 months (12 months on study treatment followed by a 30-day observation period). Subjects who met eligibility criteria assessed at screening and/or baseline were randomized and dispensed study drug on Day 1. Subjects were requested to return to the study site at Week 2 and at Months 3, 6, 9, and 12. Other visits at Months 1, 2, 4, 5, 7, 8, 10, and 11 were conducted either in person or by telephone contact.

An on-going randomized, active-controlled (UFH/warfarin), parallel group, open-label study (B0661024, CV185160) in Japanese subjects (N=80) with acute symptomatic proximal DVT or PE being conducted in Japan is scheduled to be completed by June 2014. Study treatment and duration are similar to those in the CV185056 study. No efficacy data and minimal safety data from this study have contributed to the current application.

## CV185056 (AMPLIFY) and CV185057 (Amplify-Ext)

## Methods

### *Study participants*

The in- and exclusion criteria for the population studied are appropriate to include patients that are representative of the population requiring at least 6 months of treatment for VTE. The low-risk patients with a provoked VTE without additional risk factors (eligible for less than 6 months therapy) were excluded from CV185056. According to current guidelines and practice, these patients would be treated for 3 months. Special conditions like subjects with a caval filter or subjects requiring thrombolysis/thrombectomy were also excluded. These high-risk patients are excluded in the SmPC.

In order to provide data about efficacy in subjects presenting with either a DVT or a PE, the CV185056 study pre-specified that approximately one third of the enrolled patients should have a PE and two thirds a DVT, a ratio that is consistent with the prevalence reported in the real world treatment population and therefore represents an appropriate DVT/PE population for analysis.

### *Treatments*

In study CV185056, the comparator treatment was parenteral enoxaparin (1 mg/kg SC Q12h until INR ≥ 2) and oral warfarin (target INR 2.0-3.0). Several different LMWHs are available and guidelines do not distinguish among the various LMWHs provided they are used at their recommended doses.

### *Objectives*

The primary objective of **CV185056** was to determine if apixaban was non-inferior to standard enoxaparin/ warfarin therapy in the combined endpoint of adjudicated recurrent symptomatic venous thromboembolism (VTE) (nonfatal deep vein thrombosis [DVT] or nonfatal pulmonary embolism [PE]) or VTE-related death over 6 months of therapy.

The primary objective of **CV185057** was to determine if at least 1 of the apixaban dose regimens was superior to placebo in the combined endpoint of symptomatic, recurrent VTE (nonfatal DVT or nonfatal PE or all-cause death in subjects who had an objectively documented index event of symptomatic proximal DVT or symptomatic PE, had completed approximately 6 to 12 months of anticoagulant therapy for the treatment of the index event, and had no objectively documented symptomatic recurrence of VTE after the index event.

***Outcomes/endpoints***

The primary outcomes of Studies CV185056 and CV185057 were “VTE/VTE-related death” and “VTE/All-cause death” respectively. These are consistent with the Note for Guidance on Clinical Investigation of Medicinal Products for the Treatment of Venous Thromboembolic Disease (CPMP/EWP/563/98) and the protocols and statistical analysis plans were prospectively aligned with feedback from regulatory agencies. The outcomes were independently adjudicated using obvious definitions. Most endpoints are defined as composites; the components that are used may be subsets of components that are used in other endpoints. In this way, a large number of views is taken to a relatively small number of events. Although the components are clinically relevant, the additional value of all these composites is modest.

Images were systematically adjudicated centrally. The protocols allowed short-term anticoagulant use before randomisation, thus creating some time for this process to occur; however this comes at the price of confounding the treatment effect by pre-randomisation anti-coagulants. The applicant has provided subgroup analyses to address this issue, see below.

***Sample size***

The sample size for **CV185056** was computed for a non-inferiority margin of 1.8 as agreed with the FDA. Using the method of Farrington Manning with the assumption 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 would have 90% power for a 1-sided $\alpha$=0.025 non-inferiority test assuming true RR of 1. Although the assumptions in the sample size calculation were reasonable, it was still deemed necessary after blinded review to use the predefined provision to increase the sample size during the study based on a blinded interim analysis. The actual event rates were lower than assumed (apixaban: 0.0226; comparator: 0.0269; assumed: 0.03) making this change understandable.

***Randomisation***

The randomisation procedures were acceptable. An IVRS was used to manage randomisation, dispensing of trial medication and to provide sham INR values for apixaban-treated subjects in a blinded manner. There was a small number of dispensing errors (37 errors out of 54,720 kits assigned by IVRS; 0.07%).

***Blinding (masking)***

In study CV185056, the dosing of warfarin was individualized according to each patient's response as indicated by the international normalized ratio (INR), with the goal being to achieve and maintain an INR of 2.0 to 3.0. Apixaban has little effect on INR, and so measuring and reporting INR values openly could lead to unblinding of the study. Therefore, a shamming procedure was used to provide INR measurements while effectively concealing treatment assignment. A portable point-of-care INR measuring device was used, similar to that used in the CV185030 (ARISTOTLE) study. The IVRS was used to provide sham INR values for apixaban-treated subjects in a blinded manner. This INR sham procedure is currently the standard for double blind trials with a VKA comparator.

***Statistical methods***

In general the statistical approach was acceptable. A few highlights are shown below.

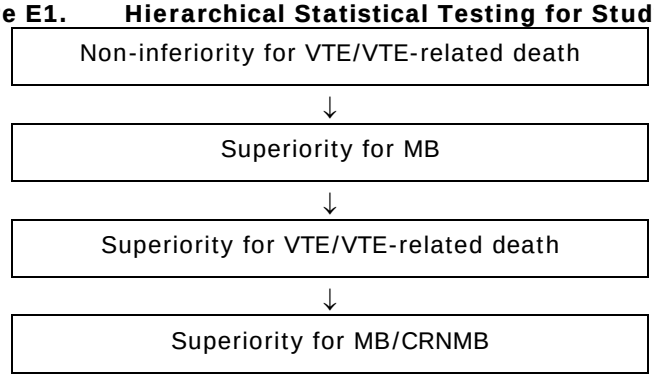
Non-inferiority margin

The non-inferiority margin for study CV185056 was 1.8 for relative risk (RR) and 0.035 for risk difference (RD). Both criteria (RR and RD) were required for a successful study. In the scientific advice, CHMP had agreed to a non-inferiority margin of 2.0; the company chose the stricter 1.8 margin based on FDA feedback.

**Study CV185056: Hierarchical statistical testing**

The hierarchical testing procedure shown in Figure 1 was used to control for family-wise type I error in study CV185056.

**Figure E1. Hierarchical Statistical Testing for Study CV185056**




VTE=venous thromboembolism, MB=major bleeding, CRNMB=clinical relevant non-major bleeding

**Study CV185057: Hochberg procedure**

The primary objective of study CV185057 was to determine if at least 1 of the apixaban doses was superior to placebo. The Hochberg procedure was used to maintain the 2-sided type I error at $\alpha = 0.05$. Superiority over placebo was claimed for a dose if the Hochberg adjusted p-value was $\leq 0.05$ and the RR was < 1. The Hochberg procedure was used to adjust for multiplicity between the two doses of apixaban in study CV185057.

**Missing data**

In line with the Guideline on Missing Data in Confirmatory Clinical Trials (EMA/CPMP/EWP/1776/99 Rev. 1), the Sponsor's primary approach to missing data was to minimize missing data. Subjects discontinuing treatment were encouraged to complete any remaining study visits and were contacted by telephone to determine their primary efficacy and safety results if they did not withdraw consent. In addition, investigators were educated on the importance of minimizing missing observations. Sensitivity analyses specified in the statistical analysis plans for studies CV185056 and CV185057 demonstrated that missing data did not impact the efficacy conclusions.

For study **CV185057**, imputation of missing endpoint data was pre-specified for the primary efficacy analysis. In line with the above guidelines (Guideline on Missing Data in Confirmatory Clinical Trials (EMA/CPMP/EWP/1776/99 Rev. 1), sensitivity analyses are typically performed to handle missing data rather than being the primary analysis. The Applicant agreed with the US FDA in January 2008 that for the primary analysis in study CV185057, subjects with missing efficacy endpoints were to be assessed as having had the event. In this study, subjects were considered to have had a missing endpoint if 1) they did not have an event during the intended treatment period and 2) it could not be substantiated

that the endpoint did not occur during the intended treatment period (for example, if the subject withdrew consent or was lost to follow-up).

Although the primary analysis in CV185057 has considered subjects with missing endpoint data as having had the event, the Applicant proposes to present non-imputed data in section 5.1 of the SmPC. The company has argued that the primary analysis (with imputations) is less relevant and of less interest to the prescriber, and that the secondary analysis (without imputations) generates data in a reliable manner.

Analysis of the primary efficacy endpoint of VTE/VTE-related death in study CV185056 was performed for the per protocol population also as pre-specified in the SAP and justified based on the non-inferiority hypothesis. This analysis included subjects in the primary efficacy dataset minus those with any of the conditions pre-specified in the analysis plan.

## Results of study CV185056 (Amplify)

### *Participant flow*

Approximately 86% of apixaban-treated subjects completed 6 months of study treatment compared to 84.7% of subjects receiving enoxaparin/warfarin (Table E3). The proportions of subjects discontinuing study treatment during the 6-month treatment period that relate to DVT, PE, or other VTE are balanced between the 2 treatment groups. Discontinuations due to deaths, adverse events and other reasons are discussed under safety. Most subjects entered the 30-day follow-up period. Reasons for not completing the follow-up period are detailed in Table E3.

**Table E3. Subject Disposition in Study CV185056**

| | Apixaban | Enoxaparin / Warfarin | Total |
|---|---|---|---|
| **Main part: Number (%) of Subjects** | | | |
| Randomized | 2691 | 2704 | 5395 |
| Treated | 2676 (99.4) | 2689 (99.4) | 5365 (99.4) |
| Completed 6 months of treatment | 2314 (86.0) | 2291 (84.7) | 4605 (85.4) |
| Discontinued for any reason | 377 (14.0) | 413 (15.3) | 790 (14.6) |
| **Efficacy event / outcome-associated reason for discontinuation from treatment (randomized subjects)** | | | |
| Death | 20 (0.7) | 26 (1.0) | 46 (0.9) |
| DVT | 15 (0.6) | 17 (0.6) | 32 (0.6) |
| PE | 9 (0.3) | 11 (0.4) | 20 (0.4) |
| VTE other than DVT/PE | 2 (<0.1) | 3 (0.1) | 5 (<0.1) |
| **Follow up: Number (%) of Subjects** | | | |
| Entered follow-up period | 2617 | 2639 | 5256 |
| Completed follow-up period | 2547 (97.3) | 2560 (97.0) | 5107 (97.2) |
| **Reasons for not completing the follow-up period** | | | |
| Death | 24/2617 (0.9) | 33/2639 (1.3) | 57/5256 (1.1) |
| Withdrawn consent | 23/2617 (0.9) | 28/2639 (1.1) | 51/5256 (1.0) |
| Lost to follow-up | 15/2617 (0.6) | 15/2639 (0.6) | 30/5256 (0.6) |
| Other | 1/2617 (<0.1) | 0 | 1/5256 (<0.1) |

Source: Study CV185056 CSR Table 14.1.1.2.2, 14.1.1.2.4.
VTE=venous thromboembolism, DVT=deep vein thrombosis, PE=pulmonary embolism, CSR=clinical study report

***Recruitment***

The study was conducted between 27 August 2008 to 12 March 2013 at 358 centres world-wide. The trial took 4.5 years to completion. The average number of subjects per centre was 5395 / 358 = 15, or about one subject randomised in 3 months, which is low compared to the incidence of VTE.

***Conduct of the study***

Internal quality assurance audits were conducted at 24% of the sites in study CV185056 and 12% of the sites in study CV185057. Both study-specific vendors and company preferred providers were subjected to audits. Any suspected misconduct in any study was thoroughly investigated. For 1 case, at a site in India, data were excluded from efficacy and safety analyses because source data could not be verified (5 subjects in CV185056; 4 subjects in CV185057). No primary efficacy or safety outcomes were reported at this site for either study, and exclusions of these subjects would not affect the efficacy or safety conclusions of the studies.

***Baseline data***

Baseline parameters were balanced among treatment groups. Most participants were white (83%). There was adequate representation of patients from the EU (2118 = 39%). Older patients (>75 years) were sufficiently represented (n=774, 14.3%).

***Numbers analysed***

Subjects in this study (n=5395) had an objectively confirmed acute symptomatic proximal DVT (66.6%) or acute symptomatic PE (33.4%).

A total of 16.1% of subjects in the apixaban group and 17.3% in the enoxaparin/warfarin group were excluded from the per protocol population, which was as expected (15% pre-specified in study protocol). Overall, the reasons for subjects being excluded from the per protocol population were similar in both treatment groups. There were no notable differences between the index event strata. The most frequent reason was treatment discontinuation (without an event having occurred, see later under Ancillary Analysis).

The primary analysis imputes subjects with missing primary endpoint data as having an event. This is a conservative approach, as discussed above. Therefore all other populations are used for supportive analyses only.

***Outcomes and estimation***

**Primary endpoint**

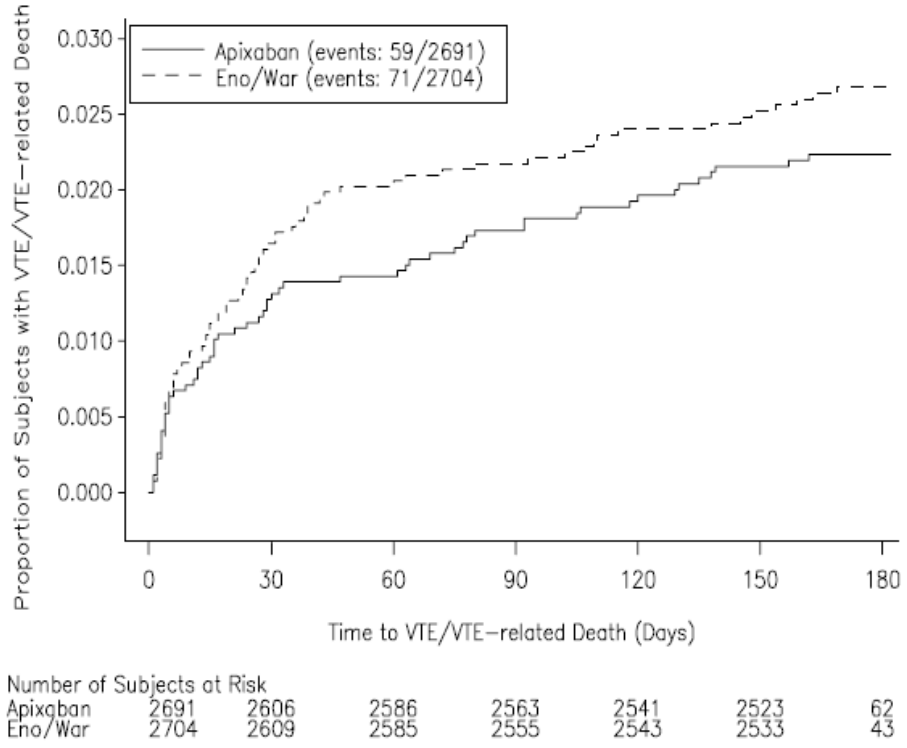
In study CV185056, apixaban given at 10 mg BID for 7 days followed by 5 mg BID for 6 months demonstrated non-inferiority to the standard of care enoxaparin/warfarin (apixaban event rate of 2.26%, enoxaparin/warfarin event rate of 2.69%; p-value (p)<0.0001) for the primary efficacy endpoint of VTE/VTE-related death (Table E4). The relative risk of VTE/VTE-related death for the apixaban-treated subjects was 0.84 compared to subjects treated with enoxaparin/warfarin, with an absolute risk difference of -0.44%. These results are corroborated by the corresponding Kaplan-Meier plot that shows overlapping lines for the initial 2 weeks of treatment followed by a clear numerical separation favouring apixaban that endures throughout the remainder of the treatment period (Figure E2).

According to the hierarchical testing sequence, superiority with respect to MB was then tested, and the results demonstrated a statistically significant reduction in MB compared to enoxaparin/warfarin (p< 0.0001). Subsequent testing for VTE/VTE-related death did not demonstrate superiority over enoxaparin/warfarin; no further hypothesis testing was performed per the hierarchical testing plan.

**Table E4. Results for the Primary Efficacy Endpoint of VTE/VTE-Related Death in Study CV185056 - Primary Efficacy Population**

| | Apixaban | Enoxaparin/ Warfarin |
|---|---|---|
| VTE/VTE-related death (n/N) | 59/2609 | 71/2635 |
| Event rate | 0.0226 | 0.0269 |
| [95% CI] | [0.0169, 0.0283] | [0.0208, 0.0331] |
| Relative risk | 0.8390 | -- |
| [95% CI] | [0.5965, 1.1802] | -- |
| p-value for non-inferiority | <0.0001 | -- |
| p-value for superiority | 0.3128 | -- |
| Risk difference | -0.0044 | -- |
| [95% CI] | [-0.0128, 0.0040] | -- |
| p-value for non-inferiority | <0.0001 | -- |
| p-value for superiority | 0.3090 | -- |

**Figure E2. Kaplan-Meier Plot for VTE/VTE-Related Death in Study CV185056 - Randomized Subjects**




The relative risk of VTE/VTE-related death for the apixaban-treated subjects was 0.84 compared to subjects treated with enoxaparin/warfarin, with an absolute risk difference of -0.44%. The clear separation of the KM curve starts around Day 7. After Day 40 the absolute risk difference seems to remain constant.

**Efficacy at 3 months**

The risk of recurrent VTE is approximately 50% lower among patients whose VTE was provoked by a transient risk factor compared with patients who have an unprovoked VTE. This lower risk of recurrence has resulted in a recommendation by current treatment guidelines (ACCP, NICE, ESC) to discontinue anticoagulation after 3 months of treatment for patients who have a VTE provoked by a transient risk factor and do not have an ongoing risk factor for recurrence.

Subjects with a provoked VTE, but without a risk factor for recurrence, may have required only 3 months of anticoagulant therapy and were not enrolled.

It is therefore of interest to assess the efficacy of apixaban at 3 months of treatment in the CV185056 study. Table E5 summarizes the results of a post-hoc analysis, which demonstrate the efficacy of apixaban compared with enoxaparin/warfarin (nominal p-value < 0.0001 for inferiority) during the initial 90 days, which show comparable results to the main cohort.

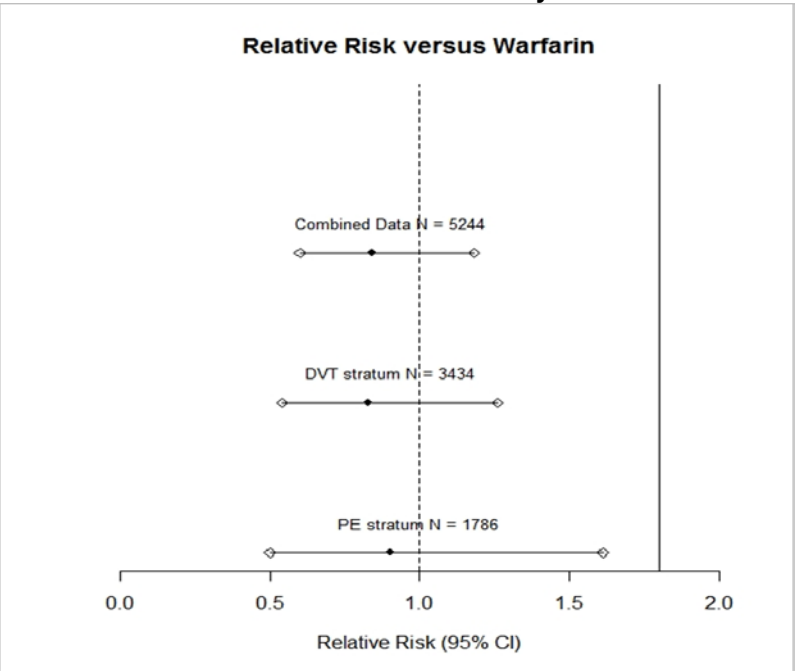
**Table E5. Summary of Adjudicated VTE/VTE-Related Death During the Initial 90 Days of Treatment in Study CV185056 - Primary Efficacy Population**

| | **Apixaban N=2609** | **Enoxaparin/Warfarin N=2635** |
|---|---|---|
| VTE/VTE-related death (n) | 46 | 58 |
| Event rate [95% CI] | 0.0176 [0.0126, 0.0227] | 0.0220 [0.0164, 0.0276] |
| Relative risk [95% CI] | 0.8010 [0.5458, 1.1756] | -- |
| p-value for non-inferiority[a] | <0.0001 | -- |
| Risk difference [95% CI] | -0.0043 [-0.0118, 0.0032] | -- |
| p-value for non-inferiority[a] | <0.0001 | -- |

**Efficacy in the DVT and PE strata for VTE treatment**

The analysis by index event shows no relevant differences between the **PE and DVT strata** of the trial. This result confirms that apixaban is equally effective in the management of DVT as well as PE.

