EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Assessment report

for

Eliquis

International Non-proprietary Name: apixaban

Procedure No. EMEA/H/C/002148

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

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

Product information

Name of the medicinal product:	Eliquis
Applicant:	Bristol-Myers Squibb / Pfizer EEIG Uxbridge Business Park Sanderson Road Uxbridge UB8 1DH United Kingdom
Active substance:	apixaban
International Non-proprietary Name:	apixaban
Pharmaco-therapeutic group (ATC Code):	Not yet assigned (Not yet assigned)
Therapeutic indication:	Prevention of venous thromboembolic events (VTE) in adult patients who have undergone elective hip or knee replacement surgery.
Pharmaceutical form:	Film-coated tablet
Strength:	2.5 mg
Route of administration:	Oral use
Packaging:	Alu-PVC/PVdC blisters
Package sizes:	10 tablets, 100 x 1 tablet (unit dose), 20 tablets, 60 tablets, 60 x 1 tablet (unit dose)

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1. Background information on the procedure

1.1. Submission of the dossier

The applicant Bristol-Myers Squibb / Pfizer EEIG submitted on 25 February 2010 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Eliquis, through the centralised procedure under Article 3 (2) (a) of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 16-19 February 2009.

The applicant applied for the following indication prevention of venous thromboembolic events (VTE) in adult patients who have undergone elective hip or knee replacement surgery.

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC, as amended - complete and independent application.

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and bibliographic literature.

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision (P/8/2009) for the following condition(s):

- Venous embolism and thrombosis

on the agreement of a paediatric investigation plan (PIP)

- Arterial embolism and thrombosis

on the agreement of a paediatric investigation plan (PIP) including a deferral

The PIP is not yet completed.

Scientific Advice:

The applicant received Scientific Advice from the CHMP in December 2005. Following the availability of the Phase III Total Knee Replacement (TKR) studies (CV185034 and CV185047), the applicant sought further advice from regulatory authorities: (US FDA – June 2009; consultation with 6 EU agencies in 2009 [Sweden, France, United Kingdom, Denmark, Germany, and Spain]). This was followed by pre-submission meetings with the Rapporteurs in December 2009.

During the current clinical development, the CHMP *Points to Consider regarding prophylaxis of intra and post-operative venous thromboembolic risk* (CHMP/EWP/707/98) was revised and came into effect in May 2008. The compliance of the pivotal studies to the available guideline is discussed under the efficacy endpoints.

Licensing status

The product was not licensed in any country at the time of submission of the application.

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**

- The application was received by the EMA on 25 February 2010.
- The procedure started on 24 March 2010.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 9 June 2010 (Annex 1).
- The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 11 June 2010 (Annex 2).
- During the meeting on 19-22 July 2010, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 22 July 2010 (Annex 3).
- The applicant submitted the responses to the CHMP consolidated List of Questions on 15 September 2010.
- The summary report of the inspection carried out at the following site(s) Bristol-Myers Squibb Manufacturing Company - P.O. Box 609, State Road No. 3, Km 77.5 – 00791 Humacao - Puerto Rico between 11-14 October 2010 was issued in January 2011.
- The Rapporteurs circulated the Joint Assessment Report on the applicant’s responses to the List of Questions to all CHMP members on 8 November 2010 and on 12 November 2010 (Annex 4).
- During the CHMP meeting on 15-18 November 2010, the CHMP agreed on a list of outstanding issues to be addressed in writing and/or in an oral explanation by the applicant (Annex 5).
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 17 January 2010.
- The Rapporteurs circulated the Joint Assessment Report on the applicant’s responses to the List of Outstanding Issues to all CHMP members on 11 February 2011 (Annex 6).
- During the CHMP meeting on 14-17 February 2011, the CHMP agreed on a second List of Outstanding Issues to be addressed in writing and/or in an oral explanation by the applicant (Annex 7).
- The applicant submitted the responses to the second CHMP List of Outstanding Issues on 24 February 2011.
- The Rapporteurs circulated the Preliminary Joint Assessment Report on the applicant’s responses to the second List of Outstanding Issues to all CHMP members on 3 March 2011 (Annex 8).
- The applicant submitted Letter of Undertaking, which is dated 11 March 2011.
- The CHMP adopted a positive opinion on 17 March 2011.

2. Scientific discussion

2.1. Introduction

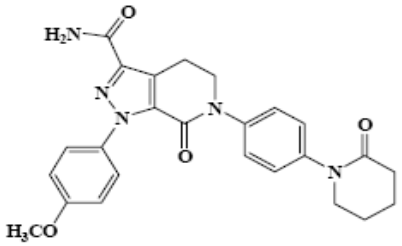
2.2. Quality aspects

2.2.1. Introduction

The product comprises as active substance apixaban: a novel, orally active, selective, direct, reversible inhibitor of the coagulation factor Xa (FXa).

2.2.2. Active Substance

The INN name of the active substance is apixaban and it chemical name is 1-(4-Methoxyphenyl)-7-oxo-6-[4-(2-oxopiperidin-1-yl)phenyl]-4,5,6,7-tetrahydro-1Hpyrazolo[3,4-c]pyridine-3-carboxamide.
The molecular formula of the active substance is $C_{25}H_{25}N_5O_4$, its relative molecular mass 459.50 and its structural formula is shown below.



Apixaban appears as a white to pale yellow, non hygroscopic crystalline powder, with an aqueous solubility of 0.028 mg/ml at 24°C. Apixaban is a non-ionizable compound and its partition coefficient at 24°C is 44.7 (log Po/w = 1.65) at pH 7.4 (n-Octanol / aqueous buffer). The molecule has no chiral centres, therefore, no stereoisomers exist.
It shows polymorphism and a number of hydrates and solvates were identified. However, only one form is consistently produced by the proposed synthetic process.

Manufacture

The commercial manufacturing process for the synthesis of apixaban involves a sequence of five reactions with two isolated intermediates.
The quality by design (QbD) concept has been used during the development of the manufacturing process for Apixaban drug substance. The critical quality attributes (CQAs) of the drug substance were identified on the basis of their potential impact on the safety and efficacy of the drug product and thus to the patient.
Based on risk assessment and development work, critical process parameters (CPPs) were identified for some of the process steps. Multivariate experimental design and mechanistic models were used to understand the effect of process parameters on those steps. The outcome of these studies is the proposed CPPs and proven acceptable ranges (PARs). The validity of the design space at commercial scale is supported by data from batches manufactured at pilot scale
In-process controls for those steps where no critical process parameters were identified are applied and they are considered sufficient for their adequate control.

Specification

The drug substance specification includes tests for appearance (visual), colour (visual), identification (Raman/IR, HPLC), assay (HPLC), impurities (HPLC), residual solvents (GC), heavy metals (ICP-MS) and particle size (laser light scattering).
The control strategy in relation to potential genotoxic impurities was developed from a detailed process understanding of the fate of these impurities in the downstream process and a combination of data from historical batches and spiking and purging experiments to understand the process clearance capability of the impurities.

All genotoxic materials are tested upstream and the proposed limits are sufficient to ensure that none of them is over the proposed limit in the final active substance. For those not tested, adequate supporting data have been provided. Batch data and results of experiments confirmed that the genotoxic impurities from the early process steps are not carried through to the drug substance. This has been confirmed on 14 batches of apixaban active substance. It was further confirmed there are no new genotoxic impurities introduced or formed at the final step of the manufacture of the active substance and therefore testing of the genotoxic impurities in the final active substance is not considered necessary in light of the supporting data provided.
In relation to the genotoxic related substances of the genotoxic impurities, these follow the same fate in the downstream process as their respective parent compound and therefore, their contribution to the total concentration is practically negligible based on the ratio of input amounts (parent compound versus related substance) and residual levels observed for each of the parent compound.
An overview of all batches used in clinical and toxicological studies, is provided. Batch analysis results were presented for eight commercial batches manufactured according to the commercial process all meeting the set requirements. The batch data provided is considered sufficient in support of the control of the active substance.

Stability

Stability studies have been performed on three batches in line with ICH Guidelines under the following conditions long-term (5°C, 25°C/60%RH), intermediate (30°C/65%RH) and accelerated (40°C/75%RH). Stability data have been provided for 36 months under long-term conditions and for six months under accelerated conditions
In addition results from studies under stress conditions (-20°C, 50°C, 40°C/75%RH open) for three batches and for photo-stability for one batch were also provided.
There were no changes from initial values observed in the tested parameters at any condition. Based on the provided data the proposed re-test period and storage condition are justified.