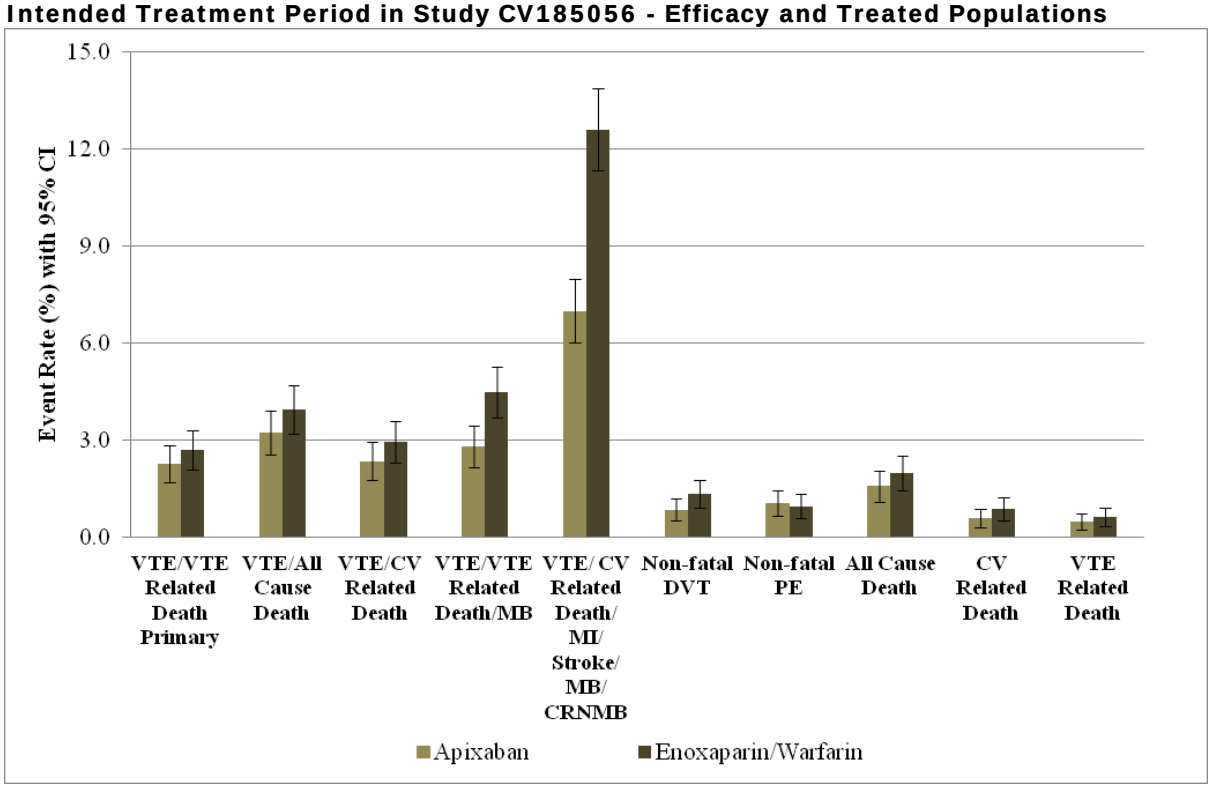
**Figure E3. Relative Risk for Apixaban versus Enoxaparin / Warfarin of VTE / VTE-Related Death for the DVT and PE Strata in Study CV185056**




**Secondary endpoints**

The **secondary endpoints** are mainly driven by (or components of) the same VTE and mortality events that have driven the primary endpoint. These analyses confirm the consistency of the results and provide reassurance that classifying the events by diagnosis or severity during adjudication has not driven the outcomes in an unexpected way (Figure E4). Results for the composite endpoints of VTE/VTE-related death/MB and VTE/CV-related death/MI/stroke/MB/CRNMB were statistically significantly lower in the apixaban group, indicating a favourable benefit/risk profile compared to enoxaparin/warfarin.

**Figure E4. Summary of Adjudicated Efficacy Endpoints that Occurred During the Intended Treatment Period in Study CV185056 - Efficacy and Treated Populations**




## Ancillary analyses

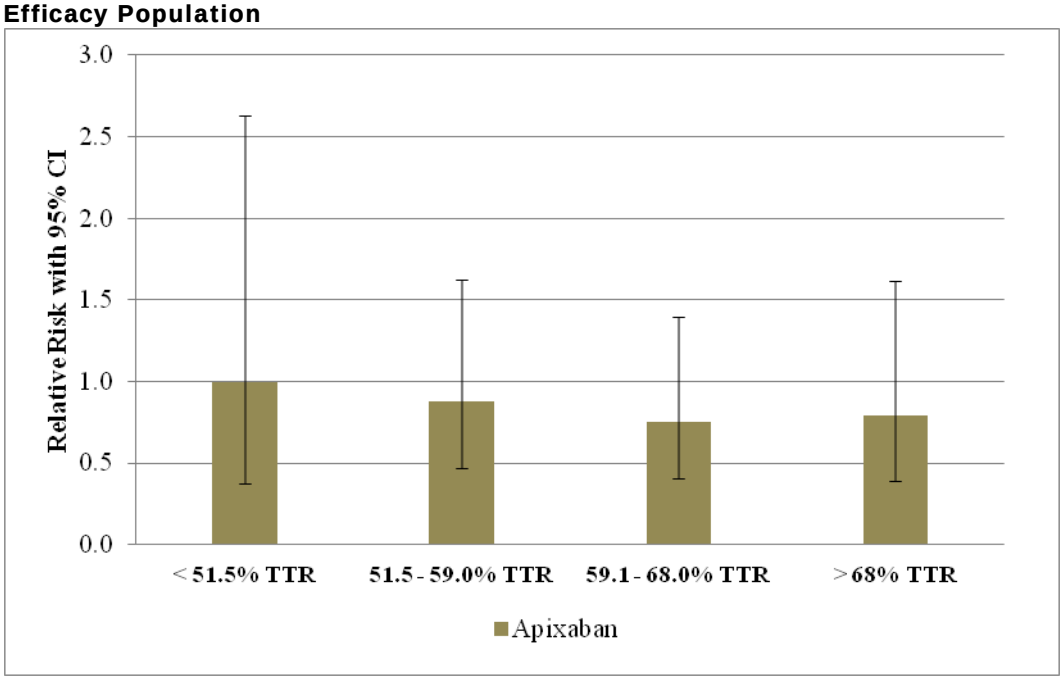
### The effect of INR control on the relative efficacy of apixaban and warfarin

Overall, subjects receiving warfarin were within the target therapeutic range (INR of 2.0-3.0) 60.9% (mean) of the time, which is consistent with recent VTE clinical trials that report a time in therapeutic range (TTR) of 58% [EINSTEIN], 60% [RECOVER], and 62.7% [EINSTEIN PE].

A centre-based analysis of VTE/VTE-related death was used to assess whether high or low TTR interacts with the treatment effects when comparing efficacy of apixaban with enoxaparin/warfarin. Subjects were not randomized to quartiles, but were in a quartile based on the degree of INR control at their investigative site. Centres were grouped by TTR quartiles based on a median TTR of 59.1%.

This analysis demonstrated that the efficacy of apixaban relative to enoxaparin/warfarin was maintained across study sites regardless of TTR quartile (Figure E5). Within the highest quartile of TTR according to centre, the relative risk for apixaban versus enoxaparin/warfarin was 0.79 (95% CI, 0.39, 1.61).

**Figure E5. Relative Risk of VTE/VTE-Related Death for Apixaban versus Enoxaparin/Warfarin by Sites Grouped by INR TTR Quartiles in Study CV185056 - Primary Efficacy Population**




Source: CV185056 CSR Table 14.2.3.1.3.13 and SCE Section 2.7.3.3.3.2.
P-value for treatment by INR control interaction=0.9624.
INR TTR quartiles based on a median TTR of 59.1%.
TTR=time in therapeutic range, INR=international normalized ratio, CI=confidence interval, SCE=summary of clinical efficacy, CSR=clinical study report.

Although it is recognized that the AMPLIFY population did not have purely **provoked events** (=provoked events without additional risk factors), the results for VTE/VTE-related death according to the qualifying index events being provoked or unprovoked were consistent with the population as a whole. The RR point estimates for provoked (0.78) and unprovoked (0.82) VTE were both < 1 compared to enoxaparin/warfarin.

The most common reasons for exclusion of subjects from the pre-specified **per protocol population** were discontinuation of treatment before the end of the intended treatment period without having had a primary efficacy endpoint and < 80% compliance with study medication. In total, 434 (16.1%) apixaban-treated subjects and 469 (17.3%) enoxaparin/warfarin-treated subjects were excluded from the per protocol group. The per protocol analysis demonstrated that the overall efficacy results (events of VTE/VTE-related death, 32/2275 for apixaban, 48/2235 for enoxaparin/warfarin, RR of 0.66; p <0.0001 for non-inferiority) are consistent with the primary efficacy analysis. The event rates in the PP group were lower (as expected because the subjects actually used their effective therapies); the numerical advantage for apixaban was larger in the PP analysis. This confirms the robustness of the primary efficacy analysis.

Subjects with missing endpoint data were excluded from the primary efficacy analysis. As **sensitivity analysis**, 4 scenarios were investigated, in which all missing data in the treatments groups were imputed as having or not having the event (see Table E6). The scenarios 3 and 4 are unreasonable extremes, as the amount of missing endpoint data is roughly equal to the number of events. It is agreed with the Applicant that the sensitivity analyses support the robustness of the primary efficacy outcome.

**Table E6. Sensitivity analyses for CV185056**

| | apixaban | Enoxaparin/warfarin | Relative risk |
|---|---|---|---|
| Primary analysis | 2609 | 2635 | |
| Observed events | 59 | 71 | 0.84 |
| Randomised | 2691 | 2704 | |
| With missing data | 82 (3.0%) | 69 (2.6%) | |
| | Imputation for missing data: | | |
| Scenario 1 | None had event (59) | None had event (69) | 0.83 |
| Scenario 2 | All had event (141) | All had event (140) | 1.01 |
| Scenario 3 | All had event (141) | None had event (69) | 1.99 |
| Scenario 4 | None had event (59) | All had event (140) | 0.42 |

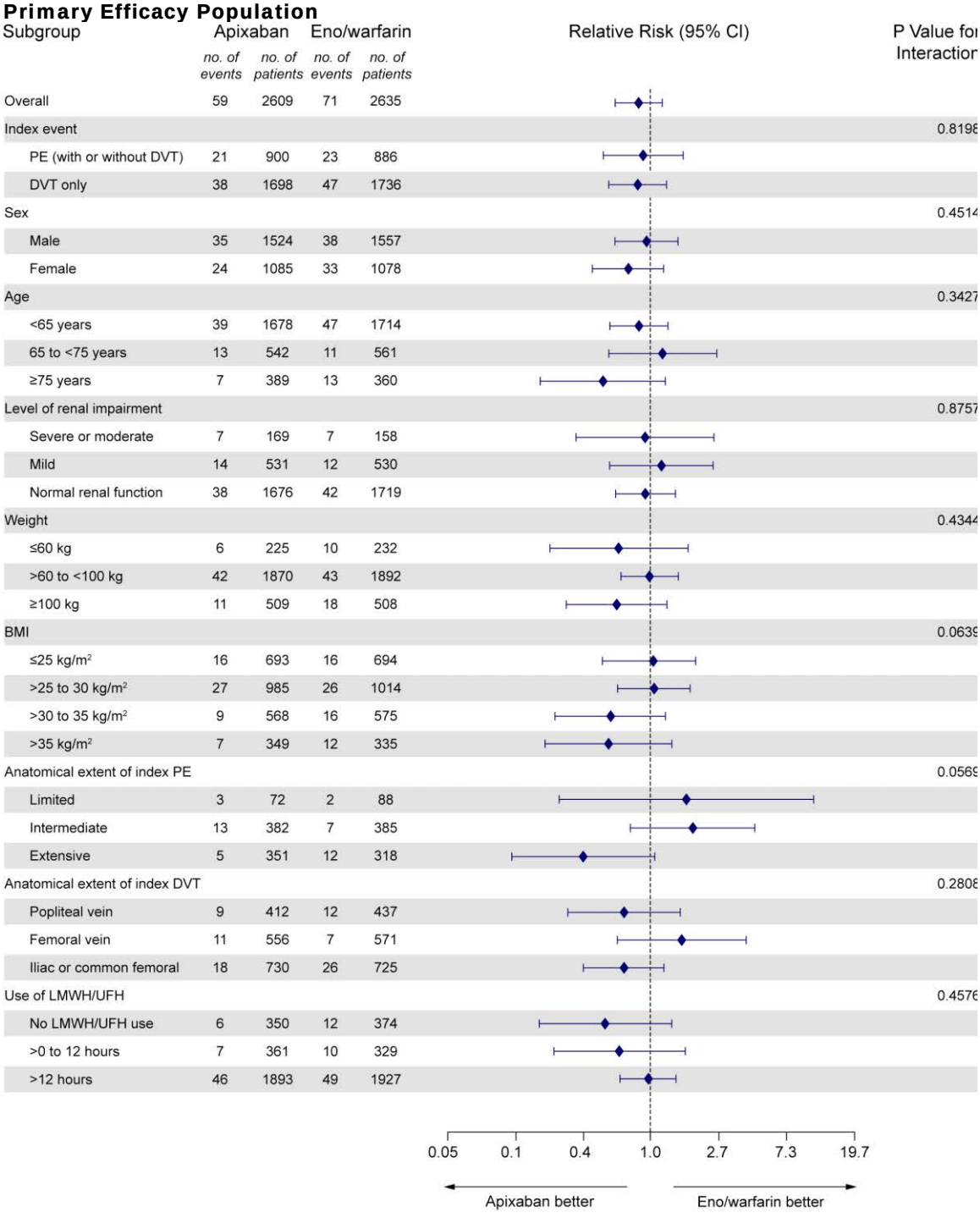
Source: Table 14.2.3.1.4 of CV185056 CSR (b0661001-report-body, page 303)

In an analysis according to the **extent of VTE**, the numerical advantage of apixaban in event rate is evident in subjects with extensive disease, but not in all subjects with limited or moderate disease (see also subgroup analysis in Figure E6). The groups are small and confidence intervals for all these subgroups included 1, and the statistical interaction was not significant (p-value for interaction 0.057 for PE and 0.28 for DVT)

The relative risk for an outcome event was numerically in favour of apixaban regardless of **prior heparin use**. The confidence intervals for all these subgroups included 1, and the statistical interaction was not significant.

Results for a number of subgroups are shown in the Figure E6. The result from the subgroup analysis by **BMI** deserves some attention as the interaction was almost statistically significant (p= 0.0639).

**Figure E6. Forest Plot for Adjudicated VTE/VTE-related Death in Study CV185056 - Primary Efficacy Population**




## Results of study CV185057 (AMPLIFY-EXT)

### *Participant flow*

Approximately 85% of apixaban-treated subjects completed 12 months of study treatment compared to 77.3% of subjects receiving placebo. During this period, a higher proportion of placebo-treated subjects discontinued due to death, DVT, PE, and other VTE, and a higher proportion of apixaban-

treated subjects discontinued due to bleeding (Table E7). The proportions of subjects completing 12 months of study treatment are similar in subjects with a DVT compared to those with a PE at baseline.

Most subjects entered the 30-day follow-up period whether or not the subject completed the 12 months of study treatment. The primary reason for not completing the follow-up period in the apixaban 2.5 mg group (n=12, 1.4%), apixaban 5 mg group (n=11, 1.4%), and placebo group (n=7, 0.9%) was withdrawal of consent.

Discontinuations for all reasons are discussed in more detail in the safety section.

**Table E7. Subject Disposition in Study CV185057**

| | Apixaban | | |
|---|---|---|---|
| | **2.5 mg BID** | **5 mg BID** | **Placebo** |
| **Number (%) of Subjects** | | | |
| Randomized | 840 | 813 | 829 |
| Treated | 840 (100) | 811 (99.8) | 826 (99.6) |
| Completed 12 months of treatment | 726 (86.4) | 684 (84.1) | 641 (77.3) |
| Discontinued for any reason | 114 (13.6) | 129 (15.9) | 188 (22.7) |
| **Efficacy event/outcome-associated reason for discontinuation from treatment (randomized subjects)** | | | |
| Death | 1 (0.1) | 3 (0.4) | 9 (1.1) |
| DVT | 5 (0.6) | 8 (1.0) | 57 (6.9) |
| PE | 4 (0.5) | 3 (0.2) | 18 (2.2) |
| Bleeding | 8 (1.0) | 8 (1.0) | 1 (0.2) |
| Venous thromboembolic event | 0 | 1 (0.1) | 6 (0.7) |
| **Number (%) of Subjects** | | | |
| Entered follow-up period | 836 | 806 | 811 |
| Completed follow-up period | 813 (97.2) | 782 (97.0) | 791 (97.5) |

Source: Study CV185057 CSR Table 14.1.1.2.2, 14.1.1.2.4.
BID=twice daily, DVT=deep vein thrombosis, PE=pulmonary embolism, CSR=clinical study report

***Recruitment***

The study was conducted between 16 May 2008 to 24 August 2012 at 328 centres worldwide.

***Baseline data***

Patients were balanced among treatment groups with respect to demographic characteristics. Most subjects were white (85%) and treated in the European Union (1182 = 48%). Older patients (≥75 year: n=329, 13%) and overweight (32%)/obese (20%) subjects were adequately represented.

The protocol excluded patients who had more than 12 months of anticoagulation planned for the most recent DVT or PE, (index event) and subjects with indications for long-term treatment with a VKA (such as mechanical valve, atrial fibrillation, multiple episodes of unprovoked DVT or PE, documented anti-phospholipid antibodies, anti-thrombin III deficiency, protein C deficiency, protein S deficiency, homozygous factor V Leiden, or homozygous prothrombin gene mutation.)

***Numbers analysed***

The primary efficacy analysis population in study CV185057 is all randomized subjects (Table E8). The treated population was used in the safety analyses. The analysis was by intention to treat. As

discussed elsewhere, subjects with missing endpoint data were imputed as having the event with additional sensitivity analyses for other imputation rules or without imputation.

**Table E8. Number of Subjects in the Analysis Populations in Study CV185057**

| | 2.5 mg BID Apixaban | 5 mg BID Apixaban | Placebo | Total |
|---|---|---|---|---|
| Randomized subjects | 840 | 813 | 829 | 2482 |
| Treated subjects | 840 | 811 | 826 | 2477 |

Source: Study CV185057 CSR Table 14.2.2.1.
BID=twice daily, CSR=clinical study report

***Outcomes and estimation***

**Primary endpoint**

In study CV185057, apixaban given at 2.5 mg BID or 5 mg BID for 12 months demonstrated superiority to placebo for the primary efficacy analysis (with imputation) for the endpoint of VTE/all-cause death. The event rates in the treatments groups were 0.0381 events/year (32/840), 0.0418 (34/813), 0.1158 (96/829) for apixaban 2.5 mg BID, 5 mg BID or placebo respectively. The corresponding relative risks were 0.33 and 0.36 ($p<0.0001$). In the analysis without imputations the relative risks were even 0.24 and 0.19, based on event rates of 0.0226 (19 events), 0.0172 (14 events) and 0.0929 (77 events). Results with no imputation gave the same p-value as the analysis with imputation (Table E9).

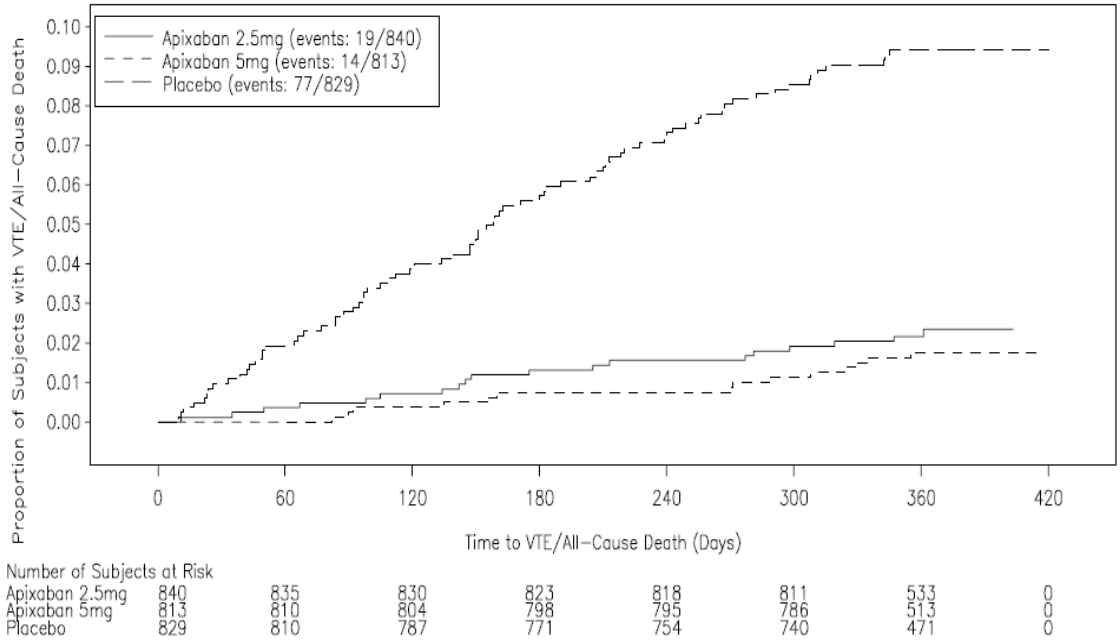
**Table E9. Results of Adjudicated VTE/All-Cause Death in Study CV185057 - Randomized Subjects**

| | Apixaban | | |
|---|---|---|---|
| | 2.5 mg BID N=840 | 5 mg BID N=813 | Placebo N=829 |
| **With imputation for missing endpoints** | | | |
| Total VTE/all-cause death (n; includes imputed events) | 32 | 34 | 96 |
| Number of imputed events | 13 (1.5%) | 20 (2.5%) | 19 (2.3%) |
| Event rate [95% CI] | 0.0381 [0.0252, 0.0510] | 0.0418 [0.0281, 0.0556] | 0.1158 [0.0940, 0.1376] |
| Relative risk [95% CI] | 0.3283 [0.2225, 0.4844] | 0.3615 [0.2475, 0.5281] | -- |
| p-value for superiority | <0.0001 | <0.0001 | -- |
| Hochberg adjusted p-value for superiority | <0.0001 | <0.0001 | -- |
| Risk difference [95% CI] | -0.0779 [-0.1032, -0.0526] | -0.0740 [-0.0997, -0.0482] | -- |
| p-value for superiority | <0.0001 | <0.0001 | -- |
| **No imputation for missing endpoints** | | | |
| VTE/all-cause death (n; no imputed events) | 19 | 14 | 77 |

| | Apixaban | | |
|---|---|---|---|
| | **2.5 mg BID N=840** | **5 mg BID N=813** | **Placebo N=829** |
| Event rate [95% CI] | 0.0226 [0.0126, 0.0327] | 0.0172 [0.0083, 0.0262] | 0.0929 [0.0731, 0.1126] |
| Relative risk [95% CI] | 0.2422 [0.1476, 0.3975] | 0.1861 [0.1062, 0.3261] | -- |
| p-value for superiority | <0.0001 | <0.0001 | -- |
| Hochberg adjusted p-value for superiority | <0.0001 | <0.0001 | -- |
| Risk difference [95% CI) | -0.0707 [-0.0928, -0.0486] | -0.0751 [-0.0968, -0.0535] | -- |

The Kaplan-Meier Plot (Figure E7) suggests that the event rates in both the placebo group and the active groups are constant. This is supportive of treatment continuation after one year if the indication (i.e. risk factors for recurrent VTE) persists.