2.2.3. Finished Medicinal Product

Pharmaceutical Development

It is remarked that the formulation and manufacturing process for the apixaban tablets were designed to produce tablets with rapid disintegration and dissolution characteristics ensuring consistent and acceptable bioavailability.
Apixaban is non-ionisable, and therefore, its aqueous solubility is not affected by changes in pH. It is highly soluble for doses up to 10 mg and is a low permeable compound since the fraction of oral dose absorbed is < 90%. Thus, as per the Biopharmaceutical Classification System (BCS), it is classified as a Class III (high solubility/low permeability) compound.
Information on different strengths that were used in the early stages of the clinical development was presented. However, only the 2.5 mg and 5 mg were selected for Phase 3 studies and commercialisation. Only the 2.5 mg tablet will be commercialised for the prevention of venous thromboembolism (VTE) which is the object of this application. Therefore, only the data related to the 2.5 mg strength is assessed on this assessment report. It is noted however, that both 2.5 and 5 mg tablets are manufactured from a common granulate.
Development work included the evaluation of the different types of granulation and the use of a film coat for the tablets. It was found that tablets made using the dry granulation process have more consistent dissolution rates. Based on a relative bioavailability study results, the minimum dissolution requirement for apixaban was established. The film coat of the tablet is non-functional and has no impact on drug product performance. It has been optimised during development with regard to the aesthetic aspect.
The actual changes between the Phase 3 and commercial tablets formulations are minor and comparative batch data including dissolution has been presented showing no significant differences in the results obtained.
The particle size of the drug substance was identified as a critical factor based on its influence on the dissolution of the tablets. A study was conducted to establish the drug substance particle size requirement that would produce the required in-vitro drug release and appropriate limit has been set.
A drug-excipient compatibility study was conducted to screen potential excipients to be used in formulation development. No incompatibilities with any excipient tested were observed.
These excipients are conventional and the amounts per tablet are within their typical levels of usage in solid dosage forms. The tablet excipients are of compendial grades. The individual components of the film-coating are of compendial grades too.

The development of the dissolution method is adequately described and the discriminative ability of the dissolution method has been sufficiently demonstrated.
To establish the design space and control strategy for the commercial manufacture, relationships between the input attributes and process parameters and the output attributes for each unit operation were evaluated. A study was conducted to determine the steps that would be required to ensure the production of a uniform blend. Process development studies for the remaining unit operations were also conducted for the development of a robust commercial manufacturing process for apixaban tablets. No additional process development was conducted for the film-coating process step as typical coating procedures are followed.
It was recognized that because of the targeted low dose for apixaban, content uniformity of the final product becomes an important product attribute Since the drug substance is mixed with most of the excipients at the 1st blending step (preblending), a quantitative on-line NIR method was developed to monitor the mixing profile during the preblending unit operation, including the acceptance criteria for determining the blending endpoint. The proposed commercial manufacturing process uses process analytical technology (PAT), as well as conventional analytical tests, to control the in-process intermediates.

Adventitious agents

Lactose used in the manufacture of tablets is of animal origin (bovine milk). Statements from the suppliers attesting and finished product manufacturer in relation to the quality of lactose are provided. It is confirmed that all lactose used complies with EMEA/410/41/00/01 Rev.2 "Note for Guidance on Minimising Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products".

Manufacture of the product

The manufacturing process comprises the following main steps: blending, granulation, blending, tabletting, film-coating and packaging.
The prospective process validation for Eliquis film coated tablets will be successfully completed prior to launch of the commercial product. The validation batches will be processed according to an approved manufacturing batch record and as per an approved Process Validation Protocol. During the validation study, process steps will be monitored and the results will be covered in a Process Validation Report. All validation sample testing, including all release testing, must meet predetermined acceptance criteria which will be based on the approved specification for release testing.
Due to the initially proposed use of NIR (as PAT) and RTR for the manufacturing of the drug product, the proposed finished product manufacturing site has been inspected in relation to this application during the clock-stop period. Responses to observations have been received and found to be mostly adequate. An Inspection Report in relation to this product specific inspection has been produced.

Product specification

The release and shelf-life specifications of the solvent include tests and limits for appearance (visual), identification (Raman, IR, HPLC), assay (HPLC), uniformity of dosage units/ content uniformity (Ph Eur), disintegration (Ph Eur), impurities/degradants (HPLC - stability only), dissolution (HPLC- stability only) and Microbial Limit Test (Ph Eur – not routinely).
The elimination of dissolution testing for apixaban drug product is considered justified in view of (a) the established surrogate (drug substance particle size control) and (b) applying a comprehensive control strategy (design space on composition and process; upstream/in-process controls).
Based on the evidence of stability of apixaban, the control of impurities in the drug substance is considered sufficient to ensure the quality of the drug product at release because the impurity content of the drug product comes only from process-related impurities contained in the drug substance. Thus, the proposal not to test for impurities/degradants for batch release is considered justified.
Batch analysis data for five batches of the commercial formulation (from two sites (including the proposed one) have been presented. All results comply with the specifications and for these bathes.
Results from 8 batches of the Phase 3 formulation provided were also within specifications. In addition results from a number of batches of early development formulations were presented all within specifications.

Stability of the product

Stability studies are presented for three batches stored under long term conditions at 5°C, 25°C/60%RH and 30°C/65%RH up to 24 months and under accelerated conditions at 40°C/75%RH up to 6 months. An increase (approximately 1%-2%) in water content values was observed for the tablets packaged in PVC/PVDC blisters. However, there was no impact on any other attributes. All tested parameters are within the proposed specification.
Additional data were presented from studies under stress conditions (50°C, 25°C/60% RH open, 40°C/75%RH open, photostability (as per ICH) and freeze-thaw cycling). The results indicate that the drug product is stable under all stress conditions employed and that any changes observed did not impact any critical quality attributes of the tablets such as appearance, potency, impurities or dissolution.
The overall data support the proposed shelf-life and storage conditions.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

The quality of Eliquis film coated tablets is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Information on development, manufacture and control of the drug substance has been presented in a satisfactory manner. The quality of the active substance is considered sufficiently described and adequately supported by data. Sufficient chemical and pharmaceutical documentation relating to development, manufacture and control of the drug product has been presented.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The results of tests carried out indicate satisfactory consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in the clinic.
Stability tests indicate that the product under ICH guidelines conditions is chemically stable for the proposed shelf life.

2.3. Non-clinical aspects

2.3.1. Introduction

2.3.2. Pharmacology

Primary pharmacodynamic studies

Apixaban inhibits free factor Xa (FXa) as well as thrombus-associated FXa and FXa within the prothrombinase complex. Unlike the direct 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.

In diabetic/obese mice, twice daily dosing of apixaban significantly decreased elevated levels of thrombotic biomarkers. 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. In addition, apixaban also effectively inhibited the growth of a preformed intravascular thrombus, suggesting the potential opportunities for apixaban in the treatment of thrombosis.
In conclusion, the results showed that apixaban is a highly potent, selective, rapid and reversible inhibitor of the human coagulation factor Xa.

Secondary pharmacodynamic studies

In the ligand binding and enzymatic assays, apixaban did not significantly alter ligand binding or activity (≥50% of control) in any of the assays, thereby suggesting high selectivity of apixaban for FXa. Next to these assays, no other secondary pharmacodynamic studies were performed.

Safety pharmacology programme

Safety pharmacology studies were performed to examine the potential effects of apixaban on cardiovascular, respiratory and central nervous systems.

Cardiovascular system

The potential effects of apixaban on the cardiovascular system were evaluated in *in vitro* and *in vivo* safety pharmacology and nonclinical toxicology studies, including the *in vitro* hERG and rabbit Purkinje fiber assay, 2 single-dose (oral and IV) cardiovascular telemetry studies in beagle dogs, an escalating IV dose cardiovascular study in mongrel dogs, a 3-month and 1-year oral toxicity study in dogs with cardiovascular assessment.
In addition, the potential effect of the major metabolite, O-desmethyl apixaban sulfate, on the cardiovascular system was evaluated independently utilizing *in vitro* assays.

At concentrations highly exceeding the human recommended dose, apixaban and its metabolite had no significant effects in the hERG and Purkinje fiber assay, indicating a low probability for prolongation of the QT interval and the action potential duration. In anesthetised dogs, apixaban caused death and adverse cardiovascular effects. However, these adverse effects are most likely related to the combination of anaesthesia and the vehicle used to deliver apixaban, since no adverse effects were observed following administration of apixaban to conscious dogs at doses that induce higher Cmax values than those reached in the anesthetised dogs. All doses tested are highly exceeding the human recommended dose.

Respiratory system

In repeat-dose toxicity studies that included assessment of respiratory rates, lung sounds (thoracic auscultation), and/or arterial oxygen saturation in dogs, apixaban caused no adverse findings at the highest doses tested (dog ≤ 20 mg/kg/day for up to 3 months, AUC is 41× the clinical AUC).

Central nervous system

Neurologic evaluations assessed mental state, gait, posture, cranial nerve function (assessed through menace response, pupillary light response, lid blink, eye retraction, gag reflex, eye position at rest, muscle palpation, and tongue examination) and peripheral nerve function (muscle tone, spinal reflexes, and postural reactions). In addition, body temperature was measured.
In a 3-month repeated dose toxicity study in dogs, apixaban produced no neurologic changes indicative of CNS toxicity at AUC values 41× the clinical AUC.

In conclusion, at doses highly exceeding the human recommended dose, apixaban did not induce respiratory or CNS toxicity.

Pharmacodynamic drug interactions

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

2.3.3. Pharmacokinetics

Analytical methods
The analytical methods used in the different pharmacokinetic and toxicokinetic studies were well-described and properly validated. Results of interday precision, intraday precision,accuracy and stability were satisfactory.

Absorption

In vitro data 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.
Absorption may also be limited by dissolution rate (at high doses).