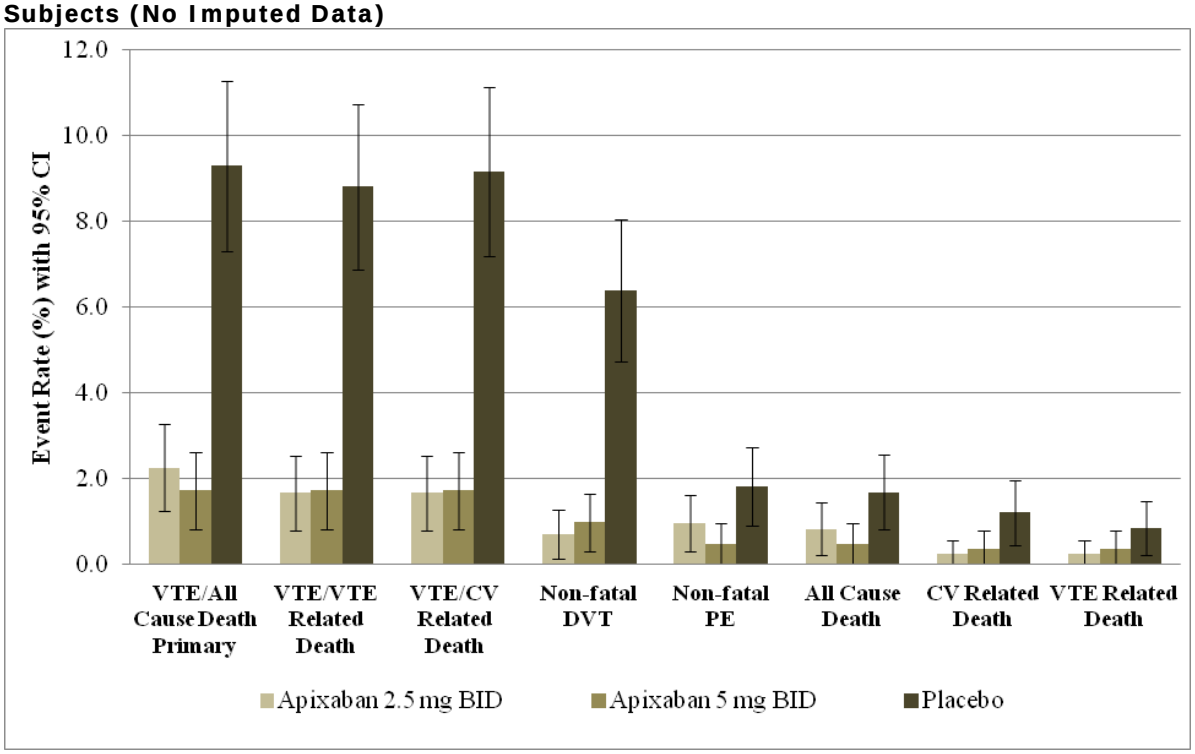
**Figure E7. Kaplan-Meier Plot for Adjudicated VTE/All-Cause Death During the Intended Treatment Period in Study CV185057- Randomized Subjects (No Imputed Data)**




**Secondary endpoints**

The secondary endpoint analyses confirm efficacy in all predefined outcomes. The relative risks for all secondary endpoints for both apixaban doses are < 1 compared to placebo, which are consistent with and support the results of the primary endpoint (Figure E8).

**Figure E8. Summary of Adjudicated Efficacy Endpoints in Study CV185057 - Randomized Subjects (No Imputed Data)**




***Ancillary analyses***

**Missing data**

Already the primary analysis was conservative with respect to missing data, as all missing data were imputed as having an event, which is unfavourable for apixaban. Other sensitivity analyses confirm the consistency of the results. Even the (apparently unreasonable) sensitivity analysis in which all missing data were interpreted in favour of placebo still showed a statistically significant benefit for apixaban.

**Provoked versus unprovoked**

The subgroup analyses with respect to whether the index event (6 months before randomisation) was provoked versus unprovoked, did not show important differences. In study CV185057, approximately 90% of qualifying VTEs were reported as unprovoked. The 8.8% rate of VTE/VTE-related death observed over the 12-month period (median treatment duration of 359 days) following cessation of anticoagulant treatment (the placebo group in Figure ) was comparable to the approximately 10% annual rate observed in other studies in an unprovoked population and the 7.1% (median treatment duration of 265 days) in the rivaroxaban EINSTEIN EXT study.

**Prior therapy**

The subgroup analyses with respect to prior therapy did not show important differences between treatments. In the placebo groups some more events were noted after enoxaparin/warfarin when compared to prior treatment with apixaban. However, as there were no extra events after 'standard therapy', presumably LMWH/VKA also, this may be a chance finding.

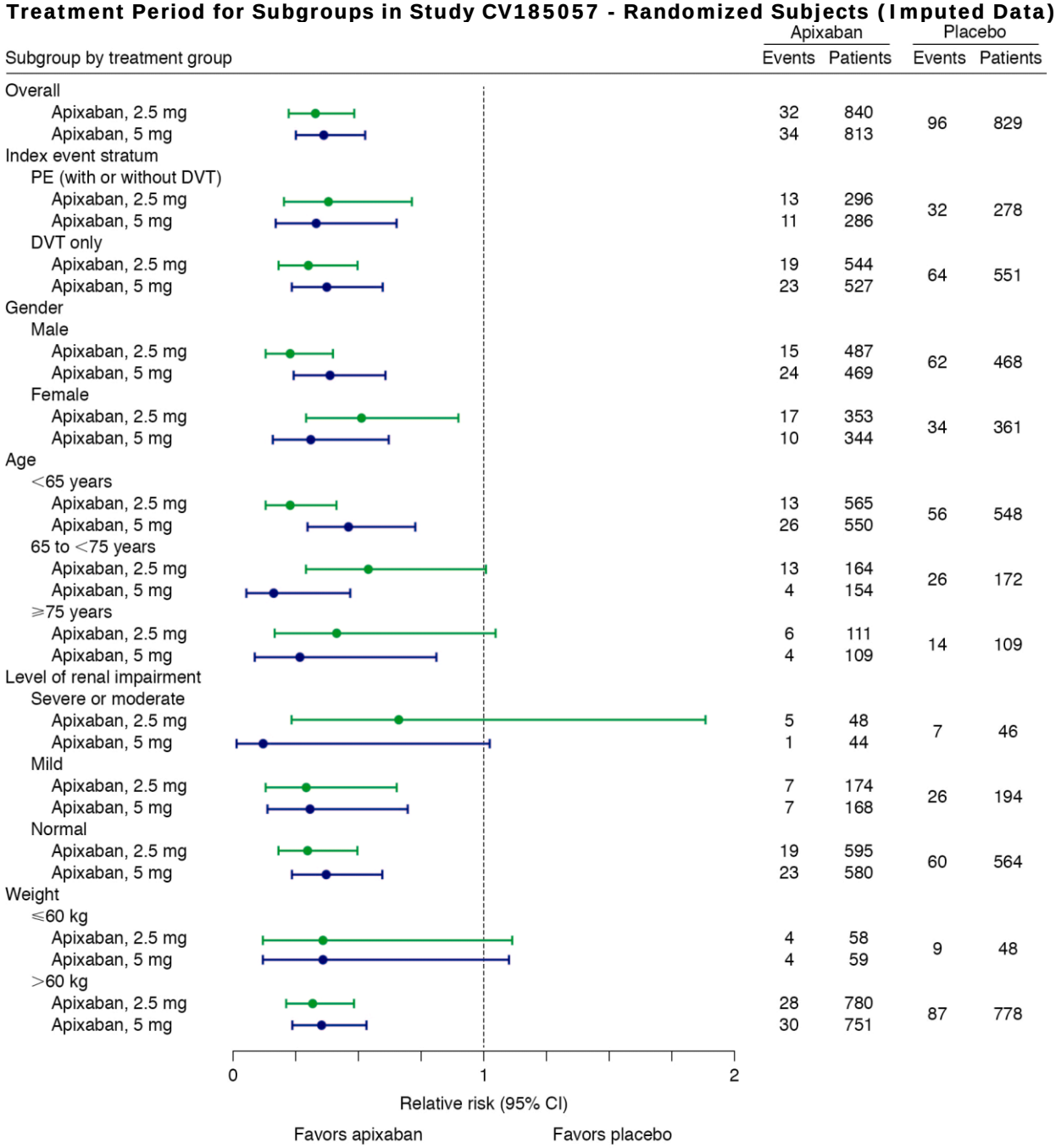
**Efficacy in the DVT and PE strata in study CV185057**

Results for the prevention of VTE recurrence for the DVT and PE strata are consistent with the population as a whole for VTE/all-cause death (Figure E9).

**Other subgroup analyses**

Analyses of VTE/all-cause death were performed for a number of subgroups (Figure E9). None of the subgroup analyses showed a statistically significant interaction. The estimates for the relative risk are all consistent with the main analysis and also the differences between the two apixaban dose levels were very small.

**Figure E9. Forest Plot for Adjudicated VTE/All-Cause Death During the Intended Treatment Period for Subgroups in Study CV185057 - Randomized Subjects (Imputed Data)**



***Summary of main study(ies)***

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

**Table E10. Summary of efficacy for trial CV185056, AMPLIFY**

| **Title: A Safety and Efficacy Trial Evaluating the Use of Apixaban in the Treatment of Symptomatic Deep Vein Thrombosis and Pulmonary Embolism** | | | |
|---|---|---|---|
| Study identifier | CV185056 (Amplify) | | |
| Design | This was a randomized, active controlled, parallel-group, double-blind, triple-dummy study in subjects with acute symptomatic proximal DVT or acute symptomatic PE. Randomization was stratified by the type of disease (symptomatic proximal DVT only or symptomatic PE with or without DVT) at baseline. If a subject had both symptomatic proximal DVT and symptomatic PE, the subject was stratified to the symptomatic PE group. Subjects were randomized (1:1 ratio) using a central interactive voice response system (IVRS) and received study treatments for 6 months. Subjects in Group 1 received enoxaparin injections, warfarin tablets, and placebo apixaban tablets. Subjects in Group 2 received placebo enoxaparin injections, placebo warfarin tablets, and apixaban tablets. Total participation in the study for each subject was approximately 7 months (6 months on study treatment followed by a 30-day observation period). Subjects who met eligibility criteria assessed at screening and/or baseline were randomized and dispensed study drug on Day 1. Subjects were requested to return to the study site at Weeks 2, 4, 8, 12, 16, 20, and 24 for study specific activities. | | |
| | Duration of main phase:<br>Duration of run-in phase:<br>Duration of extension phase: | | 6 months (+30 days observation)<br>N/A<br>See CV185057 |
| Hypothesis | Non-inferiority | | |
| Treatment groups | apixaban | | apixaban at a dose of 10 mg BID for initial 7-day treatment, followed by 5 mg BID for 6 months; n=2676 |
| | enoxaparin/warfarin | | Enoxaparin was administered for at least 5 days and was to be discontinued after the blinded international normalized ratio (INR) was ≥2, on 1 or more occasions. Warfarin with target INR 2.0-3.0; n=2689 |
| Endpoints and definitions | Primary endpoint | VTE/VTE-related death | the incidence of an adjudicated composite of symptomatic, recurrent VTE (nonfatal DVT or nonfatal PE) or VTE-related death. The primary endpoint included events that occurred at any time from randomization until the end of the originally intended treatment period regardless of whether subjects were receiving study medication (using the intent-to-treat principle). |

| | | | |
|---|---|---|---|
| | Secondary endpoint | VTE/all-cause death | adjudicated composite of recurrent symptomatic VTE and all cause death |
| | Safety endpoint | Major bleeding | The incidence of adjudicated major bleeding during the treatment period. [included in hierarchical testing] |
| Last Subject Last Visit | 12 March 2013 | | |

## Results and analysis

| **Analysis description** | **Primary analysis** | | |
|---|---|---|---|
| Analysis population and time point description | Intent to treat (6 months) | | |
| Descriptive statistics and estimate variability | Treatment group | apixaban | enoxaparin/warfarin |
| | Number of subjects | 2609 | 2635 |
| | VTE/VTE-related death (n)<br>(event rate) | 59<br>0.0226 | 71<br>0.0269 |
| | 95% CI | [0.0169, 0.0283] | [0.0208, 0.0331] |
| | VTE/all-cause death(n)<br>(event rate) | 84<br>0.0322 | 104<br>0.0395 |
| | 95% CI | [0.0254, 0.0390] | [0.0320, 0.0469] |
| | Major bleeding (n/N)(event rate) | 15/2676 | 49/2689 |
| Effect estimate per comparison | Primary endpoint VTE/VTE-related death (n) | Comparison groups | Apixaban – enox/warf |
| | | **Relative risk** | **0.8390** |
| | | 95% CI | [0.5965, 1.1802] |
| | | P-value (non-inferiority) | <0.0001 |
| | | **Risk difference** | **-0.0044** |
| | | 95% CI | [-0.0128, 0.0040] |
| | | P-value (non-inferiority) | <0.0001 |
| | Secondary endpoint VTE/all-cause death | **Relative risk** | **0.8151** |
| | | 95% CI | [0.6146, 1.0812] |
| | | P-value (superiority) | 0.1554 |
| | Safety endpoint Major bleeding | **Risk difference** | **-0.0113** |
| | | 95% CI | [-0.0170, -0.0056] |
| | | P-value (superiority) | <0.0001 |
| Notes | Other secondary and safety endpoints not shown in this summary | | |

**Table E11. Summary of efficacy for trial CV185057, AMPLIFY EXT**

| **Title: A Safety and Efficacy Trial Evaluating the Use of Apixaban for the Extended Treatment of Deep Vein Thrombosis and Pulmonary Embolism** | | |
|---|---|---|
| Study identifier | CV185057 (B0661002) (Amplify-Ext) | |
| Design | This was a randomized, parallel-group, double-blind, placebo-controlled study in subjects with symptomatic proximal DVT or symptomatic PE. Randomization was stratified by the type of disease treated (symptomatic proximal DVT only or symptomatic PE with or without DVT) and by the type of previous treatment (enoxaparin/warfarin in Study CV185056 [Apixaban after the initial Management of Pulmonary embolism and deep vein thrombosis with First-line therapy {AMPLIFY}], apixaban in Study CV185056 [AMPLIFY], or standard anti-coagulant therapy outside of Study CV185056 [AMPLIFY]). If a subject had both symptomatic DVT and symptomatic PE, the subject was stratified to the symptomatic PE group. After completing approximately 6 to 12 months of anticoagulant therapy for the treatment of the index event, eligible subjects were randomized at a 1:1:1 ratio to receive 1 of 3 oral treatments twice daily (BID): apixaban 2.5 mg, apixaban 5 mg, or placebo. Total participation in the study for each subject was approximately 13 months (12 months on study treatment followed by a 30-day observation period). Subjects who met eligibility criteria assessed at screening and/or baseline were randomized and dispensed study drug on Day 1. Subjects were requested to return to the study site at Week 2 and at Months 3, 6, 9, and 12. Other visits at Months 1, 2, 4, 5, 7, 8, 10, and 11 were conducted either in person or by telephone contact. | |
| | Duration of main phase:<br>Duration of run-in phase:<br>Duration of extension phase: | 1 year<br>not applicable<br>not applicable |
| Hypothesis | Superiority | |
| Treatment groups | Apixaban 2.5 mg BID | Subjects were randomized to receive 2.5 mg apixaban and apixaban 5 mg matching placebo, apixaban 5 mg and apixaban 2.5 mg matching placebo or apixaban 2.5 matching placebo and apixaban 5 mg matching placebo. Study subjects took 2 tablets in the morning and 2 tablets in the evening (approximately every 12 hours).<br>N=840 |
| | Apixaban 5 mg BID | N=811 |
| | Placebo | N=826 |

| | | | | | |
|---|---|---|---|---|---|
| Endpoints and definitions | Primary endpoint | VTE/all-cause death | The incidence of an adjudicated composite of symptomatic, recurrent VTE (nonfatal DVT or nonfatal PE) or all-cause death. The primary endpoint included events that occurred at any time from randomization until the end of the originally intended treatment period, regardless of whether subjects were receiving study medication (using the intent-to-treat principle). The intended treatment period was defined as the longer of the dosing period plus 2 days or 355 days.<br>If there was missing endpoint information, such as subjects who withdrew consent or were lost to follow-up, they were scored (imputed) as having had a primary efficacy outcome event | | |
| | Sensitivity analysis | VTE/all-cause death without imputation | As primary endpoint, but if there was missing endpoint information, data were not imputed | | |
| | Safety endpoint | Major bleeding | The incidence of adjudicated major bleeding during the treatment period. | | |
| Study completion | 24 August 2012 | | | | |
| **Results and analysis** | | | | | |
| **Analysis description** | **Primary analysis** | | | | |
| Analysis population | Intent to treat | | | | |
| Descriptive statistics and estimate variability | Treatment group | Apixaban 2.5 mg BID | Apixaban 5 mg BID | placebo | |
| | Number of subjects | 840 | 813 | 829 | |
| | VTE/all-cause death (n, event rate) | 32<br>0.0381 | 34<br>0.0418 | 96<br>0.1158 | |
| | <variability statistic> | (0.0252, 0.0510) | (0.0281, 0.0556) | (0.0940, 0.1376) | |
| | VTE/all-cause death without imputation (n, event rate) | 19<br>0.0226 | 14<br>0.0172 | 77<br>0.0929 | |
| | 95% CI | (0.0126,0.0327) | (0.0083, 0.0262) | (0.0731, 0.1126) | |
| | Major bleeding (n, event rate) | 2<br>0.0024 | 1<br>0.0012 | 4<br>0.0048 | |
| | 95% CI | (0.0000, 0.0057) | (0.0000, 0.0036) | (0.0001, 0.0096) | |

| | | | | |
|---|---|---|---|---|
| Effect estimate per comparison | Primary endpoint VTE/all-cause death | Comparison groups | Apixaban 2.5 mg BID v placebo | Apixaban 5 mg BID v placebo |
| | | Relative risk | 0.3283 | 0.3615 |
| | | 95% CI | (0.2225, 0.4844) | (0.2475, 0.5281) |
| | | P-value (superiority) | <0.0001 | <0.0001 |
| | VTE/all-cause death without imputation | Relative risk | 0.2422 | 0.1861 |
| | | 95% CI | (0.1476, 0.3975) | (0.1062, 0.3261) |
| | | P-value (superiority) | <0.0001 | <0.0001 |
| | Major bleeding | Relative risk | 0.4850 | 0.2457 |
| | | 95% CI | (0.0891, 2.6391) | (0.0269, 2.2437) |
| | | P-value (superiority) | 0.3925 | 0.3551 |
| Notes | 836 patients were also treated in CV185056 | | | |

## 2.4.3. Discussion on clinical efficacy

Efficacy and safety for the VTE treatment and prevention indications have been investigated in 1 Phase 2 study (CV185017) and 2 pivotal Phase 3 studies (CV185056, AMPLIFY and CV185057, AMPLIFY EXT).

Data provided by these studies address the key clinical questions with respect to determining the benefit/risk profile of apixaban compared to enoxaparin/warfarin in the acute treatment of VTE and the benefit/risk profile of apixaban compared to placebo for the prevention of recurrence of VTE over extended periods of therapy.

***Design and conduct of clinical studies***

**Comparators**

The combination of LMWH and VKA is the gold standard for treatment of VTE and the choice is in line with the NICE and ESC guidelines. The differences between the various LMWH products are small; the decision to choose enoxaparin is acceptable. Warfarin is globally the most commonly used VKA, and its choice is understandable.

Given the high efficacy of the reference treatment, a non-inferiority design was appropriate. The non-inferiority margin (relative risk of 1.8) was adapted to an FDA request and stricter than would have been required by EMA (e.g. in the scientific advice). This margin guarantees that the apixaban treatment preserves at least 50% of the effect of standard of care compared to placebo.

The **population** studied was representative of the population requiring treatment for VTE for 6 months, but two additional special sub-populations are noted. The low-risk patients with a provoked VTE without additional risk factors were excluded from CV185056 because they would only need 3 months of treatment. Some subjects with active cancer were included in the trial. However, guidelines do not support the use of VKA in these patients as the standard of care; LMWH should have been used as the active comparator. Accordingly the efficacy findings cannot be interpreted for them. This is clarified in the SmPC.

The indication for prevention of recurrent VTE was addressed in **CV185057** for an extended treatment period up to one year. The comparator for study CV185057 was placebo. This is acceptable, because at the time study CV185057 was initiated, no therapy other than a VKA was available for treatment beyond the initial 6-12 months. Because it was determined that the risk of bleeding with a VKA would offset the potential benefit of continued anticoagulation (had reached equipoise with respect to continuation or cessation of anticoagulant therapy), placebo was considered the appropriate comparator for this study.

Only patients at clinical equipoise for treatment continuation could be included. This criterion appears to be somewhat poorly defined, but the investigators recruited a population with an annual risk of around 10% of VTE recurrence, which shows that there are benefits from this extended therapy. Patients, who clearly needed extended active prophylaxis, (e.g. patients with protein C or S deficiencies) were excluded from the trial. In the Xarelto (rivaroxaban) dossier, study 11899 is comparable to CV185057 (see EPAR of EMEA/H/C/000944/X/0010). In this rivaroxaban trial, 7.1 % of placebo patients had a primary outcome event. The event rate in the placebo group of CV185057 was 9.3%, suggesting a somewhat higher risk population. The cause of this higher risk is not clear, as for 66.3% in CV185057 no risk factor for VTE recurrence was reported, whereas in the rivaroxaban trial approximately 60% had had an idiopathic DVT/PE, but 16% had had more than one DVT/PE event, 14 % had had a primary event during immobilisation, 8% had a known thrombophilic condition and 5% had active cancer, which are all risk factors for VTE. Thus, in the rivaroxaban trial, more subjects had recognised risk factors, whereas in the apixaban trial the risk was higher. It can be accepted that the apixaban patients were in 'clinical equipoise'.

**Cancer** patients were included as per clinical study protocol. This was justified by the applicant by the lack of data for such patients regarding the continuation of anticoagulation therapy after the initial 6 months of treatment for DVT or PE to guide their physicians in continuing treatment. There are also no data regarding the treatment of patients whose cancer has resolved. This argumentation is not completely accepted. In clinical practice, patients with active cancer and a VTE event will be usually treated with LMWH for extended periods (see e.g. J Clin Oncol 25:5490-5505 or NICE VTE guideline p 36/245). According to the exclusion criteria, patients who would be eligible for prolonged LMWH treatment are not in 'clinical equipoise' and are not expected in the trial.