Single dose pharmacokinetics
In a comparative study elimination half-life in rats (2-3 hrs) was shorter than in dogs (5-6 hrs) and chimpanzees (5-7 hrs). Distribution volume is 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) is low (10, 2 and 1% respectively) compared to hepatic blood flow.
The toxicokinetic data show that exposure increases less than dose-proportional. In particular at high doses and in the dietary studies exposure hardly increased with increasing dose. There is no evidence of sex-related differences. In some studies exposure increases somewhat with prolonged administration, but this is not consistently found in all studies.

Distribution
Plasma to blood ratios of about one in dog and human blood indicate uniform distribution between plasma and red blood cells and thus no specific distribution to red blood cells.

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. At the tested concentrations there was no effect of concentration or gender. In mice protein binding is much lower, with 44-67 % unbound, dependent on the tested concentration (range 100 – 2000 ng apixaban/ml). These differences between the species used in the toxicological studies and humans should be taken into account in interpreting the toxicology studies.

Two single dose radiolabel distribution studies were provided in rats. The data show a wide distribution, with the highest values in excretory organs (liver, kidney, urinary bladder (and contents), bile) and intestinal tract (and contents). After a dose of 20 mg/kg in male Long-Evans rats also relatively high Cmax and AUC were found in adrenals, lungs, thyroid gland, but after a dose of 5 mg/kg in Sprague Dawley rats (both sexes) these organs showed Cmax similar to most other organs and tissues. There was no qualitative difference in distribution between male and female rats, but the female rats showed higher Cmax values in the intestinal tract.

Distribution in pregnant rats/fetuses: Cmax in amnion was high. Significant concentrations were found in placenta and fetal blood, kidney and liver. Toxicokinetic data collected in the reproductive and developmental toxicity studies in rats, mice and rabbits showed that generally fetal plasma concentrations of apixaban were lower than those in the dams.
Distribution to rat milk: 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 (at the plasma Tmax (0.5 hr) 8.5 fold, AUC in milk was about 30 fold plasma AUC) suggests involvement of active transport (possibly BCRP transporter). Elimination half life from rat milk, blood and plasma was similar.

Metabolism
Apixaban is mainly metabolized by CYP3A4/5 with conjugation via SULT1A1, but several other CYP and SULT isozymes are also involved. No apixaban metabolites were found to have pharmacological activity and there were no unique human metabolites.

Excretion
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 (in mice about 70% in the first 12 hrs, in rats and dogs about 70% in the first 48 hrs, and in female rabbits about 55 % in the first 48 hrs) and most of the remainder of the dose in urine (mice about 14% in the first 12 hrs, rats 11-13% in 48 hrs, dogs about 8.5% in 48 hrs, and female rabbits much less : 2% in 48hrs). Bile-duct cannulated rats showed that part of the dose was eliminated 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

(male rats 21% and female rabbits 23% in 24 hrs). 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 is probably unabsorbed apixaban. Furthermore, there is evidence for secretion of apixaban and metabolites into the intestine which is mostly likely caused by excretion via P-glycoprotein. The rabbit data showed a much larger extent of biotransformation (larger role of metabolic clearance) in this species compared to the other species.

Pharmacokinetic interactions
Apixaban is not an inhibitor or inducer of CYP; inhibition was only observed at concentrations 25 times the maximal observed human plasma concentrations. In addition, apixaban does 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. The SmPC advises caution when co-administering apixaban with strong inhibitors and inducers of both CYP3A4 and P-glycoprotein.

Other pharmacokinetics studies
In fasted beagle dogs, 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).

2.3.4. Toxicology

Single dose toxicity

Single dose oral studies in mice (up to 4000 mg/kg), rats (up to 4510 mg/kg), dogs (up to 1500 mg/kg) and cynomolgus monkeys (up to 300 mg/kg) revealed no other drug-related effects than those related to the pharmacodynamic action of apixaban. In particular some monkeys died due to excessive bleeding after blood sampling.

Repeat dose toxicity

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 is concluded that the metabolite has been tested in the pivotal studies, but that these studies reveal 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.

Genotoxicity

Based on a battery of four genotoxicity assays (gene mutations in bacteria, chromosomal aberrations *in vitro* in CHO cells and in two *in vivo* assays in rat bone marrow (micronucleus assay) and rat peripheral blood lymphocytes) there was no evidence for genotoxicity of apixaban under the conditions of the assays.

Carcinogenicity

Two 2 year carcinogenicity studies were provided. In both studies apixaban was administered via the dietary route, up to a dose of 1500 mg/kg/day in male mice and 3000 mg/kg/day in female mice and up to a dose of 600 mg/kg in rats. Sufficient toxicokinetic data were provided. Both the mouse and the rat carcinogenicity study suggest a slight increase of tumours (benign – increased endometrial polyps - in the mice, malignant – lymphoma - in the rats) at the highest dose level, however, with incidences still within the range of historical controls. Taking into account the provided historical data, the negative genotoxicity results and the absence of non-genotoxic toxicity which might lead to epigenetic tumour induction at high doses, it is concluded that it is most likely that the results are due to normal variability.

Reproduction Toxicity

In an oral fertility/early embryonic development study no effects on male or female fertility or on early embryonic development was found at tested doses of 0, 50, 200 and 600 mg apixaban/kg/day (from 2 weeks before mating through GD7 (females) or sacrifice (males)). The NOAEL was 600 mg/kg/day (AUC 28 µg.h/ml in males and 36 µg.h/ml in females).
Embryo-foetal developmental studies were done in rats (doses 100-3000 mg/kg/day), mice (doses 600-1500 mg/kg/day) and rabbits (oral : 60 -1500 mg/kg/day, intravenous : 1.25 – 5 mg/kg/day). In rats systemic exposure was confirmed, but no AUC was determined. However, based on limited measurements of plasma apixaban concentrations in the embryo-foetal developmental study and the exposure data from other rat studies it is plausible that exposure has been high enough. In mice, the AUC was > 13 times human AUC at a dose of 2.5 mg BID. In the rabbit study, exposure after oral (AUC < human AUC) as well as intravenous (AUC 2.5 times human AUC) administration remained low. The mouse study was added because of the low exposure in the rabbit study. In all three species, fetal plasma apixaban concentrations were lower than in the dam. The only observed effect during these studies consisted of red perivaginal substance in the rat study, presumably due to hemorrhage caused by the pharmacodynamic action of apixaban.
In a rat pre/postnatal development study at doses of 0, 25, 200 and 1000 mg apixaban/kg/day from GD6 – post partum day 20, the only effects found in dams in addition to expected increases of PT and aPTT were increased incidence of red liquid/mucoid vaginal discharge. The only observed effects on the offspring were a slightly reduced mating and fertility indices in the F1 females. Although considered drug related the values were within the historical control range. In the absence of other changes on reproduction or development, the relevance of this finding for the clinical practice is doubtful. The NOAEL for maternal toxicity, and F1 male development was 1000 mg/kg/day (AUC 39 times human AUC) and for F1 female reproduction 25 mg/kg/day (AUC 9.75 times human AUC).

Other toxicity studies

Juvenile toxicity study
An exploratory juvenile rat toxicity study was done, in which cross-fostered rat pups were treated from postnatal day (PND) 4 to PND 23. Tested doses were 0, 25, 200 and 1000 mg/kg/day. On PND 23 the animals were sacrificed. No adverse effects were found. Toxicokinetic data show a relatively high systemic exposure on PND 10 with plasma concentrations at expected Tmax about 3-6 times the Cmax at PND23. This age-related systemic exposure is considered to reflect metabolic maturation of juvenile rats between PND 4 and 23. The AUC at the highest tested dose at PND 23 was about 50 times the human AUC. According to the non-clinical overview a definitive 90-day study (with 1 months recovery phase) in juvenile rats dosed from PND4 to 90 is currently ongoing with doses of 10, 50, and 600 mg/kg/day to support potential pediatric use.

Impurities
Since there are no impurities above the ICH qualification threshold of 0.15%, no further toxicity data of impurities are required. All potential genotoxic impurities are below the level of 150 ppm, resulting in a maximum exposure to below the TTC as defined in the Guideline on the limits of genotoxic impurities (EMEA/CHMP/QWP/251344/2006) and the Q&A document of this guideline.

Phototoxicity
Based on an *in vitro* photoxicity test (3T3 NRU PT) in Balb/c 3T3 mouse fibroblasts there is no evidence for phototoxic potential of apixaban.

2.3.5. Ecotoxicity/environmental risk assessment

The Predicted Environmental Concentration (PEC) in surface water ($PEC_{surface\ water}$) calculated in Phase I exceeded the trigger value of 0.01µg/L and a Phase II environmental fate and effects analysis was undertaken.
In phase II, the F_{pen} was refined. A $PEC_{surfacewater}$ of 0.00125 µg/L was calculated using this refined F_{pen}. Based on this $PEC_{surfacewater}$ value, the trigger value for Phase II Tier A assessment of 0.01 µg/L is not exceeded.
Although not necessary, the applicant provided a Phase II Tier A assessment. Using the No Observed Effect Concentrations (NOEC) from the Phase II Tier A studies, Predicted No Effect Concentrations (PNEC) were calculated using appropriate assessment factors.
The following values were obtained:
$PNEC_{microorganism}$ = 100,000 µg/L
$PNEC_{surface\ water}$ = 360µg/L
$PNEC_{groundwater}$ = 960µg/L
The PEC/PNEC ratios were below the trigger values for further studies in the aquatic environment or on microorganisms and based on the Koc value, a risk assessment for the terrestrial compartment is not needed.
Apixaban was not readily biodegradable and significant amounts shift into the sediment, therefore effects on sediment-dwelling organisms were investigated in Phase II Tier B.