### Statistical methods

Hierarchical statistical testing

The chosen method differs from the hierarchical testing discussed in the CHMP Scientific Advice EMEA/CHMP/SAWP/381523/2007 of 13 December 2007, where the superiority of apixaban over the comparator with regard to the endpoint of "all cause death or first recurrence of VTE" as a key secondary variable was planned to be tested in a confirmatory manner, only after non-inferiority has been shown with regard to the primary variable "VTE-related death or first recurrence of VTE". Since the *Note for Guidance on Clinical Investigation of Medicinal Products for the Treatment of Venous Thromboembolic Disease (CPMP/EWP/563/98)* guidance indicates all cause death or first recurrence of VTE is the most important analysis for superiority trials and VTE related death or first recurrence of VTE is the most important analysis for non-inferiority trials, the hierarchy was prospectively changed to focus on the latter in this non-inferiority trial. "All cause death or first recurrence of VTE" is retained as a secondary endpoint.

The hierarchical statistical testing procedure adequately controls the family-wise Type I error rate. The most important safety outcome (major bleeding) is included here, which makes this measure

statistically more robust compared to assessment as a safety parameter alone. The deviation from the EMA scientific advice (focusing on VTE related death instead of all-cause mortality) is sufficiently justified by reference to the EMA VTE guideline.

**Missing data**

The methods used to handling of missing data in **CV185056** is acceptable. Especially in a non-inferiority trial, missing data may reduce the power of a trial making the issue of importance. Sensitivity analyses have been provided to support the estimations of effect size in the light of missing data. For study CV185056, missing endpoint data were imputed for sensitivity analyses only.

**Study CV185057**

**Sample size**

The prediction of the event rates for the sample size calculation was conservative when compared to the event rates that finally occurred in the trial. This is understandable, as the target population is defined by the clinical equipoise criterion that is subjective. Based on the observed event rate in the placebo group (9.3%) the included population has a somewhat higher risk than assumed.

The Hochberg procedure was used to adjust for multiplicity between the two doses of apixaban in study CV185057. This procedure adequately controls the type I error rate in this situation.

The **conduct** of the trials appears to follow current standards. Blinding the VKA treatment required reporting of sham INRs to the investigator, which was implemented through the IVRS system. The sponsor has documented a very low number of errors in the medication dispensing process. The sponsor's GCP Quality found GCP violations in some sites and eventually decided to close one site for lack of GCP compliance. This is interpreted positively in the sense, that the QA procedures were effective in finding and resolving the issue.

***Efficacy data and additional analyses***

**Dose Selection.**

The investigated dose in the phase 3 trials was based on the results of the phase 2 trial, but further adjusted through comparisons with other products and other indications. The currently proposed dose for the treatment of VTE is apixaban 10 mg orally twice daily, followed by apixaban 5 mg twice daily until 6 months after the index event. This dose is well justified based on the efficacy data. The length of the initial phase of higher dose (10 mg BID) could be debated, and it cannot be excluded that a lower dose of apixaban e.g. between the third and the sixth month of therapy could be equally efficacious, however this is only speculation and the gain in safety that could be expected is small especially when compared to the clinical trial effort this would require.

**Results study CV185056.** The **primary endpoint** of VTE/VTE-related death for treatment of VTE was non-inferior to standard therapy and in fact numerically superior although this result did not reach statistical significance.

Subjects receiving warfarin were within the target therapeutic range (INR of 2.0-3.0) 60.9% (mean) of the time, which is consistent with recent VTE clinical trials that report a time in therapeutic range (**TTR**) of 58% [EINSTEIN], 60% [RECOVER], and 62.7% [EINSTEIN PE]. There were no clear trends in efficacy or safety in subgroup analyses based on TTR.

The robustness of the results is supported by the per protocol analysis, sensitivity analyses addressing missing data and the secondary endpoints (including more measures of mortality).

Most **subgroup analyses** also confirm the consistency of the results of the primary efficacy outcome. The subgroup analyses according to extent of VTE were inconsistent in the (small) subgroups with limited or moderate disease. There is no obvious mechanism, by which a therapy for more severe disease would not be effective in limited disease (unless the diagnosis would be different or wrong). In this issue, a chance finding is not unlikely.

The result from the subgroup analysis by BMI deserves some attention as the interaction was almost statistically significant (p= 0.0639). Surprisingly, the relative efficacy was lower in the low BMI group, although one would expect the highest concentrations of apixaban in this group while the VKA dose would be weight-corrected through INR titration. These findings may also be attributable to chance.

The **low-risk patients** with a provoked VTE without additional risk factors were excluded from CV185056 because they would only need 3 months of treatment. Although efficacy in these low risk patients is not directly investigated in this study, the applicant is explicitly including these patients in section 4.2 of the SmPC: "As per available medical guidelines, short duration of treatment (at least 3 months) should be based on transient risk factors (e.g. recent surgery, trauma, immobilisation)."

The population that should be treated for merely 3 months has lower risk of recurrence than the population included in the trial. However, a product that is effective in a situation of high risk of thrombus formation (like unprovoked VTE) could also be assumed effective in a situation of low risk of thrombus formation or when the 'provoking factor' persists.

The Kaplan Meijer curves for VTE events are clearly separated at 3 months already, favouring apixaban. It follows directly from the observations made in the previous paragraph that the relative risk of VTE/VTE-related death is also numerically favourable for apixaban at 3 months. See the Safety section for the risk of adverse events in this subgroup.

The subgroup analyses (after 6 months) of subjects with provoked events further support this approach. Compared to enoxaparin/warfarin, the relative risk of VTE/VTE related death was 0.77 (95% CI: 0.29, 2.08; 7/261 v 9/263 events); the relative risk of Major Bleeding was 0.42 (95% CI: 0.11, 1.58; 3/270 v 7/268 events).

The wording regarding short-term treatment in the proposed SmPC is similar to the approved SmPC of rivaroxaban. However, in the rivaroxaban study 11702, investigators were asked to determine treatment duration (3, 6 or 12 months) prior to randomisation. For subjects with 3 months intended treatment duration, 208 patients were randomized to rivaroxaban and 203 patients to enoxaparin/VKA and primary outcome events were 5 (2.4%) and 3 (1.5%) respectively. Thus, rivaroxaban has addressed the 3-months treatment in the trial, while apixaban has not, but based on the data provided the extrapolation can be accepted.

The inclusion of **(active) cancer** patients may be considered controversial, because they may qualify for a different therapeutic approach, e.g. long-term LMWH instead of VKA. A history of cancer was present in 518 (9.7%) and active cancer in 142 (2.6 %) of treated subjects. In the CSR, a subgroup analysis of all cancer patients is not presented, but according to Table 14.2.3.1.3.12 in the CSR, the efficacy was maintained in subjects without active cancer (relative risk 0.8581 (95% CI: 0.6036, 1.2201)). The results were not driven by the active cancer patients, which is reassuring. However, application of the results to the patients with active cancer is not possible, as the comparator is considered suboptimal. This is addressed in section 4.4 of the SmPC as highlighted below.

*Patients with active cancer*
*Efficacy and safety of apixaban in the treatment of DVT, treatment of PE and prevention of recurrent DVT and PE (VTEt) in patients with active cancer have not been established.*

**Results study CV185057.**

In this study, apixaban given at 2.5 mg BID or 5 mg BID for 12 months demonstrated superiority to placebo for the primary efficacy analysis (with imputations) for the endpoint of VTE/all-cause death. The event rates in the treatments groups were significantly lower than those recorded in the placebo group. The secondary endpoint analyses confirm efficacy in all predefined outcomes. The primary analysis can actually be seen as a sensitivity analysis, but efficacy was maintained in even more conservative other sensitivity analyses, underscoring that these results are very robust.

**Proposed dosing regimen**

The proposed dose for this indication is 2.5 BID. The efficacy differences between the two dose levels are not clinically relevant and it is agreed with the Applicant to choose between doses based on safety arguments.

The applicant addressed the issue of recommending more flexible dosing in the labelling, i.e a dose lower than 5 mg BID after 3 months, or higher than 2.5 mg doses after 6 months. For the initial period, available data from other anticoagulant studies show that a higher anticoagulant activity is needed to ensure effective dissolving of the thrombus/prevention of extension. This partly supports the 5 mg BID dose for the first 6 months. However, the important issue is that any newly proposed dose reduction/increase would be based on theoretical assumptions as only the currently proposed doses were investigated in studies CV185-056/57 with the shown benefit risk profile. This applies also to data pertaining to the use of 5 mg BID further than 6 months. This was not investigated, and the dose advice should be adapted to clearly indicate that this dose should be used for 6 months and not longer. A definite advice regarding possible alternative dosing in specific subgroups in the first 6 months, or later is not supported due to lack of clinical data.

The approved recommendation in the SmPC section 4.2 reads as follows:

[...]

*Treatment of DVT, treatment of PE and prevention of recurrent DVT and PE (VTEt)*
*The recommended dose of Eliquis for the treatment of acute DVT and treatment of PE is 10 mg taken orally twice daily for the first 7 days followed by 5 mg taken orally twice daily. As per available medical guidelines, short duration of treatment (at least 3 months) should be based on transient risk factors (e.g. recent surgery, trauma, immobilisation).*

*The duration of overall therapy should be individualised after careful assessment of the treatment benefit against the risk for bleeding (see section 4.4).*

**Dose adjustment in special populations (low body weight, patients above 75 years and severe renal impairment)**

Upon request from CHMP, the MAH provided clarifications regarding individual benefit/risk of continued prophylaxis depending on the characteristics of the patient. Subjects ≥75 years, subjects with (mild, moderate, severe) renal insufficiency and subjects with BMI ≤ 28 kg/m2 have an increased relative risk of bleeding events compared to placebo, according to the subgroup analyses. A summary is provided in the tables and figures below.

**Figure 1: Forest Plot for Adjudicated VTE / All-Cause Death During the Intended Treatment Period in Study CV185057 - Randomized Subjects (With Imputed Data)**

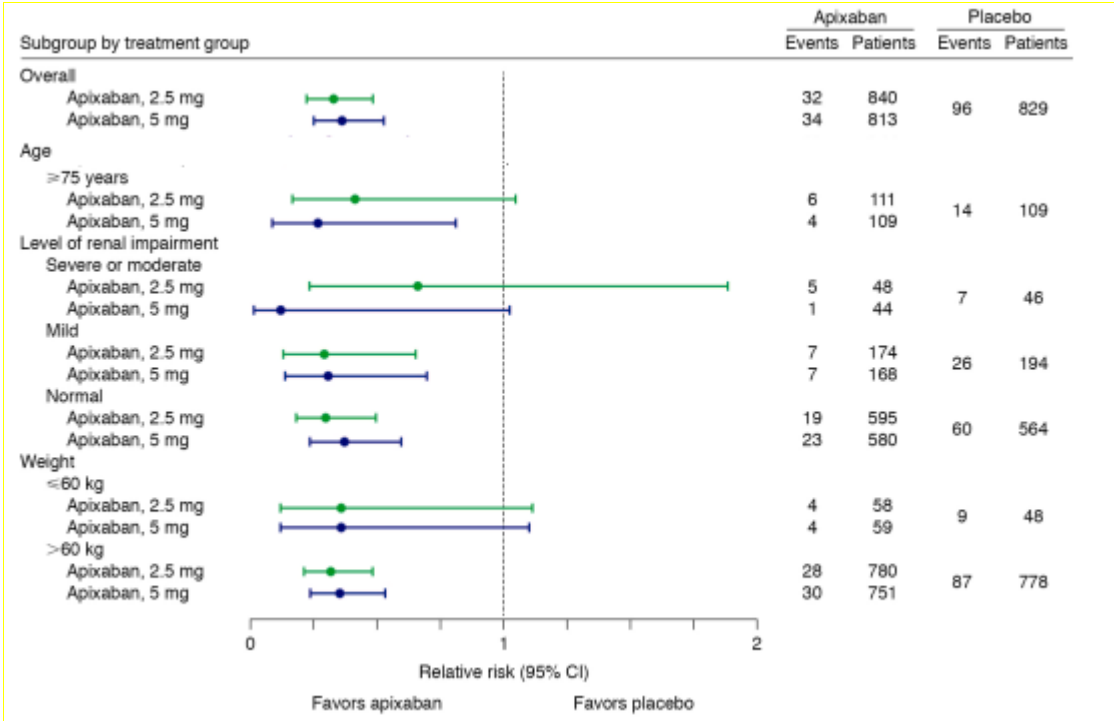



**Figure 2: Forest Plot for Adjudicated Major / Clinically Relevant Non-major Bleeding During the Treatment Period in Study CV185057 - Treated Subjects**

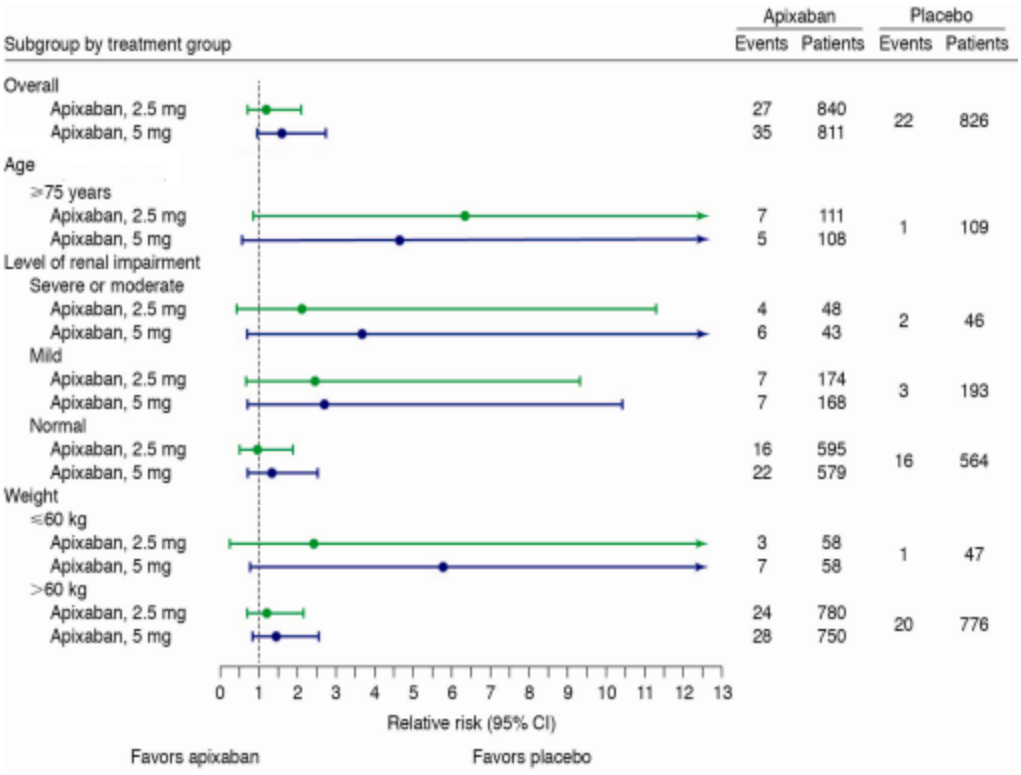


**Table 1. Data for patients with a combination of risk factors for age, weight or renal impairment vs overall population (CV185057)**

| | Patients with a combination of risk factors * | | | Overall Population (excluding patients with a combination of risk factors) | | |
|---|---|---|---|---|---|---|
| | Apixaban 2.5 mg | Apixaban 5 mg | Placebo | Apixaban 2.5 mg | Apixaban 5 mg | Placebo |
| Safety Population (N) | 5 | 11 | 13 | 835 | 800 | 813 |
| Major + CRNM Bleeding | 1 (20.0%) | 2 (18.1%) | 0 | 26 (3.1%) | 33 (4.1%) | 22 (2.7%) |
| Efficacy Population (N) | 5 | 12 | 13 | 835 | 801 | 816 |
| VTE/VTE-related Death | 0 (0.0%) | 0 (0.0%) | 2 (15.4%) | 14 (1.7%) | 14 (1.8%) | 71 (8.7%) |

*Patients with at least two of the following characteristics: age ≥ 80 years, body weight ≤ 60 kg, or serum creatinine ≥ 1.5 mg/dL (133 micromole/L)

The presented data cannot robustly conclude on a positive or negative B/R of apixaban in specific vulnerable populations like patients above 75 years, low weight (< 60 kg), moderate/severe renal impairment or the combination of these risks. This is due to the limited representation of these subgroups in the clinical trial and also the few events recorded for efficacy and safety. Importantly, a higher bleeding risk cannot be excluded, as shown in figure 2. The applicant proposed some modifications in the SmPC to warn against such bleeding risk. Further modifications were implemented to clearly inform the prescribers about the associated risks, which are considered acceptable to convey the associated risks. The finally agreed SmPC text for the different indications is presented below.

*Patients with renal impairment*

*No dose adjustment is necessary in patients with mild or moderate renal impairment (see section5.2)*

*In patients with severe renal impairment (creatinine clearance 15-29 mL/min) the following recommendations apply (see sections 4.4 and 5.2):*
*- for the prevention of VTE in elective hip or knee replacement surgery (VTEp), for the treatment of DVT, treatment of PE and prevention of recurrent DVT and PE (VTEt) apixaban is to be used with caution;*

*- for the prevention of stroke and systemic embolism in patients with NVAF, patients should receive the lower dose of apixaban 2.5 mg twice daily.*
*Patients with serum creatinine ≥ 1.5 mg/dL (133 micromole/L) associated with age ≥ 80 years or body weight ≤ 60 kg should also receive the lower dose of apixaban 2.5 mg twice daily.*

*In patients with creatinine clearance < 15 mL/min, or in patients undergoing dialysis, there is no clinical experience therefore apixaban is not recommended (see sections 4.4 and 5.2).*

*Body weight*
*VTEp and VTEt - No dose adjustment required (see section 4.4 and 5.2).*
*NVAF - No dose adjustment required, unless criteria for dose reduction are met (see Dose reduction at the beginning of section 4.2).*

**Presentation of data in the SmPC section 5.1**

The Applicant proposes to present non-imputed data in section 5.1 of the SmPC. The percentage of missing data is 2.1% and is of the same magnitude as the number of events in the apixaban study arms, but relatively small compared to the placebo groups. Therefore, the question of whether or not to report imputed data does have some impact on the presentation of the results. As per the SmPC guideline 2009, the primary analysis should be included in the SmPC, in this case the imputed data. However, it can be agreed with the applicant that such analysis is very conservative, and the non-

imputed data could form the basis of the primary analysis. It is also more informative to inform the prescriber with the actual data. In conclusion, the argumentation of the Applicant is agreed and the inclusion of non-imputed data from CV185057 in section 5.1 of the SmPC is acceptable. To avoid confusion, there is no need to also include the imputed data, which are considered of little relevance to the prescriber. This decision is also in line with the approved SmPC for other new oral anticoagulants, where no imputed data are discussed.

### 2.4.4. Conclusions on the clinical efficacy

The efficacy of apixaban in VTE, for both treatment and recurrence prevention is robustly supported by the results of the submitted clinical trials.

## *2.5. Clinical safety*

The main safety consideration for all antithrombotic agents is bleeding. There is little evidence that FXa inhibitors are associated with off-target class effects. Safety information is available for more than 60,000 treated subjects in the apixaban clinical development program who were administered apixaban or comparators from 16 completed or on-going Phase 2/3 studies across a number of indications. Apixaban has been approved for the prevention of VTE following surgery for knee and hip replacement and for reducing the risk of stroke and systemic embolism in patients with non-valvular AF, indications which imply long-term usage. The safety discussion is an extension of the data that have emerged from the experience with apixaban in these other indications.

Adjudicated **bleeding events** were the primary safety focus in the VTE treatment Phase 2 and 3 studies. Methods for collection and reporting of AEs were similar for all studies, as was oversight by an independent, unblinded DSMB. Bleeding events, thrombocytopenia, MI, stroke, and cause of death were adjudicated in a blinded manner by the same ICAC responsible for adjudication of efficacy events. In studies CV185056 and CV185057, all-cause death was a secondary efficacy endpoint for the efficacy populations and is presented in the efficacy analyses. Death was also a safety endpoint in the treated population.

Certain key safety events were prospectively identified as being of special clinical interest based on prior experience with apixaban in the clinical program and the experience of drugs in the same therapeutic class. These events included MI, non-haemorrhagic stroke, thrombocytopenia, AEs related to elevated liver function tests (LFTs), and neurologic AEs of interest.

To assess **neurological safety**, the Sponsors developed a customized, broad list of neurologic MedDRA preferred terms (PTs) to facilitate identification of potential cases of concern.

Intensive surveillance of **hepatic safety** in the apixaban VTE treatment clinical program was conducted. This enhanced surveillance program resulted in a comprehensive clinical safety database encompassing both clinical laboratory test results and liver-related AEs. Cases meeting pre-specified criteria were sent to a panel of independent hepatologists for assessment in a blinded manner.

**MI and non-hemorrhagic stroke** were examined for evidence of an increased frequency during treatment or during the first 30 days of discontinuing study drug.

#### *Patient exposure*

Data for the phase 2 and two pivotal phase 3 trials in this application were not pooled, because of important differences in design of the two trials (duration and comparator). The exposure data are shown in Table S1a and b. According to tables not shown here (SCS table 8 and table 9), exposure for

24 to <26 weeks in CV185056 was 1630 patients for apixaban and 1572 patients for active comparator. The median exposure in CV185057 was 360 days in both treatment groups, implying that more than 400 patients in each group were exposed for at least one year.

**Table S1a. Exposure in Days in Studies CV185017, CV185056, and CV185057 - Treated Subjects**

| | Apixaban | | | | | | |
|---|---|---|---|---|---|---|---|
| | 2.5 mg BID | 5 mg BID | 10 mg BID | 20 mg QD | Enoxaparin/ warfarin | LMWH/ VKA | Placebo |
| **CV185017 (N)** | -- | **128** | **133** | **124** | -- | **126** | -- |
| Mean, days (SD) | -- | 81 (21.0) | 82 (19.9) | 77 (25.4) | -- | 82 (18.9) | -- |
| **CV185056 (N)** | -- | **2676** | **-a-** | -- | **2689** | -- | -- |
| Mean, days (SD) | -- | 154.2(43.63) | -- | -- | 152.2 (47.22) | -- | -- |
| **CV185057 (N)** | **840** | **811** | -- | -- | -- | -- | **826** |
| Mean, days (SD) | 332.2 (84.35) | 328.4 (87.86) | -- | -- | -- | -- | 311.7(103.9) |
| **Total (N)** | **840** | **3615** | **133** | **124** | **2689** | **126** | **826** |

a. The number of subjects receiving 10 mg BID for the first 7 days in study CV185056 are captured in the 5 mg BID treatment group.

**Table S1b. Overview of Exposure in Apixaban VTE Treatment Studies**

| | Patients enrolled | Patients exposed to apixaban | Patients exposed to the proposed dose | | | Patients with long-term safety data[c] |
|---|---|---|---|---|---|---|
| | | | Apixaban 2.5 mg BID | Apixaban 5 mg BID | Apixaban 10mg BID for 7 days followed by 5mg BID | |
| **Placebo-controlled** | | | | | | |
| CV185057 | 2711 | 1651 | 840 | 811 | 0 | 1410 |
| **Active-controlled** | | | | | | |
| CV185056 | 5614 | 2676 | 0 | 0 | 2676 | 0 |
| **Open studies** | | | | | | |
| CV185160[a,b] | N/A | 13 | 0 | 0 | 13 | 0 |
| CV185017 | 524 | 385 | 0 | 128 | 0 | 0 |
| **Post-marketing:** None | | | | | | |
| **Compassionate use:** None | | | | | | |

Sources: Table 14.1.1.2.1 and Table 14.1.1.2.2 CV185056 CSR; Table 14.1.1.2.1 and Table 14.1.1.2.2 CV185057 CSR; Table 1, Appendix 8 VTE treatment SCS, Table S.2.2A and Table S.3.1 CV185017 CSR.
a. As of 17 May 2013.
b. Study conducted with Japanese subjects.
c. Subjects who completed 12 months of study treatment.

***Adverse events***

No new safety concerns were noted in the AE analyses.

In CV185056, the only PTs reported in >5% of subjects were Headache (6.3% apixaban; 6.2% enoxaparin/warfarin) and epistaxis (2.9% apixaban; 5.4% enoxaparin/warfarin). Results were generally consistent across the DVT and PE strata (table S2).

**Table S2. Number (%) of Subjects with MedDRA PTs Reported in >5% of Subjects in any Treatment Group with Onset During the Treatment Period in Study CV185056 – Treated Subjects**

| MedDRA PT | Apixaban N=2676 | Enoxaparin/warfarin N=2689 |
|---|---|---|
| Epistaxis | 77 (2.9) | 146 (5.4) |
| Headache | 169 (6.3) | 168 (6.2) |

Source SCS Table 16

In CV185057, PTs reported in >5% in any treatment group with onset during the treatment period are shown in Table S3. Results were generally consistent across the DVT and PE strata.

**Table S3. Number (%) of Subjects with MedDRA PTs Reported in >5% of Subjects in any Treatment Group with Onset During the Treatment Period in Study CV185057 – Treated Subjects**

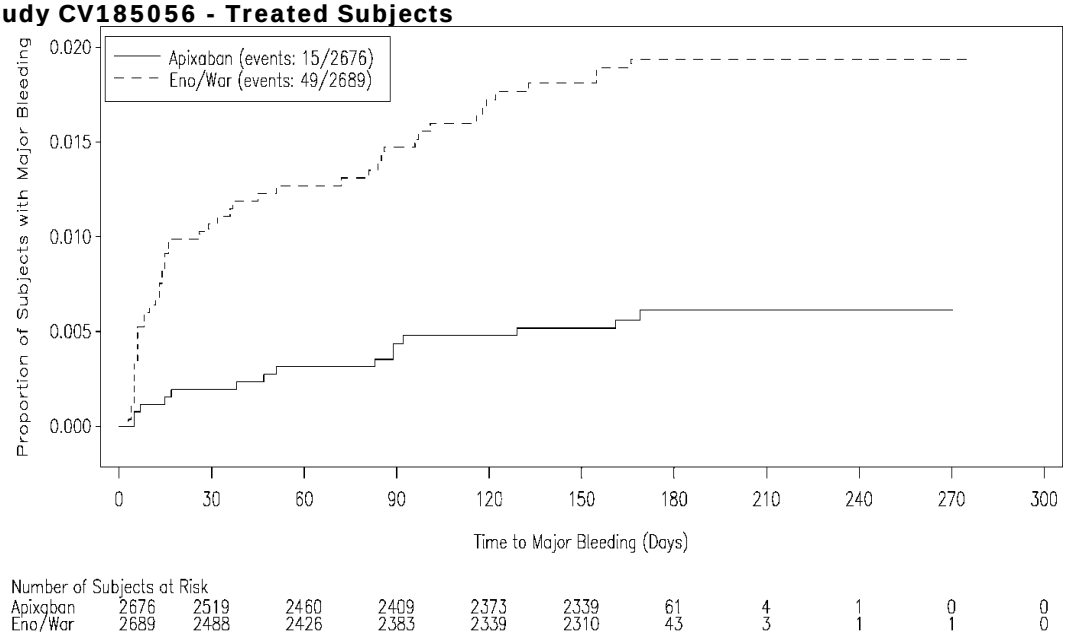
| MedDRA PT | Apixaban 2.5 mg BID N=840 | Apixaban 5 mg BID N=811 | Placebo N=826 |
|---|---|---|---|
| Deep vein thrombosis | 15 (1.8) | 17 (2.1) | 61 (7.4) |
| Pain in extremity | 43 (5.1) | 52 (6.4) | 54 (6.5) |
| Back pain | 27 (3.2) | 45 (5.5) | 24 (2.9) |
| Headache | 44 (5.2) | 42 (5.2) | 42 (5.1) |

Source: SCS Table 4.13.1.2

**Bleeding in study CV185056**

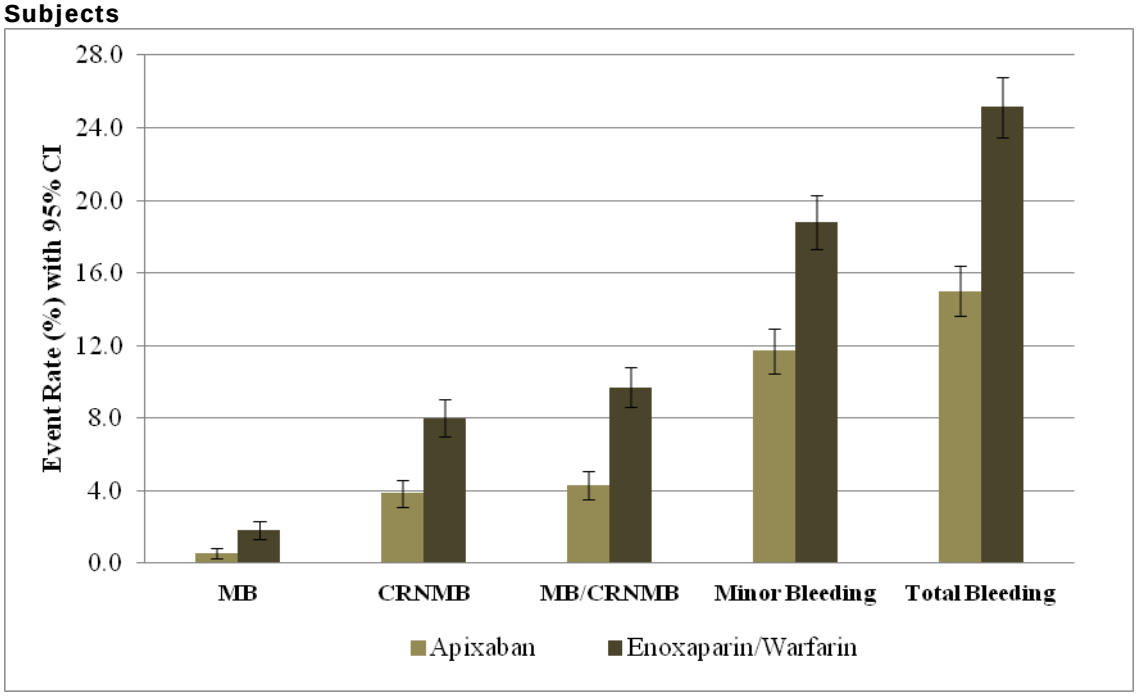
In direct comparison to enoxaparin/warfarin, apixaban was numerically and statistically significantly superior with respect to bleedings. Major bleedings (MB) were included in the hierarchical testing for the primary efficacy endpoint. A 69% reduction in adjudicated MB (p-value for superiority < 0.0001) was demonstrated for apixaban treatment compared with enoxaparin/warfarin (Figure S1). Statistically significantly decreased bleeding frequency based on nominal p-values in the adjudicated clinically relevant non-major bleeding (CRNMB), MB/CRNMB, minor bleeding, and total bleeding was observed for apixaban compared with enoxaparin/warfarin. The Kaplan-Meijer curves for bleeding (Figure S1) separate early, visualizing that the superior bleeding profile of apixaban compared to enoxaparin/warfarin is also clinically relevant for the 3-months treatment indication that is sought but not investigated in a separate trial.

**Figure S1. Kaplan-Meier Plot for Adjudicated Major Bleeding During the Treatment Period in Study CV185056 - Treated Subjects**




Eno=enoxaparin, War=warfarin,

**Figure S2. Summary of Adjudicated Bleeding Endpoints in Study CV185056 - Treated Subjects**




MB=major bleeding, CRNMB=clinically relevant non-major bleeding, CI=confidence interval, CSR=clinical study report.

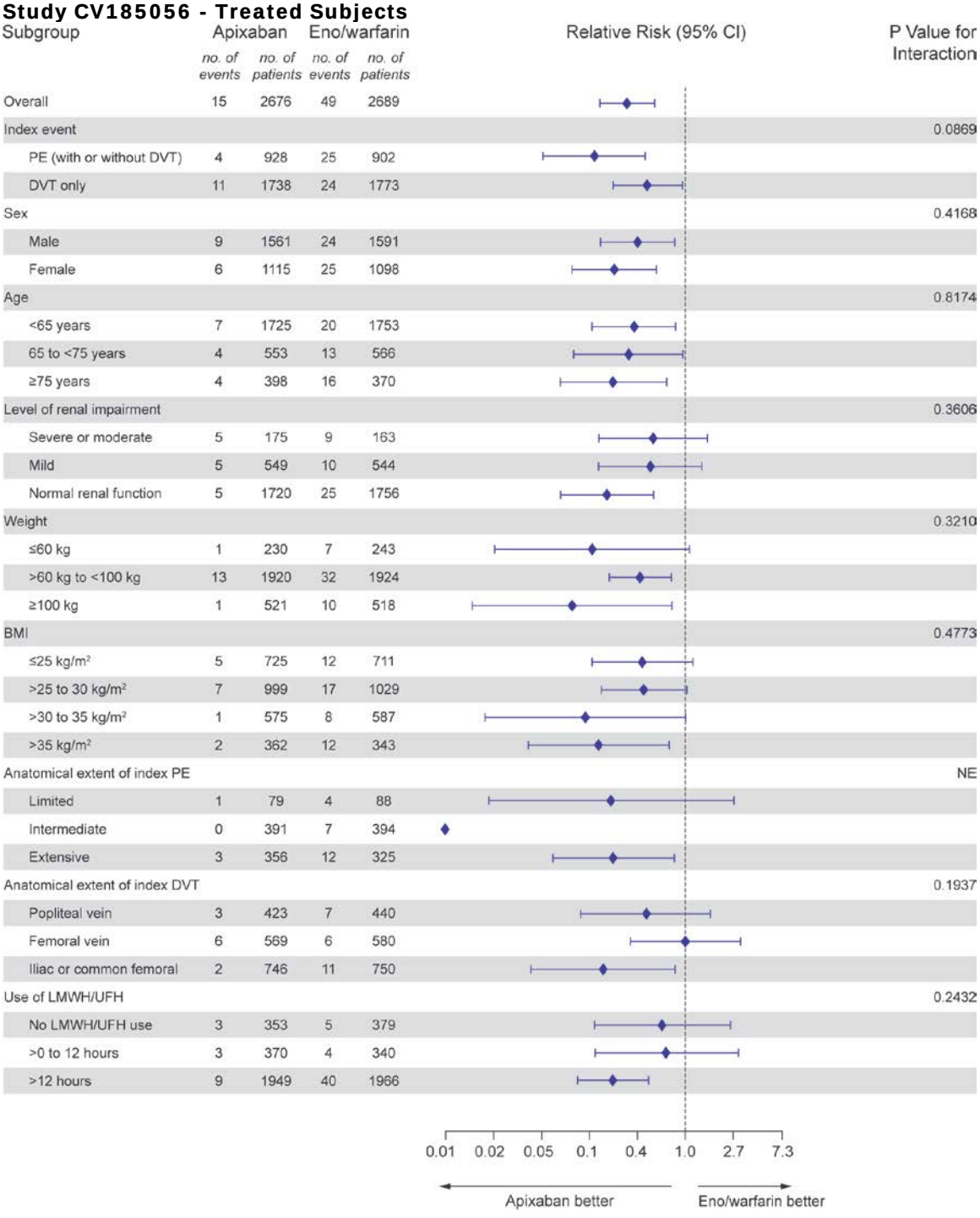
A similar distribution of bleeding events among the anatomical sites was noted for the apixaban and enoxaparin/warfarin groups. The frequencies of adjudicated MB at any anatomical site, including gastrointestinal (GI) tract (defined as GI plus rectal), was the same or lower in the apixaban group compared to the enoxaparin/warfarin group (gastrointestinal MB: apixaban 8 (0.3%) enoxaparin/warfarin 20 (0.7%)]. The frequencies of adjudicated CRNMB and minor bleeding at all

anatomical sites (including Gastrointestinal: CRNMB + minor: apixaban 59 (2.2%) enoxaparin/warfarin 81 (3.0%)]) were similar or lower in the apixaban group compared to the enoxaparin/warfarin group with the exception of minor bleeding in the uterus (24 apixaban, 15 enoxaparin/warfarin).

Based on the centre-based analysis based on TTR quartile, a reduced risk of MB was demonstrated for apixaban relative to enoxaparin/warfarin regardless of TTR quartiles. The advantage in bleedings was also similar across all TTR ranges.

The advantage in bleedings was similar across the subgroups tested (Figure S3), confirming the robustness of this finding. No treatment by subgroup interaction was statistically significant.

**Figure S3. Forest Plot for Adjudicated Major Bleeding During the Treatment Period in Study CV185056 - Treated Subjects**



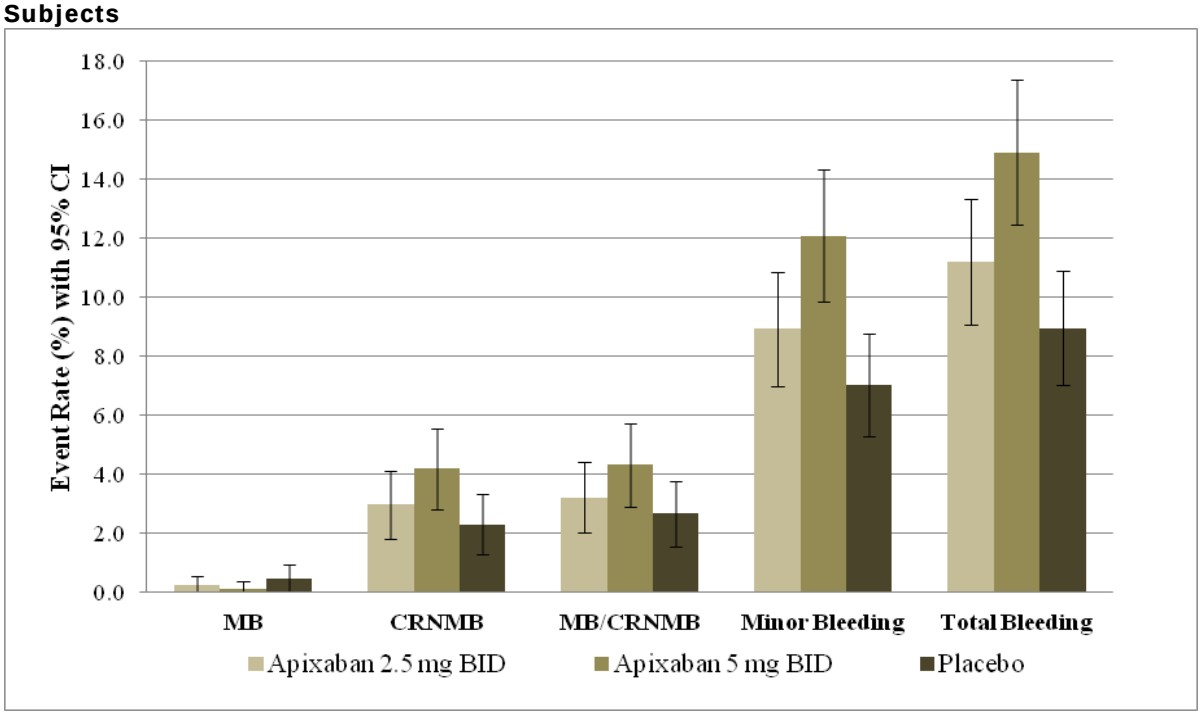

BMI=body mass index; CI=confidence interval; DVT=deep vein thrombosis; Eno=enoxaparin; LMWH=low molecular weight heparin; PE=pulmonary embolism; UFH=unfractionated heparin, NE=not estimable, no.=number, SCS=summary of clinical safety.

**Bleeding in study CV185057**

Figure S4 summarizes all adjudicated bleeding endpoints in study CV185057. No fatal bleeding events occurred in any treatment group.

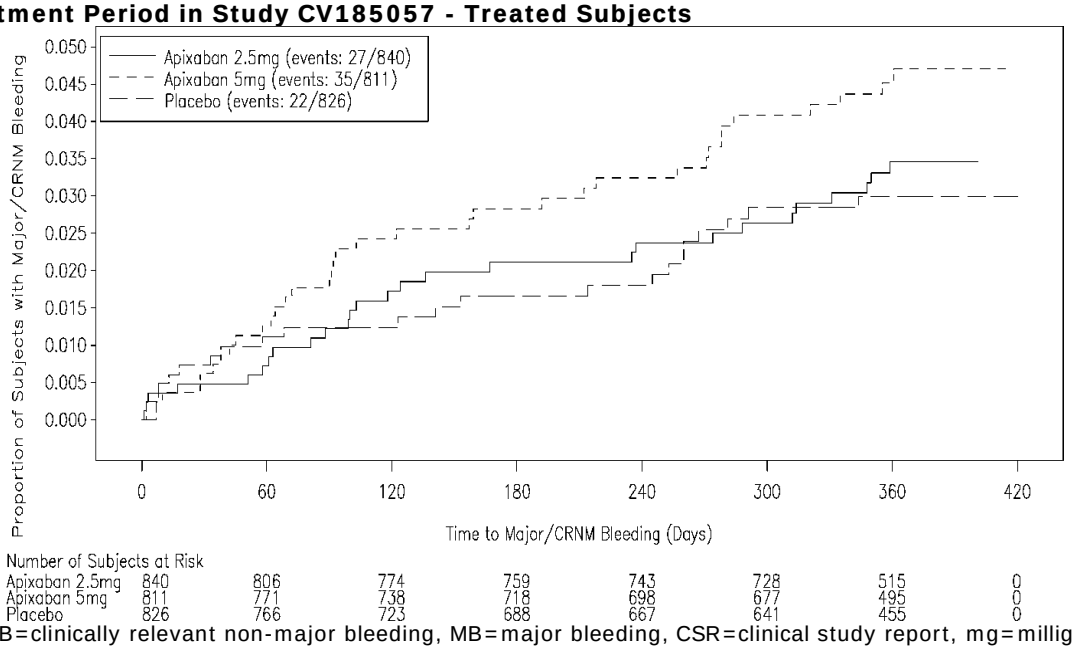
Compared to placebo, the adjudicated bleeding endpoints for apixaban 2.5 mg BID were numerically higher (but not significantly different) from placebo. For apixaban 5 mg BID, the frequency of MB/CRNMB in the apixaban 5 mg BID group was not significantly different from the placebo group, whereas the frequency of CRNMB, minor bleeding, and total bleeding was higher than the placebo group, suggesting a higher risk of non-major bleeding in the apixaban 5 mg BID group compared to placebo. A Kaplan-Meier plot for MB/CRNMB is provided in Figure S5. As could be expected, the risk of bleeding was dose dependant in CV185057. For 'total bleeding', the relative risks between the apixaban 2.5 and 5 mg and placebo were 1.25 and 1.66 respectively; corresponding to absolute risk differences of 2.0 and 5.3% respectively. However, for the much more relevant MB/CRNMB the absolute differences were 0.5 and 1.5% respectively.