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 PBT/vPvB
PBT-assessment					
Parameter	**Result relevant for conclusion**				**Conclusion**
Bioaccumulation	log K_{ow}	1.2			not B
	BCF	not triggered			
Persistence	DT50 or ready biodegradability	not readily biodegradable			potentially persistent
Toxicity	NOEC or CMR	> 1 mg/L, not CMR			not T
PBT-statement :	The compound is not considered as PBT nor vPvB				
Phase I					
Calculation	**Value**	**Unit**			**Conclusion**
PEC $_{surfacewater}$, refined	0.00125	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 $DT_{50,\ whole\ system}$ = 100-182 d % shifting to sediment = 40.2-52.0			$DT_{50,\ sediment}$ was not reported.
Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**Value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test/ *Pseudokirchneriella subcapitata*	OECD 201	NOEC	3.6×10^3	µg/L	
Daphnia sp. Reproduction Test	OECD 211	NOEC	9.6×10^3	µg/L	
Fish, Early Life Stage Toxicity Test/ *Pimephales promelas*	OECD 210	NOEC	10×10^3	µg/L	
Activated Sludge, Respiration Inhibition Test	OECD 209	EC	1.0×10^6	µg/L	
Phase IIb Studies					
Sediment dwelling organism	OECD 218	NOEC	100	mg/kg	*Chironomus riparius*

The appropriate studies have been conducted according to existing guidelines and have been found valid for use in the risk assessment. Based on the results of the Applicants' Phase II Tier A assessment, no adverse effects of apixaban are expected for the STP, surface water and groundwater compartment. Based on the results of the Applicants' Phase II Tier B assessment, no adverse effects of apixaban are expected for the sediment compartment. The overall conclusion is that no adverse effects on the environment are expected for apixaban.

2.3.6. Discussion on non-clinical aspects

Pharmacological and pharmacokinetic documentation were clear and satisfactory.

With regard to toxicology, the issues below were raised during assessment for further clarification.
1) The exposure to the major human metabolite O-desmethyl apixaban sulfate was relatively low in all animal toxicity studies, due to low formation in the animal species in spite of very high exposure to the parent compound. As a consequence the value of the toxicity studies for the safety assessment of this metabolite is very limited and additional data on the toxicity of this metabolite, e.g. by administering the metabolite instead of the parent compound, or for justification of not providing such data was further requested during assessment.

Based on the additional documentation submitted, it was concluded that O-desmethyl apixaban sulfate is not pharmacologically active and showed no significant activity in *in vitro* cardiovascular safety studies. However 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 because some results from pharmacodynamic and safety pharmacology studies were available in addition to the toxicity studies with limited exposure, no further toxicity data are requested.

2) In spite of very high systemic exposure, the toxicity studies hardly showed any toxicity related to the anticoagulatory effect of apixaban.
Therefore, the applicant was asked to discuss the sensitivity of the animal species for the pharmacodynamic effect compared to humans for the interpretation of the non-clinical results, which suggest little risk of bleeding, even at overdose, e.g. around parturition.

Based on the additional documentation provided, the CHMP concluded that based on Cmax values there is about a factor 3 – 5 between the highest values obtained in the long-term toxicity studies in rats and dogs and the lowest values at which significant pharmacodynamic effects were found. This is consistent with a difference in sensitivity between the tested species and humans. The low bleeding tendency found in toxicity studies should be interpreted with caution when extrapolating to humans. The point can be acceptable, provided that the following sentence is added to section 5.3. of the SMPC: "In the toxicity studies little to no increase of bleeding tendency was found. However, since this may be due to a lower sensitivity of the non-clinical species compared to humans, this result should be interpreted with caution when extrapolating to humans."

The CHMP raised the issue of potential hepatotoxicity referring to existing data in dogs at a dose of 30 mg/kg suggesting hepatotoxicity at a systemic exposure of 171 µg x hr/ml. The MAH provided further clarification on the results. It was concluded by the CHMP that the way of reporting the results of the two different histopathological assessments of the liver had caused confusion that needed to be further explained. After further review of the histopathological results of the other repeated dose studies, the CHMP agreed with the applicant that overall there was no evidence of hepatotoxicity.

The GLP status of some laboratories which carried out pivotal toxicity studies was further clarified and solved during the assessment. All pivotal safety studies were GLP-compliant, according to the study reports.

2.3.7. Conclusion on the non-clinical aspects

Overall preclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, fertility and embryo-foetal development. In the offspring of pregnant rats treated with apixaban there were decreases in mating and fertility. These effects were minimal and observed only at exposures considered sufficiently in excess of the maximum human exposure indicating little relevance to clinical use.

The major observed effects in the repeated dose toxicity studies were those related to the pharmacodynamic action of apixaban on blood coagulation parameters. In the toxicity studies little to no increase of bleeding tendency was found.

However, since this may be due to a lower sensitivity of the non-clinical species compared to humans, this result should be interpreted with caution when extrapolating to human. This is highlighted in the SmPC.

2.4. Clinical aspects

2.4.1. Introduction

The clinical pharmacology profile of apixaban has been characterized based on the results of 26 clinical pharmacology studies. To support the current proposed indication four additional studies were conducted (1 phase II, 3 phase III). There are 6 ongoing Phase III and 1 ongoing Phase II randomized, controlled apixaban studies that will evaluate efficacy and safety in other indications (prevention of stroke and systemic embolism in AF, VTE treatment, secondary prevention of acute coronary syndrome and VTE prevention in subjects with acute medical illness).

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.

2.4.2. Pharmacokinetics

Apixaban is an orally active, direct, selective inhibitor of the coagulation factor Xa (FXa) that reversibly binds directly to the active site of FXa. The proposed dose in adults for prevention of VTE is 2.5 mg administered orally twice daily. The clinical pharmacology profile of apixaban has been characterized based on the results of 26 clinical pharmacology studies as well as population PK and exposure-response analyses that incorporated data from Phase 1 and Phase 2/3 studies.

Analytical methods

All analytical methods fulfilled all current requirements and recommendations regarding linearity, precision, accuracy, sensitivity and specificity. Validation and analytical reports were submitted.

Absorption

- bioavailability

The C_{max} of apixaban is reached approximately 3 to 4 h after dose administration. The absolute bioavailability of orally administered apixaban is approximately 52%. Apixaban appears to be absorbed primarily from the upper GI tract, proximal to the colon. Apixaban bioavailability was altered in the presence of CYP3A4 and P-gp modulators (see below). Apixaban was found to be a substrate for efflux transport proteins, P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP) *in vitro*.

- Bioequivalence

The comparative bioavailability study (CV185024) was conducted to further understand the performance of the Phase 2 wet-granulation tablet with respect to the Phase 3 dry-granulation tablet.
It was shown that the results with the phase II tablets can be extrapolated to the phase III and commercial products. Additionally it was shown that small changes in dissolution rate seem not to affect the overall extent of absorption.

- Food interaction

The food interaction studies showed sufficiently that the apixaban phase II tablet has no clinical significant food interaction. Consistent with these results, apixaban is proposed for administration without regard to food.

Distribution

Following an IV bolus dose, mean steady-state volume of distribution for apixaban was ~ 21 L. 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 0.068 to 0.22 μg/mL) was ~93%. *In vitro*, binding of apixaban to α1-acid glycoprotein (9%) was less than its degree of binding to human serum albumin (66%). It is unlikely that saturation of binding or drug-drug interactions mediated by α1-acid glycoprotein binding will occur. The concentration of apixaban-related compounds in erythrocytes was less than that in plasma (blood:plasma ratio of 0.7 to 0.8).

Elimination and metabolism

Apixaban is eliminated by multiple pathways including metabolism, renal clearance and biliary clearance; nonclinical data suggest that direct intestinal secretion may also be involved. The mean total cumulative recovery over the 9-day period was approximately 77%. Of the TRA recovered in the urine, approximately 85% was apixaban parent and ~80% was recovered within 24 h after dosing. Recovery of TRA in the urine paralleled the disappearance of apixaban from plasma for that period. The TRA recovered in the faeces, concerned for the major part unchanged parent (~34%). Biliary excretion contributed to the elimination of apixaban and several metabolites. The radioactivity identified in biliary excreta during the 5-h collection window (approximately 5% of TRA recovery) suggested that fecal recovery consisted of both absorbed and unabsorbed drug since the fecal recovery of TRA was larger than that seen in bile.
O-desmethyl apixaban sulfate (M1) was the major circulating metabolite. O-desmethyl apixaban sulfate does not have meaningful pharmacologic activity. Additional metabolites identified in plasma

included: O-desmethyl apixaban (M2), 3-hydroxy apixaban (M7), and hydroxylated O-desmethyl apixaban sulfate-1 (M10). The total radioactivity in circulation attributed to all 3 metabolites together was less than 3%. Metabolites accounted for approximately 25% of recovered TRA. The *in vitro* formation of O-desmethyl apixaban was primarily mediated by CYP3A4 and 3A5 with relatively minor contributions of CYP1A2 and CYP2J2; a low level of formation was catalyzed by CYP2C8, CYP2C9 and CYP2C19. Sulfate conjugation was mediated primarily by SULT1A1 with minor activity observed for SULT1A3, SULT1E1, and SULT2A1.
The pharmacokinetics of O-desmethyl apixaban sulfate (M1), the major metabolite of apixaban was difficult to establish due to the low concentrations. The M1:apixaban ratio was consistent across dose groups ranging from 13 to 16%.