**Figure S4. Summary of Adjudicated Safety Endpoints in Study CV185057 - Treated Subjects**




MB=major bleeding, CRNMB=clinically relevant non-major bleeding, CI=confidence interval, CSR=clinical study report, BID=twice daily

**Figure S5. Kaplan-Meier Plot for Composite of Adjudicated MB or CRNMB During the Treatment Period in Study CV185057 - Treated Subjects**




Number of Subjects at Risk

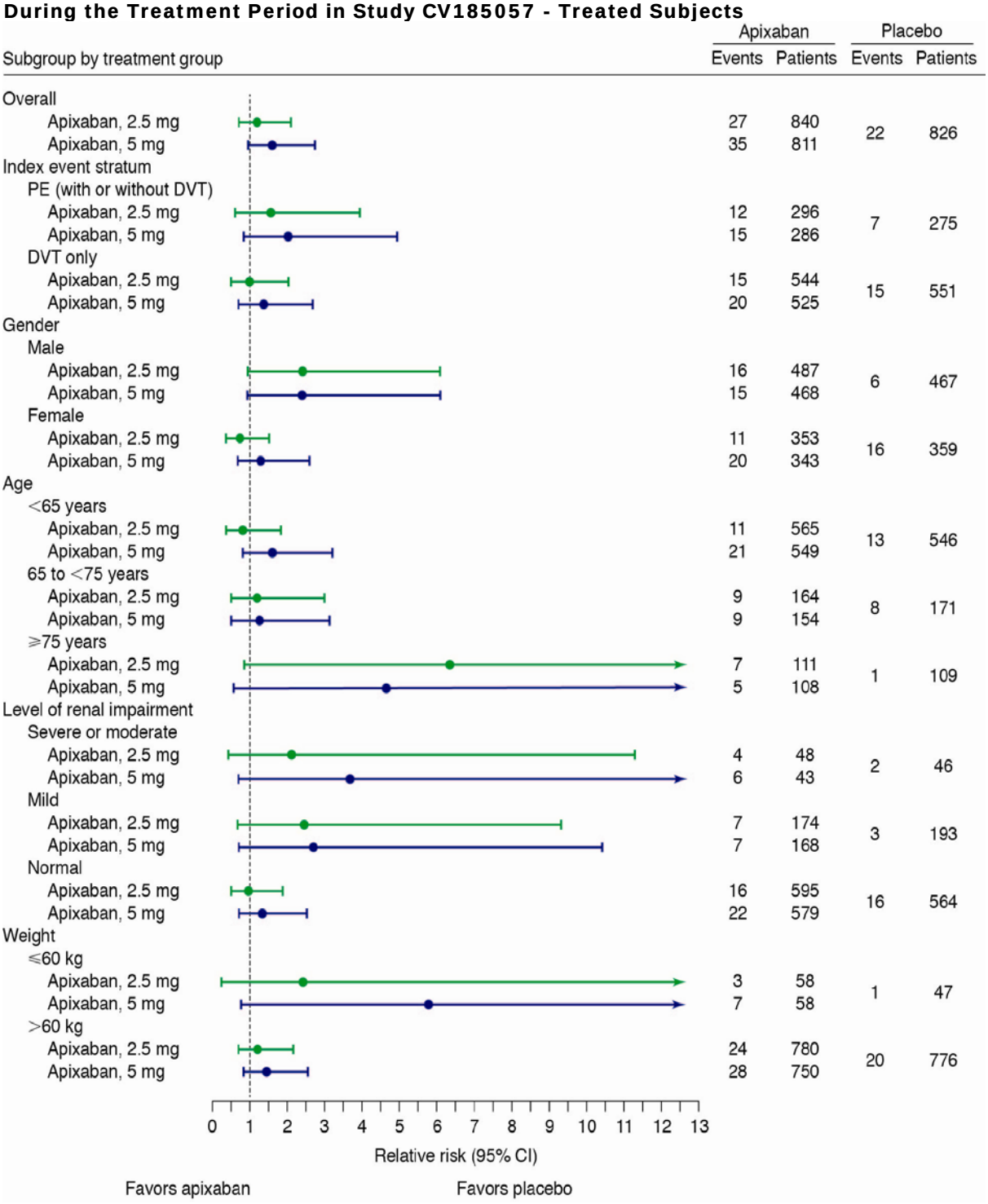
| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Apixaban 2.5mg | 840 | 806 | 774 | 759 | 743 | 728 | 515 | 0 |
| Apixaban 5mg | 811 | 771 | 738 | 718 | 698 | 677 | 495 | 0 |
| Placebo | 826 | 766 | 723 | 688 | 667 | 641 | 455 | 0 |

CRNMB=clinically relevant non-major bleeding, MB=major bleeding, CSR=clinical study report, mg=milligram.

The locations of the small number of MB were: apixaban 2.5 mg BID group (2 intraocular), apixaban 5 mg BID group (1 GI), and placebo group (1 each urogenital, GI, intraocular, and intracranial). Overall a similar distribution of bleeding events among the anatomical sites was noted for the apixaban 2.5 mg BID, apixaban 5 mg BID, and placebo groups.

Figure S6 shows that the RR for MB/CRNMB for all subgroups are generally consistent with the study population as a whole. None of the interaction values were statistically significant.

**Figure S6. Forest Plot for Adjudicated Major/Clinically Relevant Non-major Bleeding During the Treatment Period in Study CV185057 - Treated Subjects**




**Rebound**

The Applicant has searched for evidence of rebound phenomena after study drug discontinuation, as shown in the following tables:

**Number of Subjects with an Adjudicated Endpoint of Interest in the 3-9 Days following Study Drug Discontinuation in Study CV185057 - Treated Subjects**

| | 3-9 Days after Discontinuing[b] | | |
|---|---|---|---|
| | Apixaban | | |
| | 2.5 mg BID N=840 | 5 mg BID N=811 | Placebo N=826 |
| Non-fatal VTE/MI/ischemic stroke | 1 | 0 | 1 |
| Non-fatal DVT | 1 | 0 | 0 |
| Non-fatal PE | 0 | 0 | 1 |
| MI | 0 | 0 | 0 |
| Ischemic stroke | 0 | 0 | 0 |
| All-cause death | 0 | 2 | 0 |
| CV-related death[a] | 0 | 2 | 0 |
| VTE-related death | 0 | 2 | 0 |
| **Total of non-fatal VTE, MI, ischemic stroke, and all cause death** | **1** | **2** | **1** |

Source: Apixaban VTE treatment Clinical Overview in-text Table 19.
N=number of subjects in group, PE=pulmonary embolism, DVT=deep vein thrombosis, MI=myocardial infarction, CV=cardiovascular, VTE= venous thromboembolism, BID=twice daily.
a. Includes VTE-related deaths.
b. The 3-9 day period was considered an appropriate period following discontinuation during which time any rebound effects of anticoagulant withdrawal would occur.

**Number of Subjects with an Adjudicated Endpoint of Interest in the 3-30 Days following Study Drug Discontinuation in Study CV185057 - Treated Subjects**

| | 3-30 Days after Discontinuing | | |
|---|---|---|---|
| | Apixaban | | |
| | 2.5 mg BID N=840 | 5 mg BID N=811 | Placebo N=826 |
| Non-fatal VTE/MI/ischemic stroke | 8 | 5 | 1 |
| Non-fatal DVT | 4 | 2 | 0 |
| Non-fatal PE | 3 | 2 | 1 |
| MI | 0 | 0 | 0 |
| Ischemic stroke | 1 | 1 | 0 |
| All-cause death | 2 | 3 | 1 |
| CV-related death[a] | 0 | 2 | 1 |
| VTE-related death | 0 | 2 | 1 |
| **Total of non-fatal VTE, MI, ischemic stroke, and all cause death** | **10** | **8** | **2** |

Source: Apixaban VTE treatment Clinical Overview in-text Table 19, apixaban VTE treatment Summary of Clinical Safety in-text Table 55.
N=number of subjects in group, PE=pulmonary embolism, DVT=deep vein thrombosis, MI=myocardial infarction, CV=cardiovascular, VTE= venous thromboembolism, BID=twice daily.
a. Includes VTE-related deaths.

In this respect, no differences were found in comparison to enoxaparin/warfarin.

**Myocardial Infarction**

The numbers of subjects with myocardial infarction in the phase 3 studies were too small to allow any conclusion. These numbers are summarised in Table S4.

**Table S4. Adjudicated myocardial infarctions in VTE phase 3 trials**

| | n | events | event rate | relative risk |
|---|---|---|---|---|
| **cv185056** | | | | |

| | | | | |
|---|---|---|---|---|
| **treatment period** | | | | |
| apixaban | 2676 | 4 | 0,0015 | 2,0179 |
| enoxaparin/warfarin | 2689 | 2 | 0,0007 | |
| **Follow-up period** | | | | |
| apixaban | 2604 | 2 | 0,0008 | 1,0161 |
| enoxaparin/warfarin | 2634 | 2 | 0,0008 | |
| **cv185057** | | | | |
| **treatment period** | | | | |
| apixaban 2.5 | 840 | 2 | 0,0024 | 0,4850 |
| apixaban 5 | 841 | 3 | 0,0036 | 0,7699 |
| placebo | 826 | 4 | 0,0048 | |
| **Follow-up period** | | | | |
| apixaban 2.5 | 836 | 0 | 0,0000 | n/a |
| apixaban 5 | 805 | 0 | 0,0000 | n/a |
| placebo | 808 | 0 | 0,0000 | |

Three cases of deaths related to acute MI were recorded in study **cv185056 (see AR for more details)**. These are offset by 1 versus 2 cases of myocardial infarction (not coded as acute). The total for cardiac disorders was 10 vs. 7. Of the three cases, the circumstances of case 166-1440 are only poorly documented as the family refused to share all information with the investigator. The death certificate noted 'cardiogenic shock'. The second case (207-2239) occurred on Day 7 of apixaban treatment and was associated with rectal bleeding and pulmonary embolism at the same moment. The third case (712-1723) occurred 11 days after completion of the planned 6-months treatment. The patients also suffered from type-2 diabetes.

**Liver safety**

Based on the experience with ximelagatran, the Applicant has implemented an extensive system for evaluation of potential liver toxicity. Liver safety in the VTE treatment clinical program includes pooled analyses of liver enzymes and liver-related AEs.

Overall, most LFT elevations were asymptomatic and without clinical sequelae. SAEs related to LFT elevations with onset during the treatment period were reported for 13 (0.3%) subjects in the apixaban group and 17 (0.5%) subjects in the comparator group (Table 4.12.3.2, SCS tables). The only SAEs reported in at least 2 subjects in either treatment group were hepatic function abnormal (apixaban: 2 subjects), liver function test abnormal (apixaban: 2 subjects), drug-induced liver injury (apixaban: 2 subjects), hepatic failure (comparator: 2 subjects), and hepatitis (comparator: 2 subjects).

A panel of independent hepatologists provided blinded assessments of subjects with concurrent elevations of ALT > 3 x ULN and total bilirubin > 2 x ULN and/or pre-selected SAEs (jaundice, hepatitis, and hepatic failure). Two SAEs in Study CV185057 with onset during the treatment period were assessed as possibly related to apixaban treatment by the panel of independent hepatologists.

In Study CV185056, one non-serious AE of concurrent elevations of ALT >3 x ULN and total bilirubin >2 x ULN reported in a 60-year-old female subject with a history of cholelithiasis who received apixaban 5 mg BID, was considered to be probably related to apixaban treatment by the panel of independent hepatologists.

Most drugs that are associated with drug induced liver injury (DILI) are also associated with an increased frequency of asymptomatic elevation of ALT > 3 x ULN. In the Phase 3 VTE treatment studies, the frequency of ALT > 3 x ULN elevations was lower in the apixaban group compared with the comparator group. In Study CV185017, the frequency of ALT elevations > 3 x, 5 x, or 10 x ULN was similar in the apixaban and comparator (placebo) group, suggesting no increased risk of ALT elevation due to apixaban. There were few outliers (peak ALT > 3xULN, peak Bili > ULN), in both the apixaban and comparator treatment groups (4 subjects in each group).

Among the 212 (5.1%) subjects in the apixaban group and 339 (10.1%) subjects in the comparator group with AEs related to LFT elevations, 9 (0.2%) subjects in the apixaban group and 19 (0.6%) subjects in the comparator group discontinued treatment because of the AE.

Liver toxicity is addressed in the RMP. “Transient elevation of liver enzymes” should be included as an important identified risk for the VTEp indication, based on the findings of the increase in liver enzyme values in the pivotal clinical studies. “Liver injury” is currently included as an important potential risk for the other indications of apixaban (except VTEp) which is based on cases from the clinical trial program reporting liver injury. For these cases a relationship to the study medication could not definitively be excluded, which means that “liver injury” should be classified as an important potential risk. However, the Rapporteur is of the opinion that this should be applied to all indications, and therefore “liver injury” should be added as an important potential risk to the VTEp indication as well.

**Neurologic events of interest**

One case of post treatment Amyotrophic Lateral Sclerosis (ALS) and 1 case of Guillain Barre Syndrome (GBS) were reported in subjects who received apixaban in the VTE treatment studies. In both cases the neurology consultants judged the event as not likely related to apixaban.

One case of ALS was reported post treatment in Subject CV185057-136-308 who prematurely discontinued study medication in the apixaban 2.5 mg treatment group in Study CV185057. The neurologist consultants concluded that the subject’s ALS symptoms were present prior to study onset, and the relationship to blinded study drug (apixaban) was assessed as not likely.

The narrative of the potential case of GBS is provided in the AR. The investigator judged the event to be possibly related to study drug. The neurologist consultants considered the relationship to blinded study drug (apixaban) as not likely related.

Review of the pooled database across all apixaban studies, identified a very low incidence of neurologic AEs of special interest. (17 of more than 57,000 subjects in apixaban or comparator arms) observed in 15 completed, concluded, and ongoing studies across multiple indications (Appendix 13.7, VTEp SCS):

- GBS n = 6 (apixaban 3, comparator 3)
- ALS n = 3 (apixaban 2, comparator 1)
- Other acute polyneuropathies n = 8 (apixaban 2, comparator 6)

Review of these cases identified the frequencies of the events to be similar in the apixaban and comparator groups, with no features suggesting a causative role of apixaban.

Based on the total frequency of GBS, ALS and other acute polyneuropathies, no increase of risk can be concluded.

**Rebound effect in study CV185057 during the 30-day period post treatment.**

Upon request from the CHMP, the MAH has provided the information having reanalysed the data for any rebound effect. The reanalysis does not suggest a clear rebound phenomenon especially for occurrence of MI or stroke although there is a trend for VTE events.
The applicant has argued that withdrawal effect is a recognised phenomenon with factor Xa inhibitors and cited another example.
While there is some similarity between different drugs in the same class, it is still of some concern that remains a risk.
It would have been useful for the applicant to have evaluated the specifics of the risk in those with recurrent events in comparison to those with no such events to discern potential differences and this should be for further follow up through the PSURs.

***Serious adverse event / deaths / other significant events***

**Deaths**

A summary of the deaths that occurred during the intended treatment period and in the follow-up period for Study **CV185056** is provided in Table S5. Event rates for the adjudicated efficacy endpoint of all-cause death were similar for both treatment groups. A similar proportion of subjects experienced an SAE with an outcome of death during the treatment period in the apixaban (1.4%) and enoxaparin/warfarin (1.6%) treatment groups. A Summary of SAEs with an outcome of death that occurred during the treatment period in CV185056 is presented in Table S6. Among the SAEs with outcome of death in CV185056, 3 cases of acute myocardial infarction are noted and none in the comparator group (Table S5). These are discussed before.

**Table S5. Summary of deaths that occurred during the intended treatment period and in the follow-up period in Study CV185056**

| | **Apixaban** | **Enoxaparin / Warfarin** |
|---|---|---|
| **Total number of deaths** | **53** | **60** |
| Deaths during intended treatment period (Day 168 or last drug + 2 days) | 41 | 52 |
| Deaths in the 30 days following the intended treatment period (Day 170 through Day 199) | 7 | 6 |
| Deaths > 30 days after intended treatment period (after Day 200) | 5 | 2 |

2 subjects died during the screening period in Study CV185056; Subject CV185056-579-4629 and Subject CV185056- 729-2909 (Table 16.2.1.1 and Table 16.2.6.3.12, CV185056 CSR).

**Table S6. Summary of Serious Adverse Events With Outcome of Death During the Treatment Period - Treated Subjects, Study CV185056**

| **System Organ Class**<br>**Preferred Term** | **Apixaban**<br>**N=2676**<br>n (%) | **Enoxaparin / Warfarin**<br>**N=2689**<br>n (%) |
|---|---|---|
| **Total subjects with an event** | **37 (1.4)** | **44 (1.6)** |
| Cardiac disorders [1] | 10 (0.4) | 7 (0.3) |
| General disorders and administration site conditions | 8 (0.3) | 4 (0.1) |
| Infections and infestations | 8 (0.3) | 6 (0.2) |
| Respiratory, thoracic and mediastinal disorders | 8 (0.3) | 10 (0.4) |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | 5 (0.2) | 12 (0.4) |
| Vascular disorders | 1 (<0.1) | 2 (<0.1) |
| Blood and lymphatic system disorders | 0 | 2 (<0.1) |
| Gastrointestinal disorders | 0 | 4 (<0.1) |

| System Organ Class<br>Preferred Term | Apixaban<br><br>N=2676 | Enoxaparin/<br>Warfarin<br>N=2689 |
|---|---|---|
| Hepatobiliary disorders | 0 | 2 (<0.1) |

[1] Acute myocardial infarction: 3 (0.1%) v 0

A summary of the deaths that occurred during the intended treatment period and in the follow-up period for Study **CV185057** is provided in Table S7, which shows a summary of Serious Adverse events with outcome of death during the treatment period among treated subjects in Study CV185057.

**Table S7. Summary of deaths that occurred during the intended treatment period and in the follow-up period in Study CV185057**

| | Apixaban 2.5 mg BID | Apixaban 5 mg BID | Placebo |
|---|---|---|---|
| **Total number of deaths** | **9** | **7** | **16** |
| Deaths during intended treatment period (Day 363 or last drug + 2 days) | 7 | 4 | 14 |
| Deaths in the 30 days following the intended treatment period (Day 365 through Day 394) | 1 | 3 | 2 |
| Deaths > 30 days after intended treatment period (after Day 395) | 1 | 0 | 0 |

Source: Table 16.2.6.1, CV185057 CSR.
No subjects died during the screening period in Study CV185057 (Table 16.2.1.1 and Table 16.2.6.3.12, CV185057 CSR).

**Table S8. Summary of Serious Adverse Events With Outcome of Death During the Treatment Period - Treated Subjects, Study CV185057**

| System Organ Class<br>Preferred Term | Apixaban 2.5 mg BID (N=840), n (%) | Apixaban 5 mg BID (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) |
| General disorders and administration site conditions | 1 (0.1) | 2 (0.2) | 5 (0.6) |
| Respiratory, thoracic and mediastinal disorders | 0 | 0 | 2 (0.2) |
| Renal and urinary disorders | 1 (0.1) | 0 | 0 |

**Serious Adverse Events**

The overall frequency of SAEs with onset during the treatment period was similar in the apixaban and comparator treatment groups in studies CV185017 and CV185056. There was a higher rate of SAEs in the placebo group (19.1%) compared to both apixaban treatment groups (13.3% and 13.2% in the apixaban 2.5 mg and apixaban 5 mg treatment groups, respectively) in Study CV185057.

DVT and PE were among the most frequently reported SAEs in studies CV185056 and CV185057. There was a higher rate of these SAEs in the comparator groups compared with the apixaban groups in both studies. These SAEs were also included in the efficacy analyses.

The frequency of treatment-related SAEs in the VTE treatment studies was low with a large proportion only being reported in 1 subject. The proportion of subjects who experienced a treatment related SAE in studies CV185056 and CV185057 was higher in the comparator groups compared with the apixaban groups.

A summary of the most frequently reported (>1%) SAEs reported in the Phase 3 efficacy and safety study, **CV185056**, with onset during the treatment period is presented in Table S9. Similar proportions of subjects in the apixaban (15.6%) and enoxaparin/warfarin (15.2%) treatment groups experienced an SAE with onset during the treatment period. No SAEs were reported in >1% of subjects in the apixaban treatment group, and PE and DVT were the only events reported in >1% of subjects in the enoxaparin/warfarin treatment group (1.4% and 1.2%, respectively). Review of SAEs by index event strata did not reveal any difference between treatment groups.

**Table S9. Summary of Serious Adverse Events (>1% in Any Treatment Group) Reported in Subjects With Onset During the Treatment Period - Treated Subjects, Study CV185056**

| **System Organ Class**<br>**Preferred Term** | **Apixaban**<br>**(N = 2676)**<br>**n (%)** | **Enoxaparin/ Warfarin**<br>**(N = 2689)**<br>**n (%)** |
|---|---|---|
| **Total subjects with an event** | 417 (15.6) | 410 (15.2) |
| **Respiratory, thoracic and mediastinal disorders** | **65 (2.4)** | **73 (2.7)** |
| Pulmonary embolism | 24 (0.9) | 38 (1.4) |
| **Vascular disorders** | **43 (1.6)** | **55 (2.0)** |
| Deep vein thrombosis | 20 (0.7) | 33 (1.2) |

The proportion of subjects who experienced an SAE considered related to treatment by the investigator was lower in the apixaban treatment group (1.8%) compared with the enoxaparin/warfarin group (3.3%) (Table 14.3.2.2.1.7, CV185056 CSR). The only treatment-related SAEs reported in >0.1% of subjects were gastrointestinal hemorrhage (apixaban 5 mg: 0.2% and enoxaparin/warfarin: 0.4%) and hematuria (apixaban 5 mg: 0.1% and enoxaparin/warfarin: 0.4%).

A summary of the most frequently reported (>0.1%) SAEs reported in the Phase 3 efficacy and safety study, **CV185057**, with onset during the treatment period is presented in Table S10. There was a higher rate of SAEs in the placebo group (19.1%) compared to both apixaban treatment groups (13.3% and 13.2% in the apixaban 2.5 mg and apixaban 5 mg treatment groups, respectively). This difference was seen consistently in both index event strata (DVT and PE). The most frequently reported SAEs (>1% in any treatment group) with onset during the treatment period were DVT (apixaban 2.5 mg: 0.4%, apixaban 5 mg: 1.1%, and placebo: 4.8%) and PE (apixaban 2.5 mg: 0.6, apixaban 5 mg: 0.4%, and placebo: 2.4%). The cases of DILI are discussed above.

**Table S10. Summary of Most Frequently Reported Serious Adverse Events (>0.1% in Any Treatment Group) Reported in Subjects With Onset During the Treatment Period - Treated Subjects, Study CV185057**

| System Organ Class (%)<br>Preferred Term (%) | Apixaban 2.5 mg BID (N = 840)<br>n (%) | Apixaban 5 mg BID (N = 811)<br>n (%) | Placebo (N = 826)<br>n (%) |
|---|---|---|---|
| **Total subjects with an event** | **112 (13.3)** | **107 (13.2)** | **158 (19.1)** |
| Infections and infestations | 18 (2.1) | 17 (2.1) | 15 (1.8) |
| Neoplasms benign, malignant and unspecified (including cysts and polyps) | 17 (2.0) | 16 (2.0) | 17 (2.1) |
| Injury, poisoning and procedural complications | 11 (1.3) | 13 (1.6) | 7 (0.8) |
| Vascular disorders | 9 (1.1) | 13 (1.6) | 50 (6.1) |
| Cardiac disorders | 14 (1.7) | 12 (1.5) | 16 (1.9) |
| Respiratory, thoracic and mediastinal disorders | 11 (1.3) | 12 (1.5) | 28 (3.4) |
| Gastrointestinal disorders | 8 (1.0) | 10 (1.2) | 5 (0.6) |
| Nervous system disorders | 9 (1.1) | 8 (1.0) | 9 (1.1) |
| Musculoskeletal and connective tissue disorders | 9 (1.1) | 7 (0.9) | 7 (0.8) |
| Metabolism and nutrition disorders | 0 | 5 (0.6) | 1 (0.1) |
| Hepatobiliary disorders [1] | 5 (0.6) | 4 (0.5) | 2 (0.2) |
| Renal and urinary disorders | 5 (0.6) | 4 (0.5) | 10 (1.2) |
| Pregnancy, puerperium and perinatal conditions | 3 (0.4) | 4 (0.5) | 1 (0.1) |
| Blood and lymphatic system disorders | 0 | 4 (0.5) | 2 (0.2) |
| General disorders and administration site conditions | 3 (0.4) | 3 (0.4) | 8 (1.0) |
| Surgical and medical procedures | 0 | 2 (0.2) | 2 (0.2) |
| Eye disorders | 3 (0.4) | 1 (0.1) | 2 (0.2) |
| Ear and labyrinth disorders | 1 (0.1) | 0 | 2 (0.2) |

[1] Drug induced liver injury: 0 v 2 (0.2%) v 0

The proportion of subjects who experienced an SAE considered related to treatment by the investigator was low in all treatment groups (0.7% in the apixaban 2.5 mg treatment group, 1.4% in the apixaban 5 mg treatment group, and 1.2% in the placebo group) (Table 14.3.2.2.1.7, CV185057 CSR). The treatment-related SAEs reported in >0.1% of subjects were hematemesis (apixaban 2.5 mg treatment group only: 0.2%), anemia (apixaban 5 mg treatment group only: 0.2%), hematuria (apixaban 5 mg: 0.2%, placebo: 0.1%, and not reported in apixaban 2.5 mg treatment group), eye hemorrhage (placebo group only: 0.2%), and deep vein thrombosis (placebo group only: 0.2%).