Dose proportionality and time dependencies

Apixaban exhibits linear PK dose range of 2.5 to 10 mg for the tablet formulation in healthy volunteers. Apixaban AUC(INF) increased in proportion to increases in IV dose from 0.5 to 5 mg. There was no indication of time-dependent pharmacokinetics.

Variability

Within-subject variability of apixaban PK parameters was approximately 20%. The between-subject variability in the exposure of apixaban was 30% to 40% for AUC parameters and independent of dose. Inter-individual variability in PK parameters is slightly higher in patients (~40% CV).

General pharmacokinetics in healthy volunteers and patients

Based on pooled analysis of PO doses between 2.5 and 10 mg, the terminal T-half of apixaban is approximately 8-13 h. The shorter T-half observed following administration of PO doses <2.5 mg may reflect the inability to fully characterize the terminal phase with an assay LLOQ of 1 ng/mL. No pharmacokinetics were measured in patients using full pharmacokinetic sampling. Apixaban PK in subjects who received apixaban for VTEp following TKR or THR are described by the population PK analysis. In general, the effect of intrinsic factors (age, gender, body weight, renal function) characterized in Phase 1 clinical pharmacology studies accounted for the differences in exposure observed between the Phase 1 and Phase 2/3 study participants. In addition, surgery accounted for a transient 24% reduction in apixaban CLT/F in the first 3 days following surgery.
To date, apixaban has not been studied in pregnant or lactating women. The effects of smoking, diet composition, herbal products and alcohol use on the PK of apixaban have not been specifically studied in the apixaban development program.

Intrinsic factors

Mild to moderate hepatic impairment had no effect on apixaban PK or PD. However, representation of patients with moderate and severe hepatic impairment (based on Child-Pugh classification) in study CV185025 is limited, which is reflected in the SmPC. Higher apixaban exposures, up to approximately 30%, were observed for intrinsic factors such as age, female gender, or low body weight (≤ 50 kg).

Pharmacokinetic interaction studies

Based on nonclinical data, the potential for other drugs to affect apixaban exposure appear to be primarily related to the inhibition or induction of CYP3A4 and 3A5 metabolism and/or P-gp mediated efflux and represented the greatest potential for drug interactions involving apixaban.

Ketoconazole (a strong inhibitor of CYP3A4 and P-gp) had the largest effect on apixaban PK (approximately 2-fold increase in exposure). Co-administration of apixaban with such agents is not recommended.
Diltiazem, a less potent CYP3A4 and P-gp inhibitor, resulted in a 40% increase in apixaban exposure.
Naproxen, an inhibitor of P-gp, resulted in an approximately 60% increase in apixaban exposure. Naproxen appeared to affect apixaban bioavailability via inhibition of P-gp mediated transport.
Rifampin (a strong CYP inducer and P-gp inducer) reduced apixaban exposure by ~40% after IV administration and ~ 50% after PO administration; bioavailability was reduced 25% by rifampin. In light of the decrease in exposure following induction, care should be taken when administering apixaban with strong inducers of CYP enzymes or P-gp.

Famotidine had no effect on apixaban pharmacokinetics. This indicates that apixaban PK are not likely to be altered by alterations in gastric pH or coadministration with organic cation transporter (OCT) inhibitors.
Coadministration of enoxaparin with apixaban had no clinical significant effect on apixaban exposure.

Apixaban has little potential to affect the PK of other P-gp substrates based on the lack of effect on digoxin exposure, a commonly used P-gp substrate. In addition, *in vitro* data indicate that apixaban is not likely to alter the metabolism of other drugs. Apixaban did not influence pharmacokinetics of naproxen or atenolol. Based on a phase I study, no significant interaction between apixaban and aspirin or clopidogrel were seen on some bleeding parameters (see later for clinical experience).
Therefore, the potential for apixaban to affect the PK of concomitantly administered medications seems to be low.
Apixaban was found to be a substrate for efflux transport proteins P-gp and breast cancer resistance protein (BCRP). P-gp is also called ABCB1, ATP-binding cassette sub-family B member 1, and MDR1.

2.4.3. Pharmacodynamics

Mechanism of action

Apixaban is an orally active, direct, selective inhibitor of coagulation factor Xa (FXa) that reversibly binds directly to the active site of FXa, and exerts anticoagulant and antithrombotic effects by diminishing the conversion of prothrombin to thrombin (Fig PD1).

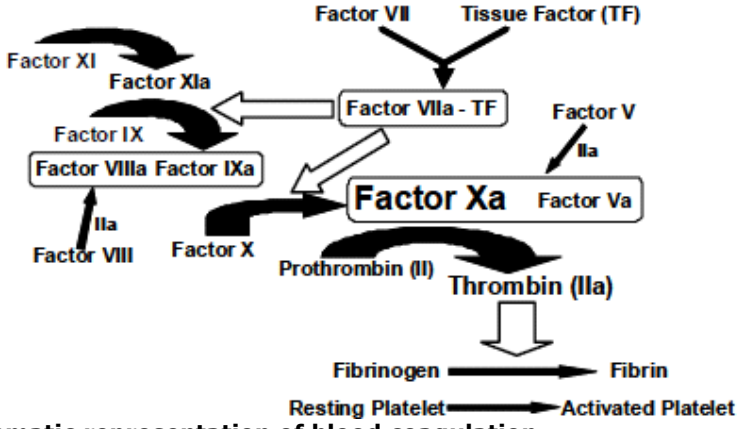


Figure PD1: Schematic representation of blood coagulation.

2.4.4. Discussion on clinical pharmacology

Primary and Secondary pharmacology

The PD effects of apixaban include inhibitory effects on FXa activity, the prolongation of clotting tests such as PT/INR, aPTT, and mPT, as well as ex vivo thrombin generation. The effect of apixaban on anti-Xa activity was assessed in multiple clinical trials with the Rotachrom® Heparin assay, covering a range of 2.5 to 20 mg. Concentration-related increases in anti-Xa activity were observed following administration of apixaban (fig PD2).

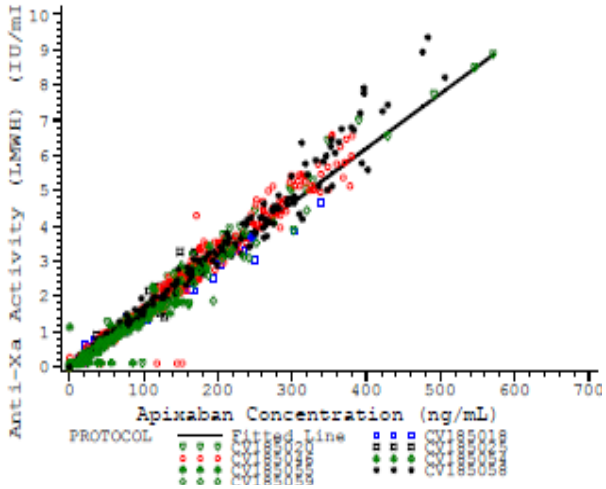


Figure PD2: Anti-Xa Activity vs Apixaban Plasma Concentration

Although apixaban does not require monitoring, the Rotachrom® Heparin assay is one available method to measure anti-Xa. The feasibility of this assay in clinical practice is discussed in the clinical section. Following administration of apixaban single PO doses of 2.5 to 50 mg, dose-related increases in International Normalised Ratio (INR) and activated partial thromboplastin time (aPTT) were observed.

Single doses of apixaban produced transient, dose-related changes in parameters of the thrombin generation curve, consistent with a direct factor Xa inhibitor. Such activity was evident over a 12 h dosing interval in line with the proposed dosing. Apixaban has no direct effect on platelet aggregation. The actual clinical implications when apixaban is co-administered with platelet aggregation inhibitors will be further discussed under safety.

Secondary Pharmacology

Study CV185031 investigated the QT prolongation potential of apixaban in a thorough QT/QTc study. This is an appropriately designed study where administered doses were much higher than those proposed in the current indication (up to 50 mg compared to the proposed 2.5 mg BID).

The lower bound of the 95% CI for the placebo-adjusted change in QTcF after treatment with moxifloxacin was >5 msec, confirming assay sensitivity. The upper bound of the 95% CI for the placebo-adjusted differences for both apixaban doses were < 10 msec, indicating that apixaban had no relevant effect on the QTcF interval in contrast to moxifloxacin.
This is further supported by pre-clinical studies showing that apixaban and O-desmethyl apixaban sulfate had negligible effects in the human related gene (hERG) and Purkinje-fiber assays (IC50 values >30 µM), indicating a low probability for QT prolongation. Available data support that apixaban has no relevant effect on the QTc interval at concentrations exceeding those anticipated in patients who receive apixaban for VTEp following TKR or THR.

2.4.5. Conclusion on clinical pharmacology

The effect of apixaban on anti-Xa activity was assessed in multiple clinical trials with the Rotachrom® Heparin assay, covering a range of 2.5 to 20 mg. Concentration-related increases in anti-Xa activity were observed following administration of apixaban. Although apixaban does not require monitoring, the Rotachrom Heparin assay is considered one method to measure anti-Xa and can help in cases where overdosing is suspected (refer SmPC section 5.1).
Apixaban has no relevant effect on QTc.

Overall, the absorption, distribution elimination and metabolism was well characterised in humans.
The O-desmethyl apixaban sulfate is the major circulating metabolite and does not have meaningful pharmacologic activity. Apixaban is eliminated by multiple pathways including metabolism, renal clearance and biliary clearance; nonclinical data suggest that direct intestinal secretion may also be involved.

The food interaction studies showed that the apixaban phase II tablet had no clinical significant food interaction. Therefore, apixaban is proposed for administration with or without food.

Apixaban exhibits linear PK dose range of 2.5 to 10 mg for the tablet formulation in healthy volunteers.

Within-subject variability of apixaban PK parameters was approximately 20%. The between-subject variability in the exposure of apixaban was 30% to 40% for AUC parameters and independent of dose. Inter-individual variability in PK parameters is slightly higher in patients (~40% CV).

To date apixaban has not been studied in pregnant or lactating women.

Mild and moderate hepatic impairment (estimated by Child-Pugh classes) had no influence on the pharmacokinetics of apixaban. Severe hepatic impairment or hepatic impairment associated with clinically-relevant coagulopathy has not been studied due to known increased bleeding risk.
It is agreed that apixaban can be given without dose adjustment to patients with mild and moderate hepatic impairment. Treatment of apixaban in severely hepatic impaired patients is not recommended.

The potential for other drugs to affect apixaban exposure appears to be primarily related to the inhibition or induction of CYP3A4 and 3A5 metabolism and/or P-gp mediated efflux and represented the greatest potential for drug interactions involving apixaban.

In conclusion, the pharmacodynamic properties of apixaban are adequately characterized and in line with a direct FXa inhibitor.
Regarding pharmacokinetic effects, a summary of the main conclusions as per the agreed SmPC is detailed below:
Food effect
ELIQUIS can be taken with or without food.

Renal impairment
There is no clinical experience in patients with creatinine clearance < 15 ml/min, or in patients undergoing dialysis therefore, apixaban is not recommended in these patients.
Limited clinical data in patients with severe renal impairment (creatinine clearance 15-29 ml/min) indicate that apixaban plasma concentrations are increased in this patient population, therefore apixaban is to be used with caution in these patients.
No dose adjustment is necessary in patients with mild or moderate renal impairment.

Hepatic impairment
ELIQUIS is contraindicated in patients with hepatic disease associated with coagulopathy and clinically relevant bleeding risk. It is not recommended in patients with severe hepatic impairment.
It should be used with caution in patients with mild or moderate hepatic impairment (Child Pugh A or B). No dose adjustment is required in patients with mild or moderate hepatic impairment.

Patients with elevated liver enzymes (ALT/AST >2 x ULN) or total bilirubin ≥1.5 x ULN were excluded in clinical trials. Therefore Eliquis should be used with caution in this population. ALT should be measured as part of the standard pre-operative evaluation.

In the case of low and high body weight, the differences in apixaban, Cmax and AUC were within 30% and 20% of the reference group, respectively. The modest influence of weight on apixaban PK is consistent with its low volume of distribution and clearance. These data indicate that the effects of extreme body weight were modest and it is agreed that no dose adjustment is recommended.

No dose adjustment is required for elderly, gender and extreme body weight since no clinically significant effect was observed on the pharmacokinetics of apixaban.

To date apixaban administration has only been studied in adult subjects (≥ 18 years of age) and no data are available in pediatric subjects.

2.5. Clinical efficacy

Four clinical studies were conducted to demonstrate the efficacy of apixaban relative to enoxaparin (table E1): one Phase II, dose-ranging study in subjects undergoing TKR surgery (CV185010), two Phase III pivotal studies in patients undergoing THR (CV185035), and TKR (CV185047), and a supportive phase III study in patients undergoing TKR (CV185034). All 4 studies were designed as

multi-centre, international, randomized, double-blind, double-dummy, active-controlled studies with a total of 11,964 subjects randomized.

Table E1: Main Efficacy studies for Apixaban in VTE-p.

Study No. Study Phase # of sites Regions	Subject Population Study Design	Study Start Enrollment Status Randomized	Treatment Number Randomized Treatment Duration	Primary and Key Secondary Endpoints / Objectives and Testing Strategy
Phase II				
CV185010 North America, Europe, Latin America, Asia/Pacific	Elective unilateral total knee replacement Randomized, multicenter, dose-ranging, double-blind study for apixaban and enoxaparin (warfarin was open-label)	14-Oct-2004 Complete Target: 1200 (150 per group)	Apixaban 5, 10, and 20 mg QD PO: 157, 156, 156, respectively Apixaban 2.5, 5, and 10 mg BID PO: 153, 157, 154, respectively Enoxaparin 30 mg q12h SC: 152 Warfarin titrated to 1.8-3.0 INR: 153 12±2 days	Primary: all VTE/all-cause death
Phase III				
Pivotal				
CV185035 Europe, North America, Asia/Pacific, Latin America	Elective unilateral total hip replacement Randomized, multicenter, double-blind, active-controlled study	08-Mar-2007 Complete Target: 5406 (2703 per group)	Apixaban 2.5 mg BID PO: 2708 Enoxaparin 40 mg QD SC: 2699 35±3 days	Primary: all VTE/all-cause death during the Intended Treatment Period Key Secondary: Major VTE during the Intended Treatment Period NI margins:[a] for primary endpoint margin is 1.25 based on RR; for key secondary endpoint margin is 1.5 based on RR Objectives and Testing: NI for primary, followed by NI for key secondary, followed by superiority for primary, followed by superiority for key secondary
CV185047 Europe, Asia/Pacific, Latin America, Africa	Elective unilateral or same-day bilateral total knee replacement Randomized, multicenter, double-blind, active-controlled study	29-Jun-2007 Complete Target: 3058 (1529 per group)	Apixaban 2.5 mg BID PO: 1528 Enoxaparin 40 mg QD SC: 1529 11±2 days	Primary: all VTE/all-cause death during the Intended Treatment Period Key Secondary: Major VTE during the Intended Treatment Period NI margins[a]: for primary endpoint both 1.25 margin based on RR and 5.6% margin based on risk difference must be met.; for key secondary endpoint margin is 1.5 based on RR Objectives and Testing: NI for primary, followed by superiority for primary, followed by NI for key secondary, followed by superiority for key secondary
Supportive				
CV185034 North America, Europe, Latin America, Asia/Pacific	Elective unilateral or same-day bilateral total knee replacement Randomized, multicenter, double-blind, active-controlled study	07-Nov-2006 Complete Target: 3058 (1529 per group)	Apixaban 2.5 mg BID PO: 1599 Enoxaparin 30 mg q12h SC: 1596 12±2 days	Primary: all VTE/all-cause death during the Intended Treatment Period Key Secondary: Major VTE/all-cause death during the Intended Treatment Period NI margin:[a] for primary endpoint both 1.25 margin based on RR and 5.6% margin based on risk difference must be met. Objectives and Testing: NI for primary, followed by superiority for primary. Superiority for key secondary was tested.

BID = twice daily, DVT = deep vein thrombosis, NI = non-inferiority, PE = pulmonary embolism, RR = relative risk, PO = orally, SC = subcutaneous, QD = once daily, and VTE = venous thromboembolism

2.5.1. Dose response study

The currently proposed apixaban dose is 2.5 mg BID, with the first dose administered 12-24 hours post surgery.

In the dose-response study CV185010, 6 doses of apixaban: 5 and 10 QD and BID, 2.5 mg BID and 20 mg QD were administered compared to enoxaparin 30 mg BID or warfarin in patients undergoing knee surgery. The main study design is outlined in Figure E1.

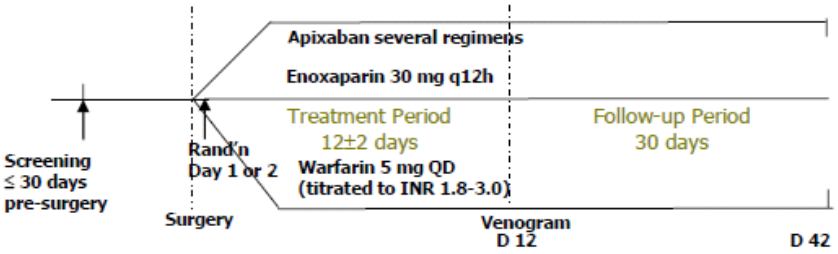


Figure E1: Study design CV185010

The study endpoints are acceptable for an exploratory study and are in line with the CHMP relevant guideline (CPMP/EWP/707/98 Rev.1 corr).

Results.
No significant dose response can be observed in the incidence of VTE/death, contrary to an obvious dose response for bleeding incidence (fig E2).