***Laboratory findings***

The analysis of laboratory findings did not uncover new or relevant findings. There are no relevant differences in laboratory values between apixaban and comparator treatments. Most notably, there were no findings with respect to liver enzymes (see above).

***Safety in special populations***

The subgroup analyses (see above) addressed the question of whether there were subgroups in which the safety profile of apixaban was markedly different from that observed in each of the overall studies. The results of the subgroup analyses suggest that the bleeding and overall AE profile of apixaban compared to enoxaparin/warfarin (Study CV185056) or placebo (Study CV185057) are similar to the overall profiles observed for the overall population in each study.

Adverse Event findings in the pivotal trials (CV185056 AMPLIFY and CV185057 AMPLIFY - EXT) for older patients are summarised tables below S11 and S12.

**Table S11: Adverse events of interest in Elderly patients in study AMPLIFY (Study CV185056)**

| | Age < 65 years | | 65-74 years | | 75-84 years | | ≥ 85 years | |
|---|---|---|---|---|---|---|---|---|
| | Apixaban | Enox/ warfarin | Apixaban | Enox/ warfarin | Apixaban | Enox/ warfarin | Apixaban | Enox/ warfarin |
| Total Subjects (N) [a] | 1725 | 1753 | 553 | 566 | 337 | 312 | 61 | 58 |
| | | | | | | | | |
| Fatal n (%) [b] | 14 (0.8) | 18 (1.0) | 9 (1.6) | 10 (1.8) | 14 (4.2) | 7 (2.2) | 0 (0) | 9 (15.5) |
| Serious n (%) [c] | 217 (12.6) | 230 (13.1) | 94 (17.0) | 89 (15.7) | 88 (26.1) | 67 (21.5) | 18 (29.5) | 24 (41.4) |
| Withdrawal n (%) [d] | 92 (5.3) | 117 (6.7) | 36 (6.5) | 38 (6.7) | 29 (8.6) | 29 (9.3) | 4 (6.6) | 15 (25.9) |
| CNS (confusion/extrapyramidal) n (%) [e] | 31 (1.8) | 35 (2.0) | 13 (2.4) | 13 (2.3) | 17 (5.0) | 6 (1.9) | 3 (4.9) | 3 (5.2) |
| AE related to falling n (%) [a] | 5 (0.3) | 4 (0.2) | 2 (0.4) | 7 (1.2) | 8 (2.4) | 5 (1.6) | 4 (6.6) | 2 (3.4) |
| CV events n (%) [a] | | | | | | | | |
| Cardiac disorders SOC n (%) | 52 (3.0) | 55 (3.1) | 26 (4.7) | 31 (5.5) | 23 (6.8) | 18 (5.8) | 4 (6.6) | 5 (8.6) |
| Vascular disorders SOC n (%) | 138 (8.0) | 194 (11.1) | 55 (9.9) | 70 (12.4) | 39 (11.6) | 41 (13.1) | 4 (6.6) | 8 (13.8) |
| Cerebrovascular events n (%) [f] | 15 (0.9) | 13 (0.7) | 7 (1.3) | 8 (1.4) | 5 (1.5) | 2 (0.6) | 1 (1.6) | 2 (3.4) |
| Infections n (%) [a] | 408 (23.7) | 364 (20.8) | 106 (19.2) | 123 (21.7) | 87 (25.8) | 72 (23.1) | 20 (32.8) | 19 (32.8) |

**Table S12: Adverse Events of interest in Elderly patients in AMPLIFY-EXT (Study CV185057)**

| | Age < 65 years | | | 65-74 years | | | 75-84 years | | | ≥ 85 years | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Apixaban | | Pbo | Apixaban | | Pbo | Apixaban | | Pbo | Apixaban | | Pbo |
| | 2.5 mg | 5 mg | | 2.5 mg | 5 mg | | 2.5 mg | 5 mg | | 2.5 mg | 5 mg | |
| Total Subjects (N) [a] | 565 | 549 | 546 | 164 | 154 | 171 | 98 | 96 | 9 | 13 | 12 | 14 |
| | | | | | | | | | | | | |
| Fatal n (%) [b] | 0 (0) | 2 (0.4) | 5 (0.9) | 2 (1.2) | 1 (0.6) | 2 (1.2) | 0 (0) | 0 (0) | 3 (3.2) | 1 (7.7) | 1 (8.3) | 0 (0) |
| Serious n | 61 | 57 | 87 | 34 | 27 | 44 | 15 | 20 | 23 | 2 | 3 | 4 |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| (%) [c] | (10.8) | (10.4) | (15.9) | (20.7) | (17.5) | (25.7) | (15.3) | (20.8) | (24.2) | (15.4) | (25.0) | (28.6) |
| Withdrawal n (%) [d] | 29 (5.1) | 35 (6.4) | 74 (13.6) | 20 (12.2) | 15 (9.7) | 41 (24.0) | 11 (11.2) | 8 (8.3) | 15 (15.8) | 3 (23.1) | 2 (16.7) | 3 (21.4) |
| CNS (confusion/ extrapyramidal) n (%) [e] | 22 (3.9) | 14 (2.6) | 11 (2.0) | 2 (1.2) | 5 (3.2) | 6 (3.5) | 3 (3.1) | 3 (3.1) | 2 (2.1) | 0 (0) | 0 (0) | 1 (7.1) |
| AE related to falling n (%) [a] | 2 (0.4) | 4 (0.7) | 3 (0.5) | 0 (0) | 1 (0.6) | 1 (0.6) | 1 (1.0) | 2 (2.1) | 0 (0) | 0 (0) | 1 (8.3) | 0 (0) |
| CV events n (%) [a] | | | | | | | | | | | | |
| Cardiac SOC | 12 (2.1) | 15 (2.7) | 10 (1.8) | 10 (6.1) | 9 (5.8) | 13 (7.6) | 9 (9.2) | 5 (5.2) | 8 (8.4) | 1 (7.7) | 2 (16.7) | 0 (0) |
| Vascular SOC | 54 (9.6) | 45 (8.2) | 75 (13.7) | 21 (12.8) | 16 (10.4) | 40 (23.4) | 11 (11.2) | 11 (11.5) | 17 (17.9) | 1 (7.7) | 0 (0) | 3 (21.4) |
| Cerebrovascular events n (%) [f] | 2 (0.4) | 2 (0.4) | 3 (0.5) | 0 (0) | 0 (0) | 4 (2.3) | 2 (2.0) | 3 (3.1) | 1 (1.1) | 0 (0) | 0 (0) | 1 (7.1) |
| Infections n (%) [a] | 154 (27.3) | 126 (23.0) | 139 (25.5) | 40 (24.4) | 51 (33.1) | 47 (27.5) | 24 (24.5) | 26 (27.1) | 25 (26.3) | 3 (23.1) | 5 (41.7) | 1 (7.1) |

***Safety related to drug-drug interactions and other interactions***

For interactions, only antiplatelet drugs were separately analysed in the pivotal trials. The data show that the combination of an antiplatelet drug and apixaban is associated with an increased risk of bleeding (relative risk: 2.8); the relative risk in comparison to enoxaparin/warfarin is not affected: Apixaban's RR compared to enoxaparin/warfarin for MB was 0.30 for subjects taking an antiplatelet and 0.31 for subjects not taking an antiplatelet. As with the other analyses of bleeding, the risk of bleedings during apixaban compares very favourably to the risk during enoxaparin/warfarin use.

***Discontinuation due to adverse events***

In **CV185056** no pattern for discontinuations related to AEs could be found, except for events related to VTE and bleeding. AEs related to discontinuation were 162/2676 (6.1%) for apixaban and 199/2689 (7.4%) for enoxaparin/warfarin. These data provide no new insights.

In **CV185057** the vast majority of AE related discontinuations were related to VTE. There were some (0.4%) discontinuations because of headache. The number of treated subjects who discontinued due to AEs was lower in the apixaban treatment groups (67/840 (8.0%) and 61/811 (7.5%) in the

apixaban 2.5 mg and apixaban 5 mg treatment groups, respectively) compared to the placebo group 134/826 (16.2%).

***Post marketing experience***

No new insights are gained from the post marketing experience.

Since receiving its first marketing authorization on 18 May 2011, 404 spontaneous reports including 607 AEs have been received by the sponsor through 17 May 2013; 321 of these reports were Health Professional confirmed (SCS Section 2.7.4.6.2). Of the spontaneously reported cases, 165 met criteria to be classified as serious and 4 cases had a fatal outcome (all HP-confirmed).

The most common types of AEs represented some form of haemorrhage, which is expected. The second most common type of event represented sequelae of the underlying indication, for example, PE, drug ineffective, or thrombosis. Two liver-related events were reported (Hepatocellular injury and Transaminases increased). Neither case suggested any significant liver-related risk associated with apixaban use.

***Ancillary analyses***

The analysis of **efficacy and safety to Day 9 in Study CV185056** confirms the safety of the initially higher dose in VTE treatment. These data are of visualised in the Kaplan Meijer curves for the primary endpoint (Figure E2) and for bleedings (Figure S1), which are superimposed or in favour of apixaban from the start.

The selection of an initial 7-day treatment period with the higher 10 mg BID dose of apixaban was designed to ensure that subjects received maximum benefit during the hypercoagulable state following initial clot formation in stabilizing the clot and preventing a potentially fatal VTE. To establish that this benefit was achieved without a cost of unacceptable bleeding, both VTE/VTE-related death and adjudicated bleeding endpoints were analyzed for the first 9 days of study CV185056 (7 days of apixaban 10 mg BID plus 2 days of apixaban 5 mg BID).

During the first 9 days, events of VTE / VTE-related death were 19/2659 for apixaban and 25/2676 for enoxaparin/warfarin; relative risk 0.7661 [0.4228, 1.3879]. For MB/CRNMB, events were 27 (apixaban) versus 66 (LMWH/VKA), Risk difference -0.0130 [-0.0198, -0.0063].

## 2.5.1 Discussion on clinical safety

**Exposure**

The presented exposure numbers are considered sufficient to characterise the safety profile in the sought indications.

No specific trends were observed in the three major groups participating in study CV185057 (switchers from SOC vs switchers from enox/VKA and patients already on apixaban from study CV185056), except from a lower bleeding in switchers from enox/VKA. However, it can be agreed that the groups are of limited numbers, complicating interpretation of the results. Current recommendations in the SmPC for switching between different anti-coagulants were considered adequate by the CHMP.

The key safety issue for an anti-coagulant is **bleeding**. In the adjudicated class of bleeding, most notably major bleedings and clinically relevant non-major bleeding (but also total bleeding), apixaban was superior to enoxaparin/VKA in VTE treatment.

**TTR**

Based on the centre-based analysis based on TTR quartile, a reduced risk of MB was demonstrated for apixaban relative to enoxaparin/warfarin regardless of TTR quartiles. The advantage in bleedings was also similar across all TTR ranges. The results are somewhat surprising, as centres with worse INR control did not have more bleedings in the control group. Presented data further confirms the lack of correlation between center TTR and the reported events in the warfarin group; there is also no statistical interaction. It can be due to the limited sample size in each group and that the study is not powered to show such differences. Similar observations were also shown in the Einstein study for rivaroxaban.

In the VTE recurrence prevention indication, the differences with placebo were small, especially for the lower 2.5 mg dose, and the number of major bleeding events was low.

No new safety signals have been identified in the VTE treatment studies. The Applicant has searched for evidence of rebound phenomena after study drug discontinuation. In this respect, no differences were found in comparison to enoxaparin/warfarin. Further analysis of the data does not suggest a clear rebound phenomenon especially for occurrence of MI or stroke although there is a trend for VTE events. The applicant has argued that withdrawal effect is a recognised phenomenon with factor Xa inhibitors. While there is some similarity between different drugs in the same class, it was still considered of some concern in view of the CHMP. It would have been useful for the applicant to have evaluated the specifics of the risk in those with recurrent events in comparison to those with no such events to discern potential differences and this should be for further follow up. Issue is resolved with further follow-up in the PSURs.

Regarding MI, there are numerical imbalances in occurrence of MI in study ***CV185056***. Based on further assessments the results from the study-CV185056 appears to be the only one among the apixaban clinical program with a suggestion of increased events. It is not possible to judge whether this difference from other studies signifies a true risk or is a chance finding. The issue can be solved by further follow-up in the PSURs.

Consistent with the safety profile established in previous apixaban clinical studies, there was no evidence of hepatotoxicity, neurologic toxicity, increased risk of non-bleeding adverse events, or laboratory test abnormalities.

**Hepatotoxicity**

Two SAEs in Study CV185057 were assessed as possibly related to apixaban treatment by the panel of independent hepatologists. The assessment is appropriate, as in the first case ciprofloxacin use could provide an alternate explanation and in the second case the study drug was restarted uneventfully some days after the event had resolved.

Overall, the clinical experience with apixaban in studies CV185017, CV185056, and CV185057 supports the hepatic safety of apixaban for VTE treatment. There is no evidence that apixaban causes drug-induced liver injury based on data for 4712 subjects treated with apixaban in the single Phase 2 and 2 Phase 3 VTE treatment studies. Likewise, review of the liver safety profile across all apixaban indications indicates that apixaban is not associated with drug-induced hepatotoxicity, regardless of apixaban dose, treatment duration, or study population. Based on the above data , “liver injury” is considered an important potential risk for all indications of apixaban.

**Safety in certain subgroups. *Study CV185056***

The advantage in bleedings was similar across the subgroups tested (Figure S3). No treatment by subgroup interaction was significant. The dose recommendations in special subgroups is addressed above.

**Bleeding in study** CV185057.

The Forest plot presented in figure S6, shows a higher bleeding risk in some subpopulations, though not associated with a significant interaction. These include patients ≥75 years , patients with different degrees of renal insufficiency and for low-weight subjects ≤ 60 kg. Presented data cannot robustly conclude on a positive or negative B/R of apixaban in such specific vulnerable populations. This is due to the limited representation of these subgroups in the clinical trial and also the few events recorded for efficacy and safety. Importantly, a higher bleeding risk cannot be excluded. The applicant proposed some modifications in the SmPC to warn against such bleeding risk. These are not considered sufficient. For each of these groups (>75 years, <60 kg and severe renal impairment) more clear and specific warnings regarding the limited clinical data and that apixaban should be used with caution due to the higher bleeding risk are warranted. This could clearly inform the prescribers about the associated risks. See SmPC assessment.

As presented in tables S11 and S12, there is adequate representation of patients from 65 to 75 years, but quite limited for patients above 85 years. In both studies, the rate of AEs increases with age in both the apixaban and the comparator group, which is expected. In general the data does not point to any consistent problems in the older age groups administered apixaban. However, there is a trend for more fatal and serious events recorded in the apixaban group in the 75-84 years group. On the other hand, in the oldest group, there are 9 fatal cases recorded with enoxaparin/warfarin and none in the apixaban, and also the serious events were more frequently recorded in the former group.

No post-marketing events were identified that altered the established safety profile of apixaban.

### 2.5.2 Conclusions on clinical safety

The safety profile of apixaban is well-established. In the indication of VTE treatment, safety in terms of bleeding was superior to enoxaparin/warfarin. In the indication of VTE recurrence prevention, the numbers of bleeding events are low, but obviously more than placebo. The safety of the 2.5 mg BID dose in the latter indication compares favourably to the 5 mg BID dose, supporting its choice as recommended dose.

### 2.5.3 PSUR cycle

The PSUR cycle remains unchanged.

## *2.6. Risk management plan*

### 2.6.1. PRAC advice

The CHMP received the following PRAC advice on the submitted Risk Management Plan.

### PRAC Advice

Based on the PRAC review of the Risk Management Plan version 12.2, dated 11 June 2014, the PRAC considers by consensus that the risk management system for apixaban (Eliquis) in the treatment of

deep vein thrombosis (DVT) and pulmonary embolism (PE) and prevention of recurrent DVT and PE in adults is acceptable.

This advice is based on the following content of the Risk Management Plan:

***Safety concerns***

The applicant identified the following safety concerns in the RMP:

Summary of the Safety Concerns

| **Summary of safety concerns** | |
|---|---|
| Important identified risks | • Bleeding<br>• Transient elevation of liver enzymes |
| Important potential risks | • Liver injury<br>• Medication errors |
| Missing information | • Paediatrics<br>• Pregnant or lactating women<br>• Severe hepatic impairment<br>• Severe renal impairment<br>• Black/African American Population<br>• Hip fracture surgery<br>• AF with valvular disease,<br>• patients with prosthetic heart valve,<br>• haemodynamically unstable PE patients<br>• Non-Caucasian and non-asian ethnicity<br>• Long-term therapy > 3 years<br>• Off-label use |

The PRAC agreed.

***Pharmacovigilance plans***

**Table 2.2:** Ongoing and planned studies in the PhV development plan

**Table :** Ongoing and planned studies in the PhV development plan

| **Activity / Study title (type of activity, study title [if known] category 1-3)*** | **Objectives** | **Safety concerns addressed** | **Status Planned, started,** | **Date for submission of interim or final reports (planned or actual)** |
|---|---|---|---|---|
| PASS STUDY CV185365 - Evaluation of the effectiveness of Eliquis (apixaban) risk minimization tools in European Economic Area (EEA) countries (category 3) | The primary objective is to evaluate the effectiveness of the Eliquis® Prescriber Guide and Patient Alert Card in terms of distribution, awareness, | Bleeding | Planned (draft protocol submitted to PRAC on 30 May 2014) | Study Report Available – June 2015 (dependent on protocol approval by PRAC) |

| Activity/Study title (type of activity, study title [if known] category 1-3)* | Objectives | Safety concerns addressed | Status Planned, started, | Date for submission of interim or final reports (planned or actual) |
|---|---|---|---|---|
| | utilization, knowledge and comprehension of these RM tools, and behaviour by healthcare professionals and patients. An exploratory objective is to examine if correlations exist between aggregated knowledge/behavioural results from the questionnaire and the proportion of spontaneous adverse drug reaction (ADR) case reports from individual countries identified as potentially preventable cases concerning bleeding. | | | |

*Category 1 are imposed activities considered key to the benefit risk of the product.
Category 2 are specific obligations
Category 3 are required additional PhV activity (to address specific safety concerns or to measure effectiveness of risk minimisation measures)

The PRAC, having considered the data submitted, was of the opinion that the proposed post-authorisation PhV development plan is sufficient to identify and characterise the risks of the product.

***Risk minimisation measures***

**Table 5.3-1: Summary of Risk Minimization Measures**

| Safety Concern | Routine Risk Minimization Measures | Additional Risk Minimization Measures |
|---|---|---|
| **Bleeding** | The risk of bleeding will be communicated in sections of the product information with explicit description of measures to be taken to avoid haemorrhage and measures to be taken in the event of haemorrhagic complications.<br>• guidance for administration of apixaban in high risk groups such as the elderly, renally impaired and subjects with hepatic impairment<br>• guidance for patients with hepatic disease associated with coagulopathy and clinically relevant bleeding risk.<br>• Dose reduction in 2 of the 3: elderly, severe renal impairment, low body weight<br>• Information regarding interaction with other medicinal products affecting haemostasis<br>• Listed as ADR | Prescribers Guide<br>Patient Alert Card<br>DHCP letter (distributed in September 2013) |
| **Transient elevation of liver enzymes & Liver Injury** | Communication of elevated liver tests in appropriate product literature | Prescribers Guide |
| **Medication errors** | Communication of the posology for each indication and the need for patient counseling for specific dosing regimen in the appropriate product literature | Prescribers Guide<br>Drug Utilization Study |

The PRAC, having considered the data submitted, was of the opinion that the proposed risk minimisation measures are sufficient to minimise the risks of the product in the proposed indications.

The CHMP endorsed this advice without changes.

## *2.7. Update of the Product information and user test*

**Product information**

As a consequence of this new indication, sections 4.1, 4.2, 4.4, 4.5, 4. 5.1 and 6.5 of the SmPC have been updated. The Package Leaflet has been updated accordingly.

In addition, the MAH applied for a variation to add a new pack size of 28 film coated tablets for Eliquis 5mg strength (SmPC section 6.5). The Package Leaflet and Labelling were proposed to be updated in accordance.

In addition the Patient Alert Card approved currently was reviewed in a parallel procedure (MEA) by the CHMP and an amended more concise text is agreed upon, with no changes to the scientific content. In particular simplification and removal of redundancies with the Package leaflet have been implemented. The revised text is now implemented as part of this procedure and introduced in the labelling as annex III. This is for consistency and harmonisation with the other NOACs approved as CAPs (pradaxa, Xarelto) aiming at a better compliance and tracking of the Patient Alert Card.

**User test**

A Readability User Focus User test has been performed with the Eliquis 2,5 mg film-coated tablets PIL as during the lifecycle of the product, several changes have been approved and revisions were also introduced into the SmPC and the PIL correspondingly, including the extension of the indication. To comply with the European Commission Directive 2001/83 EC, modified 2004/27/EC (Articles 59 (3) and 61(1), the revised PIL was subjected to a Readability User Focus Test with 10 participants to evaluate the impact of the implemented changes on the readability of the new leaflet. This is sufficient as the original PIL for Eliquis 2.5 mg film-coated tablets already successfully passed a Readability User Test in 2010.
All 10 participants within the focus test found and understood the information to each question. From the results of focus test, it can be concluded that the user should be able to find and understand the necessary information in the revised PIL.
The bridging with Eliquis 5.0 mg film-coated tablets PIL is justified and acceptable.