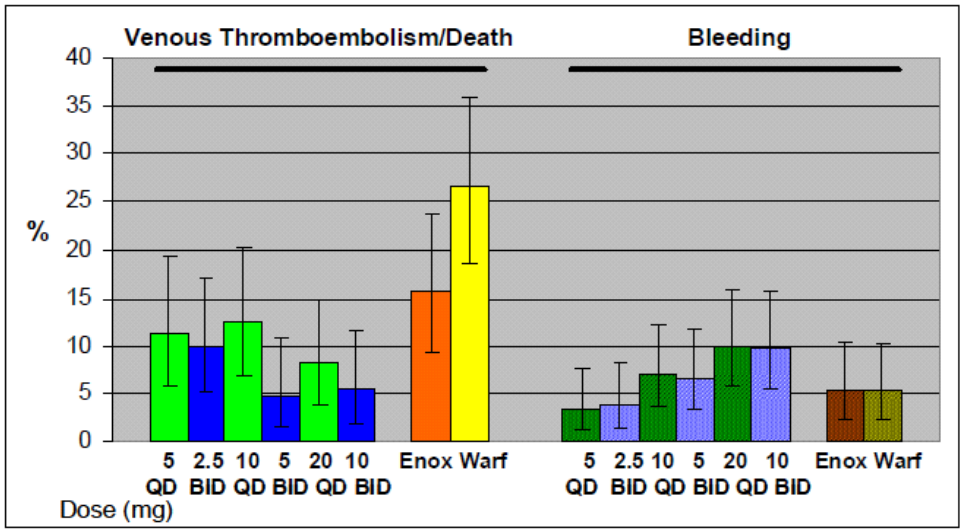


Figure E2: Summary of Primary Efficacy and Bleeding Results in CV185010

From the presented figure (E2) the dose choice appears to be limited to 2.5 bid and 5 mg QD, the only doses associated with lower bleeding incidences than enoxaparin. The incidence of death, or symptomatic PE appears sporadic, with one case of symptomatic PE each in the apixaban 20 mg QD and 10 mg BID and 2 in the enoxaparin group, and one case of death in the apixaban 2.5 mg BID (further discussed under Safety table S4).
Twice daily administration (2.5 mg BID) appears to be associated with a trend of better efficacy and lesser major bleeding events (0% versus 2.6% with the once daily administration of 5 mg) when exposure (AUC)-response is taken into account.

The administration of the first dose of apixaban post surgery (12-24 hours post-surgery) is not in line with the schedule of enoxaparin administration in EU, where the first dose is administered pre-surgery. On one hand the motivations for post-surgery application appear logical: observation of residual surgery-related bleedings before starting the anti-coagulant, also allows time for removal of indwelling epidural catheters used for neuraxial anesthesia. Both dabigatran (*treatment should be initiated orally within 1 – 4 hours of completed surgery with a single capsule and continuing with 2 capsules once daily thereafter*) and rivaroxaban (*6 to 10 hours after surgery*) are also approved for post-surgery administration; but now apixaban allows even more delayed initiation. The possible implications of this delayed administration are further discussed under the results of the phase III studies.

2.5.2. Main studies

Three phase III studies are submitted to support the indication. Two of these studies CV185035 and CV185047 are considered the pivotal studies to support the VTEp in THR and TKR indications respectively, as they employed the EU regimen of enoxaparin (40 mg QD). The third study CV185034 is considered supportive as it employed the US regimen of enoxaparin (30 mg BID).

Pivotal Studies

- ✓ **CV185035 and CV185047**

Objectives

To compare the effect of apixaban 2.5 mg BID PO vs. enoxaparin 40 mg QD SC on the composite endpoint of adjudicated asymptomatic and symptomatic DVT, non-fatal PE, and all cause death at the end of the double-blind intended treatment period in subjects undergoing elective THR (CV185035) or TKR (CV185047).

The key secondary objective was to compare the effect of apixaban vs. enoxaparin on the composite endpoint of adjudicated proximal DVT, nonfatal PE, and VTE-related death (major VTE) at the end of the double-blind intended treatment period.

Study design

The design of the clinical studies was comparable and is depicted in figure E4.

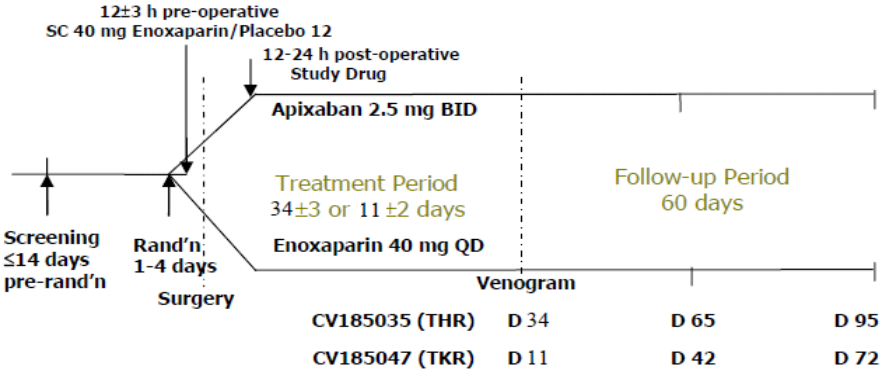


Figure E4: Study Design - CV185035 and CV185047

This design is in line with studies previously submitted for the approval of other drugs for the same indications. The comparator enoxaparin is administered in the EU approved dose for VTEp both in TKR and THR, of 40 mg QD. The duration of prophylaxis of 35 and 12 days for the THR and TKR respectively is also in line with common practice guidelines. The direct comparator used in the trial is enoxaparin.

Study participants

The stated inclusion/exclusion criteria appear appropriate. The recruited populations in both studies suffered from some symptoms of CV co-morbidity, mainly hypertension. Around 20% of the patients had repeat surgery. Patients with previous VTE/PE were less represented (around 2%), which is acceptable. Differences in co-morbidity can be seen between the two pivotal studies, reflecting the older age group of the TKR study. Importantly, the distribution is balanced between the treatment groups in each study.
Both ASA > 165 mg/day as well as NSAIDs were not permitted pre-operatively.

Outcomes / endpoints

The primary efficacy endpoint was the composite of all adjudicated VTE (PE, symptomatic DVT, asymptomatic DVT) and all-cause death during the intended treatment period in subjects undergoing elective THR surgery (period includes first day of randomization and for treated subjects, the period ended at the later of a) 2 days after last dose of study drug or b) 38 days (THR) and 14 days (TKR) after the first dose (pre- or post-surgery) of study drug.

The key secondary efficacy endpoint was the composite of adjudicated asymptomatic and symptomatic proximal DVT, non-fatal PE, and VTE-related death during the intended treatment period in subjects undergoing elective THR/TKR surgeries.

Diagnosis: For subjects with suspected symptomatic DVT during the treatment period, a physical examination and an ultrasound assessment of the symptomatic leg were performed. If diagnosis is positive, the study medication was discontinued and the subject was treated per the investigator's standard of care. If the ultrasound was inconclusive, bilateral ascending contrast venography was performed. If this was positive, the subject was managed as noted above. If the ultrasound and venogram were normal or indeterminate, the study medication and study schedule were continued. Bilateral ascending contrast venography at the end of study medication treatment was used to assess subjects who were asymptomatic for DVT.
All VTE (DVT and PE) events and events leading to death were adjudicated by one independent, expert panel of physicians, for all 4 studies.

Conduct of the studies

In study CV185035, the most important amendment was Amendment 4. The study sample size was subsequently increased from 4022 to 5406 to provide adequate power for the NI test for the primary efficacy endpoint (see before).
In study CV185047: After the results of CV185034 were known, the primary objective in CV185047 was changed from a superiority assessment to a NI assessment (prior to un-blinding) (amendment 5).

Randomisation

Study Populations. In both studies, 8,464 subjects (4,236 on apixaban and 4,228 on enoxaparin) were randomized. Within each study, a similar proportion of randomized subjects completed the protocol-specified treatment period in both treatment groups (table E3).

Table E3: Subject Disposition at the End of Treatment Period - Randomized Subjects

	CV185035		CV185047	
	Apixaban 2.5 mg BID	Enoxaparin 40 mg QD	Apixaban 2.5 mg BID	Enoxaparin 40 mg QD
Subjects randomized	2708	2699	1528	1529
Subjects completed (%)	2484 (91.7)	2447 (90.7)	1392 (91.1)	1393 (91.1)
Subjects not completing (%)	224 (8.3)	252 (9.3)	136 (8.9)	136 (8.9)
Reason for not completing				
Death	2 (<0.1)	0	1 (<0.1)	0
Adverse Event	93 (3.4)	112 (4.1)	40 (2.6)	44 (2.9)
Stroke	1 (<0.1)	4 (0.1)	2 (0.1)	0
Thrombocytopenia	0	3 (0.1)	1 (<0.1)	1 (<0.1)
MI	5 (0.2)	2 (<0.1)	1 (<0.1)	1 (<0.1)
Bleeding	15 (0.6)	13 (0.5)	4 (0.3)	5 (0.3)
DVT	3 (0.1)	6 (0.2)	11 (0.7)	8 (0.5)
PE	2 (<0.1)	6 (0.2)	3 (0.2)	1 (<0.1)
Other	66 (2.4)	77 (2.9)	18 (1.2)	28 (1.8)
Subject withdrew consent	86 (3.2)	99 (3.7)	68 (4.5)	57 (3.7)
Lost to follow-up	4 (0.1)	3 (0.1)	1 (<0.1)	0
Poor/non-compliance	1 (<0.1)	1 (<0.1)	1 (<0.1)	2 (0.1)
Pregnancy	0	0	0	0
No longer meets study criteria	15 (0.6)	15 (0.6)	18 (1.2)	22 (1.4)
Administrative reason by Sponsor	0	0	0	0
Other	23 (0.8)	22 (0.8)	7 (0.5)	11 (0.7)

The majority (61.6%) of randomized subjects in CV185035 and CV185047 were enrolled in Europe. The countries with the greatest proportions of randomized subjects were Russia (10.1%) and Ukraine (9.4%).