## *2.8. Variation B.II.e.5 Addition of a new pack size of 28 film coated tablets for Eliquis 5mg strength*

The scope of this Type IAIN variation, which has been submitted in the grouped variation EMEA/H/C/002148/II/0014/G, is to add a pack size of 28 film-coated tablets for Eliquis 5 mg film-coated tablets, in the range of the currently approved pack sizes, corresponding to 7 days of treatment of 10 mg twice daily (i.e. 4 tablets per day for 7 days). Proposed mock-ups have been included in Module 1.3.2 of the dossier. Not all pack sizes may be marketed.

The primary packaging material and the cavity design remain unchanged therefore no changes to the quality of tablets is expected during stability testing and the shelf life testing parameters and specifications will be unaffected by this variation.

*Justification for grouping:*

The recommended dose of Eliquis for the treatment of acute DVT and treatment of PE is 10 mg taken orally twice daily for the first 7 days followed by 5 mg taken orally twice daily.

The currently approved pack-sizes for Eliquis 5 mg film-coated tablet are 14, 20, 56, 60, 168 and 200 film-coated tablets and perforated unit dose blisters of 100x1 film-coated tablets.

A pack size of 28 film-coated tablets for Eliquis 5 mg is associated with the new DVT/PE Treatment indication and will be implemented after approval of this variation application.

**CHMP comments**
The blister strip of 14 film-coated tablets remain unchanged. Stability will not be affected by the proposed new pack size as there is no change in the primary packaging material. Furthermore, the proposed new pack size is within the currently approved range of pack sizes. The proposed pack size is approvable.

# 3. Benefit-Risk Balance

Eliquis (apixaban) a factor Xa inhibitor is one of the novel oral anti-coagulants is currently registered for prevention of VTE after orthopedic surgery (2.5 mg BID) and prevention of stroke in Atrial Fibrillation (5 mg BID). The current application concerns a type 2 variation for extension of the indication to include treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE) (10 mg taken orally twice daily for 7 days followed by 5 mg taken orally twice daily) and prevention of recurrent DVT and PE in adults (2.5 mg taken orally twice daily after at least 6 months).

## *Benefits*

## Beneficial effects

Efficacy and safety for the proposed indication have been investigated in two pivotal Phase 3 studies (CV185056, AMPLIFY and CV185057, AMPLIFY EXT) and one supportive Phase 2 study (CV185017).

**CV185056** was a randomized, active controlled, parallel-group, double-blind, triple-dummy study in 5395 subjects with acute symptomatic proximal DVT or acute symptomatic PE. This was a non-inferiority trial, comparing the proposed treatment to enoxaparin / warfarin, which represents the current standard of care, in a 1:1 randomisation. The primary endpoint was a composite of VTE / VTE-related death and was in line with Note for Guidance on Clinical Investigation of Medicinal Products for the Treatment of Venous Thromboembolic Disease (CPMP/EWP/563/98). The non-inferiority margin was set at a relative risk of the primary endpoint of 1.8, which ensures that at least 50% of the efficacy of the comparator is maintained. This margin was adequate.

Apixaban given at 10 mg BID for 7 days followed by 5 mg BID for 6 months demonstrated non-inferiority to enoxaparin/warfarin. Event rates were 2.26% (59/2609 and 2.69% (71/2635), respectively. The relative risk of VTE/VTE-related death for the apixaban-treated subjects was 0.84 (95% CI: 0.5965, 1.1802; p for non-inferiority: <0.0001) compared to subjects treated with enoxaparin/warfarin, with an absolute risk difference of -0.44%. Statistical superiority was not achieved.

The robustness of the results is supported by the per protocol analysis, sensitivity analyses addressing missing data, subgroup analyses and the secondary endpoints (including more measures of mortality). The efficacy was maintained across all quartiles by Time in Therapeutic Range TTR.

**CV185057** was a randomized, parallel-group, double-blind, placebo-controlled study in 2483 subjects with symptomatic proximal DVT or symptomatic PE. After completing approximately 6 to 12 months of anticoagulant therapy for the treatment of the index event, eligible subjects were randomized to receive either apixaban 2.5 mg, apixaban 5 mg, or placebo in a 1:1:1 randomisation.

For the primary efficacy analysis results for the endpoint of VTE/all-cause death were imputed as having the event in case of missing data. The event rates in the treatments groups were 0.0381 events/year (32/840), 0.0418 (34/813), 0.1158 (96/829) for apixaban 2.5 mg BID, 5 mg BID or placebo respectively. The corresponding relative risks were 0.33 and 0.36, which were highly statistically significant. In the (sensitivity) analysis without imputations the relative risks were even 0.24 and 0.19, based on event rates of 0.0226 (19 events), 0.0172 (14 events) and 0.0929 (77 events). Results with no imputation gave the same p-value as the analysis with imputation.

The secondary endpoint analyses confirm efficacy in all predefined outcomes. The relative risks for all secondary endpoints for both apixaban doses are < 1 compared to placebo, which are consistent with

and support the results of the primary endpoint. The results are further supported by the subgroup analyses and other sensitivity analyses.

The trials were **conducted** according to current standards. Randomisation and blinding were managed through an IVRS system. There was only a small number of dispensing errors (37 errors out of 54,720 kits assigned by IVRS; 0.07%). The IVRS also managed providing sham INRs for blinding VKA treatment in CV185056. Endpoint events were systematically, independently and blinded adjudicated. Follow-up was about 97%.

The included populations in both trials were representative of the intended target population. The assumptions in the sample size calculations were sufficiently accurate.

The sponsor's internal GCP audits uncovered cases of possible misconduct, requiring closing of two trial sites. This supports the effectiveness of the internal audits and provides reassurance about the implemented quality system.

## Uncertainty in the knowledge about the beneficial effects

The exact **doses** for the phase 3 studies were not tested in the dose-finding trial CV185017. Based on comparison to approved treatment regimens with other products (e.g. LMWH) and the approved regimen for apixaban in atrial fibrillation, the Applicant chose a BID regimen with a higher dose during the first week of treatment for further development. This initial dose of 10 mg BID is the highest investigated in the apixaban clinical program and has not been approved for any other indication yet.

The proposed dose for treatment of VTE including prevention of recurrence is 10 mg BID for 7 days followed by 5 mg BID for 6 months after the index event; if after that continued prophylaxis is required, a lower dose of 2.5 mg BID is equally effective. Thus, it might be questioned if the dose could have been reduced earlier than 6 months from 5 mg BID to 2.5 mg BID. However, based on the small difference in safety profile of both dose levels and the large effort it would require to investigate this in a clinical trial, the currently proposed posology is not further questioned.

For extended VTE prophylaxis, the dose is again primarily based on extrapolation of data from other products and other indications. It was decided to bring both doses to phase 3, which both proved effective with (small) differences mainly in safety.

Although most subgroup analyses in CV185056 are consistent with the main analysis, two analyses deserve some extra attention. In an analysis according to **extent of VTE**, the numerical advantage of apixaban in event rate is evident in subjects with extensive disease, but not in all subjects with limited or moderate disease. There is no obvious mechanism, by which a therapy for more severe disease would not be effective in limited disease. Surprisingly, the relative efficacy was worse in the low **BMI** group, although one would expect the highest concentrations of apixaban in this group while the VKA dose would be weight-corrected through INR titration. Both these subgroup findings may be attributable to chance.

The definition of the target population for prevention of VTE recurrence depends on equipoise between the risk of VTE and the risk of bleeding by anti-coagulation treatment. This assessment of equipoise remains subjective.

## *Risks*

## Unfavourable effects

Data for the phase 2 and two pivotal phase 3 trials in this application were not pooled, because of important differences in design of the two trials (duration and comparator).

**Exposure** for 24 to <26 weeks in CV185056 was 1630 patients for apixaban and 1572 patients for active comparator. The median exposure in CV185057 was 360 days in both treatment groups, resulting in more than 400 patients in each group exposed for at least one year. These exposures are sufficient to characterise the safety profile in the sought indications.

In study **CV185056** major bleedings were defined as second in the statistical testing hierarchy. Statistical superiority was shown for **major bleedings** compared to active control (LMWH/VKA) ( 15/2676 for apixaban and 49/2689 for enoxaparin/warfarin; the risk difference [95% CI] was -0.0113 [-0.0170, -0.0056], p-value for superiority <0.0001). Other grades of bleeding were not included in the statistical testing hierarchy, but still nominally superior to comparators, e.g. clinically relevant non-major bleedings (CRNMB) were 103/2676 for apixaban and 215/2689 for enoxaparin/warfarin; the risk difference [95% CI] was -0.0382 [-0.0506, -0.0259].

The advantage in bleedings was consistent when analysed according to quartiles or Time in Therapeutic Range for INR.

In study CV185057, bleedings with either dose of apixaban were more frequent than with placebo. The differences were small for MB/CRNMB (Apixaban 2.5 : 27/840; Apixaban 5: 35/811; Placebo: 22/826) the risk differences (95% CI) were 0.0048 (-0.0113, 0.0210) and 0.0158 (-0.0018, 0.0335) respectively.

Certain **key safety events** were prospectively identified as being of special clinical interest based on prior experience with apixaban in the clinical program and the experience of drugs in the same therapeutic class.

**Myocardial infarction** occurred with apixaban in 6 cases and with enoxaparin/warfarin in 4 cases in CV185056, but incidence was very low; in CV185057 the numbers were 2 (apixaban 2.5 mg), 3 (apixaban 5 mg) and 4 (placebo) respectively.

SAEs related to **liver function** tests elevations with onset during the treatment period were reported for 13 (0.3%) subjects in the apixaban group and 17 (0.5%) subjects in the comparator group. There were few outliers (peak ALT > 3xULN, peak Bili > ULN), in both the apixaban and comparator treatment groups (4 subjects in each group). Two SAEs in Study CV185057 with onset during the treatment period (both drug-induced liver injury) were assessed as possibly related to apixaban treatment by the panel of independent hepatologists.

Review of the pooled database of **neurologic events** across all apixaban studies, identified a very low incidence of neurologic AEs of special interest: Guillain Barre Syndrome (apixaban 3, comparator 3), amyotrophic lateral sclerosis (apixaban 2, comparator 1) and other acute polyneuropathies (apixaban 2, comparator 6) were not more frequent with apixaban. One case of possible GBS occurred in the VTE studies.

Routine monitoring for **adverse events** confirmed the established safety profile for apixaban, which is already based on a large safety database including >60,000 subjects. AEs that were reported by >5% of participants in CV185056 included epistaxis (apixaban 2.9%; enoxaparin/warfarin 5.4%) and headache (apixaban 6.3%; enoxaparin/warfarin 6.2%). In CV185057 (with percentages for apixaban

2.5, apixaban 5 and placebo respectively): Deep vein thrombosis (1.8, 2.1, 7.4), Pain in extremity (5.1, 6.4, 6.5), Back pain (3.2, 5.5, 2.9) and Headache (5.2, 5.2, 5.1).

Discontinuations due to AEs were more in the comparator groups than with apixaban. An analysis by event type revealed no specific pattern.

Post marketing experience confirms what is already known about apixaban's safety profile.

Safety and efficacy through Day 9 in CV185056, which is the period of the higher (10 mg BID) dose for VTE treatment, was separately analysed. The results for apixaban were similar to those for enoxaparin/warfarin with only a low number of events.

## Uncertainty in the knowledge about the unfavourable effects

Switching anti-coagulant treatment from VKA to apixaban may occur frequently in clinical practice. No specific trends were observed in the three major groups participating in study CV185057 (switchers from SOC vs switchers from enox/VKA and patients already on apixaban from study CV185056), except from a lower bleeding in switchers from enox/VKA. However, it can be agreed that the groups are of limited numbers, complicating interpretation of the results.

The applicant presented data regarding exposure in elderly patients showing adequate representation of patients from 65 to 75 years, but quite limited for patients above 85 years. In both studies, the rate of AEs increases with age in both the apixaban and the comparator group, which is expected. In general the data does not point to any consistent problems in the older age groups administered apixaban. However, there is a trend for more fatal and serious events recorded in the apixaban group in the 75-84 years group. On the other hand, in the oldest group, there are 9 fatal cases recorded with enoxaparin/warfarin and none in the apixaban, and also the serious events were more frequently recorded in the former group.

### *Benefit-risk balance*

## Importance of favourable and unfavourable effects

In the indication for VTE treatment, efficacy was statistically non-inferior but numerically superior to the current standard of care. Moreover, bleeding events were statistically robustly included in the efficacy analysis and proved superior to the standard of care. The standard of care was adequately implemented as shown by maintaining the INR within the target therapeutic range (INR of 2.0-3.0) 60.9% (mean) of the time, which is consistent with recent VTE clinical trials that report a time in therapeutic range (TTR) of 58% [EINSTEIN], 60% [RECOVER], and 62.7% [EINSTEIN PE]. The studies were well conducted and the robustness of the results further confirmed by sensitivity analyses.

For the prevention of VTE recurrence indication, efficacy was superior to placebo with a limited cost, in terms of bleeding events. The choice of the 2.5 mg BID further optimises the B/R balance. The importance of the benefits is dependent on the characterisation of the targeted patients, i.e. the risk of VTE recurrence. In trial CV185057 the risk of recurrence (as observed in the placebo group) was 9.3%. Clinical guidelines are expected to further define the patients that will benefit from this continued prophylaxis.

The additional safety data from the current program confirm the established safety profile of apixaban. Long term experience has been obtained for the SPAF indication using the 5 mg BID dose which so far is reassuring. The 10 mg BID dose currently recommended in the treatment of VTE is the highest used

so far, but that is only for the first week of therapy and no special safety signals were identified during this period.

## Benefit-risk balance

The Benefit risk balance for the requested indication both in terms of treatment and prevention is positive.

## Discussion on the benefit-risk balance

**DVT and PE** are currently considered manifestations of the same disease. It is estimated that about half of the subjects presenting with DVT also have asymptomatic PE; in subjects with PE, DVT (whether in the legs or a different anatomical location) must be the cause. For treatment of VTE, both with or without symptomatic PE, the current standard of care includes treatment with low molecular weight heparin (LMWH, e.g. enoxaparin) for at least 5 days and combined with vitamin K antagonists (VKA, e.g. warfarin) for 6 months. The proposed treatment for PE and DVT with apixaban follows the same lines. Efficacy is comparable, with a better safety profile for the general cohort.

The population studied was representative of the population requiring treatment for VTE for 6 months. However, the ***low-risk patients*** with a provoked VTE without additional risk factors were excluded from CV185056 because they would only need 3 months of treatment. The Kaplan Meijer curves for VTE events are clearly separated at 3 months already, favouring apixaban. The pathophysiology of a clot is expected to be quite comparable between subjects who need 3 or 6 months of therapy. Based on this reasoning, the company-proposed extrapolation of efficacy findings from the high risk to the low risk patient groups can be accepted, although this was not a priori evident. This reasoning is supported, especially in light of the favourable benefit/risk ratio.

***Dose in special populations***.

Based on the Pharmacokinetic data presented in the population PK study, comparable dose recommendations would have been expected for the SPAF and the VTE treatment indications. Considering that **dose adaptations** are required in certain patient groups in the SPAF indication, e.g. patients with exclusive severe renal impairment, or patients with at least two of the following risks: age ≥ 80 years, body weight ≤ 60 kg, or serum creatinine ≥ 1.5 mg/dlL (133 micromole/lL), applying no dose adjustments for these same groups in the current program was extensively discussed by the CHMP. The difference in the goal during the management of SPAF from that in VTEt necessitates different dose recommendations, i.e prophylaxis vs acute treatment.

A dose of 10 mg BID is used in the first week of VTEt to ensure maximal efficacy for dissolving the clot and prevention of extension. In this population, available exposure data in patients with severe renal impairment (n=29) in relation to efficacy and safety are not helpful due to the small number of bleeding events (MB = 1) but shows a higher risk of major bleeding of 1.18 (95% CI 0.13, 10.98) for apixaban vs. enoxaparin/warfarin. Pooled data of moderate and severe renal impairment patients were submitted to allow interpretation of the results. For the whole treatment period, efficacy and safety results are in line with those of patients with mild renal impairment, in which no dose adaptations are recommended. Specific results for the first 9 days to address safety of the highest dose include very limited events precluding any robust conclusions. However, a higher bleeding tendency cannot be excluded. However, in conclusion, it can be agreed that the B/R of non-investigated dose reductions is not known and accordingly cannot be advised. Comparable data were presented for patients with a combination of risk factors (age, weight or renal impairment) who constituted around 100 patients in AMPLIFY. The presented data did not indicate any increased risk

compared to the general cohort. Thus it was considered acceptable that the current dose recommendations are the only one investigated in study AMPLIFY. Available data are reassuring but cannot robustly exclude a bleeding risk due to the limited patients numbers. Theoretical dose adaptations cannot be advised either. In conclusion, recommendations for posology were agreed together with information clearly reflecting the limited clinical trial data and the associated risks.

Apixaban is a substrate for both CYP3A4 and P-gp and therefore the concomitant use of systemic treatment with strong inhibitors of both CYP3A4 and P-gp is not recommended. Concomitant use of concomitant strong inducers of both CYP3A4 and P-gp may potentially result in decreased efficacy and it is likely to have greater clinical significance in the treatment of VTE population than for the VTEp and NVAF indications. Therefore, apixaban is not recommended for the treatment of DVT and PE in patients receiving concomitant systemic treatment with strong inducers of both CYP3A4 and P-gp since efficacy may be compromised, and should be used with caution for the prevention indications.

The indication for continued prophylaxis is not clearly defined and remains subjective. This subjectivity was already recognised during the assessment of the rivaroxaban application for the same indication. It is left to the physician's assessment to identify patients in whom the B/R would be positive for such an extended use after careful assessment of the treatment benefit against the bleeding risk.

However, the B/R in some patient groups is not considered optimal due to a higher bleeding risk, e.g , subjects ≥ 75 years; subjects with mild, moderate or severe renal impairment and subjects with BMI ≤ 28 kg/m2. Presented data cannot robustly conclude on a positive or negative B/R of apixaban in these sub populations. This is due to their limited representation and also the few events recorded for efficacy and safety. Importantly, a higher bleeding risk cannot be excluded. For each of these groups (>75 years, <60 kg and severe renal impairment) clear and specific warnings regarding the limited clinical data and that apixaban should be used with caution due to the higher bleeding risk are introduced in the SmPC to clearly inform the prescribers about the associated risks.

# 4. Recommendations

## *Outcome*

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

| **Variation(s) accepted** | | **Type** |
|---|---|---|
| C.I.6.a | C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one | II |
| B.II.e.5.a.1 | B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes | IAin |

Extension of indication for the treatment of deep vein thrombosis and pulmonary embolism and prevention of recurrent DVT and PE in adults. Consequently, the sections 4.1, 4.2, 4.3, 4.4, 4.5, 4.8, 4.9, 5.1, 5.2 and 6.6 of the SmPC are updated. The Package leaflet was amended accordingly

In addition, the MAH applied for a variation to add of a new pack size of 28 film coated tablets for Eliquis 5mg strength (SmPC section 6.5).

In addition, the Patient Alert card text currently approved has been reviewed in a parallel procedure and was amended to make it more concise. The amended text of the PAC is now inserted as part of the labelling in this application in order to harmonise with similar products, where the Patient Alert Card is part of the labelling.

The requested group of variations proposed amendments to the SmPC, Annex II, Labelling and Package Leaflet.

The updated annex II information is detailed below.

## *Conditions and requirements of the marketing authorisation*

- **Periodic Safety Update Reports**

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

D. **CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

- **Risk Management Plan (RMP)**

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

An updated RMP should be submitted:

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

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

- **Additional risk minimisation measures**

The MAH shall provide an educational pack prior to launch, targeting all physicians who are expected to prescribe/use Eliquis. Key safety messages have to be included in the educational pack for all indications.

The educational pack is aimed at increasing awareness about the potential risk of bleeding during treatment with Eliquis and providing guidance on how to manage that risk.
The MAH must agree the content and format of the educational material, together with a communication plan, with the national competent authority in each Member State prior to distribution of the educational pack in their territory.

The physician educational pack should contain:
- The Summary of Product Characteristics
- Prescriber Guide
- Patient Alert Cards

The Prescriber Guide should contain the following key safety messages:
- Details of populations potentially at higher risk of bleeding
- Recommended dosages and guidance on the posology for different indications

- Recommendations for dose adjustment in at risk populations, including renal or hepatic impairment patients
- Guidance regarding switching from or to Eliquis treatment
- Guidance regarding surgery or invasive procedure, and temporary discontinuation
- Management of overdose situations and haemorrhage
- The use of coagulation tests and their interpretation
- That all patients should be provided with a Patient alert card and be counselled about:
- Signs or symptoms of bleeding and when to seek attention from a health care provider.
- Importance of treatment compliance
- Necessity to carry the Patient alert card with them at all times
- The need to inform Health Care Professionals that they are taking Eliquis if they need to have any surgery or invasive procedure.

The Patient alert card should contain the following key safety messages:
- Signs or symptoms of bleeding and when to seek attention from a health care provider.
- Importance of treatment compliance
- Necessity to carry the Patient alert card with them at all times
- The need to inform Health Care Professionals that they are taking Eliquis if they need to have any surgery or invasive procedure.

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

Not applicable.

These conditions do fully reflect the advice received from the PRAC.

# 5. EPAR changes

The EPAR will be updated following Commission Decision for this group of variations. In particular the EPAR module 8 "*steps after the authorisation*" will be updated as follows:

## *Scope*

Extension of indication for the treatment of deep vein thrombosis and pulmonary embolism and prevention of recurrent DVT and PE in adults. Consequently, the sections 4.1, 4.2, 4.3, 4.4, 4.5, 4.8, 4.9, 5.1, 5.2 and 6.6 of the SmPC are updated.

In addition, the MAH applied for a variation to add a new pack size of 28 film coated tablets for Eliquis 5mg strength (SmPC section 6.5).

In addition, the Patient Alert card text currently approved has been reviewed in a parallel procedure and was amended to make it more concise. The amended text of the PAC is now inserted as part of the labelling in this application in order to harmonise with similar products, where the Patient Alert Card is part of the labelling.

The requested group of variations proposed amendments to the SmPC, Annex II, Labelling and Package Leaflet.

## *Summary*

Refer to the Assessment report.