Baseline data

The subjects randomized in each study were representative of the population encountered in clinical practice.
Both randomized groups appear well matched in each study. Most of the patients were white, with Asian representation more apparent in the TKR study. Patients >75 are well represented in the TKR indication (around 19%), but less so in the THR study (around 12%), which probably also reflects the distribution in the target population. Patients with BMI ≥ 33 kg/m^2 were also adequately recruited (around 400 patients per treatment group in THR and more than 300 patients in TKR).

Recruitment

It is not possible to classify the recruited patients based on the Child-Pugh classification of hepatic impairment as some parameters were not measured at baseline (albumin or Prothrombin Time). Spinal and general anaesthesia were used to a comparable extent in the THR and TKR studies. The proposed apixaban regimen is applicable for both types of anaesthesia. Post-operative utilization of NSAIDs in the main studies ranged from 52% till 71% and of ASA from 5.5% till 17.6%; comparable to previous studies in THR and TKR.
In study CV185035, apixaban was administered within 12 hours in around 10% of the patients, and within 12-24 hours in 85%. The corresponding figures in the TKR study were 6% and 89%. As mentioned earlier, the proposed timing of administration of apixaban is more delayed compared to the recently approved oral anti-coagulants. This is further discussed later.

Results

Efficacy Results
In both studies, apixaban resulted in significantly lower incidence of the primary efficacy endpoint (THR: 1.39%; TKR: 15.06%) compared to enoxaparin (THR: 3.86% and TKR: 24.37%) as shown in table (E5). In study CV185035, the upper bound of the 95% CI for RR was well below 1.25 (the NI margin for the risk ratio); therefore, the Non Inferiority (NI) criterion for the primary efficacy endpoint was met. In study CV185047, the upper bound of the 95% CI for risk difference was below 5.6% (the NI margin for the risk difference), and the upper bound of the 95% CI for RR was below 1.25 (the NI margin for the risk ratio); therefore, the NI criteria for the primary efficacy endpoint were met. The corresponding 1-sided p-values for both NI tests were < 0.0001 (table E5).

Table E5: Results of Primary Efficacy Endpoint (All VTE/All-cause Death) During the Intended Treatment Period - Primary Efficacy Population

	Apix 2.5 mg BID	Enox 40 mg QD
CV185035 (HIP, ENOX 40 MG QD, PHASE 3)		
All VTE/ALL-CAUSE DEATH, n/N	27/ 1949	74/ 1917
EVENT RATE (%)	1.39	3.86
95% CI	(0.95, 2.02)	(3.08, 4.83)
RELATIVE RISK (APIX/ENOX)	0.36	
95% CI	(0.22, 0.54)	
RISK DIFFERENCE (%) (APIX-ENOX)	-2.47	
95% CI	(-3.54, -1.50)	
TWO-SIDED P-VALUE	<0.0001	
CV185047 (KNEE, ENOX 40 MG QD, PHASE 3)		
All VTE/ALL-CAUSE DEATH, n/N	147/ 976	243/ 997
EVENT RATE (%)	15.06	24.37
95% CI	(12.95, 17.46)	(21.81, 27.14)
RELATIVE RISK (APIX/ENOX)	0.62	
95% CI	(0.51, 0.74)	
ADJ. RISK DIFFERENCE (%) (APIX-ENOX)	-9.27	
95% CI	(-12.74, -5.79)	
TWO-SIDED P-VALUE	<0.0001	

Key Secondary endpoints: Also in both studies, apixaban demonstrated significantly lower incidence of the key secondary efficacy endpoint (Major VTE: proximal DVT, non-fatal PE and VTE-related death) compared to enoxaparin. In study CV185035 (THR), the event rates were 0.45% for apixaban and 1.14% for enoxaparin (table E6). The observed RRR of apixaban vs. enoxaparin for the key secondary efficacy endpoint was 60%. In study CV185047, the event rates were 1.09% for apixaban and 2.17% for enoxaparin. The observed RRR of apixaban vs. enoxaparin for the key secondary efficacy endpoint was 50%.
In both studies, as NI for the key secondary efficacy endpoint was demonstrated, superiority of apixaban vs. enoxaparin on the primary efficacy endpoint was then assessed. The upper bound of the 2-sided 95% CI for the RR was < 1; therefore, superiority for the primary efficacy endpoint was demonstrated (table E6).

Table E6: Key Secondary Efficacy Endpoints During the Intended Treatment Period

	Apix 2.5 mg BID	Enox 40 mg QD
CV185035 (HIP, ENOX 40 MG QD, PHASE 3)		
MAJOR VTE (PROXIMAL DVT/NON-FATAL PE/VTE-RELATED DEATH), n/N*	10/ 2199	25/ 2195
EVENT RATE (%)	0.45	1.14
95% CI	(0.24, 0.85)	(0.77, 1.69)
RELATIVE RISK (APIX/ENOX)	0.40	
95% CI	(0.15, 0.80)	
RISK DIFFERENCE (%) (APIX-ENOX)	-0.68	
95% CI	(-1.27, -0.17)	
TWO-SIDED P-VALUE	0.0107	
CV185047 (KNEE, ENOX 40 MG QD, PHASE 3)		
MAJOR VTE (PROXIMAL DVT/NON-FATAL PE/VTE-RELATED DEATH), n/N*	13/ 1195	26/ 1199
EVENT RATE (%)	1.09	2.17
95% CI	(0.62, 1.88)	(1.47, 3.18)
RELATIVE RISK (APIX/ENOX)	0.50	
95% CI	(0.26, 0.97)	
ADJ. RISK DIFFERENCE (%) (APIX-ENOX)	-1.04	
95% CI	(-2.03, -0.05)	
TWO-SIDED P-VALUE	0.0373	

The NI analysis was primarily performed on the primary efficacy analysis set.
The definition of primary efficacy data set, on which the NI analysis was based includes patients with protocol violations. Such analysis should have been done on the per protocol population, corresponding to Evaluable Subjects Data Set. However, results are presented later for both populations.
Per protocol analysis of the primary and major secondary endpoints revealed comparable results.
A summary of individual components of primary and key secondary efficacy endpoints with onset during the intended treatment period is tabulated in table E7.

Table E7: Summary of Some Components of Primary and Key Secondary Efficacy Endpoints with Onset During the Intended Treatment Period

	CV185035		CV185047	
	Apix 2.5 mg BID	Enox 40 mg QD	Apix 2.5 mg BID	Enox 40 mg QD
ALL-CAUSE DEATH, n/N *	3/2708	1/2699	2/1528	0/1529
EVENT RATE (%)	0.11	0.04	0.13	0.00
VTE-RELATED DEATH, n/N *	1/2708	0/2699	1/1528	0/1529
EVENT RATE (%)	0.04	0.00	0.07	0.00
NON-FATAL PE, n/N *	2/2708	5/2699	3/1528	0/1529
EVENT RATE (%)	0.07	0.19	0.20	0.00
PROXIMAL DVT, n/N ***	7/2196	20/2190	9/1192	26/1199
EVENT RATE (%)	0.32	0.91	0.76	2.17
SYMPTOMATIC DISTAL DVT, n/N *	1/2708	1/2699	3/1528	7/1529
EVENT RATE (%)	0.04	0.04	0.20	0.46

Each event was only counted once per subject, but subjects could be counted in multiple categories
* Data set = Randomized Subjects.
** Data set = Randomized subjects with an adjudicated and evaluable bilateral venogram or an adjudicated event associated with the endpoint, during the Intended Treatment Period.
*** Data set = Randomized subjects with either an adjudicated and evaluable bilateral proximal venogram or an adjudicated event associated with the endpoint, during the Intended Treatment Period.
**** Data set = Randomized subjects with either an adjudicated and evaluable bilateral distal venogram or an adjudicated event associated with the endpoint, during the Intended Treatment Period.

Intended Follow-up Period

Event rates for individual efficacy endpoints were low for both apixaban and enoxaparin during this 60-day period. In study CV185035, no subject had a PE in the apixaban group vs. 4 subjects (0.16%) in the enoxaparin group. There were 2 deaths (0.08%) in apixaban and 1 death (0.04%) in enoxaparin group. In study CV185047, three subjects (0.21%) had a PE in the apixaban group (1 was a fatal PE) vs. 1 subject (0.07%) in the enoxaparin group.

Deaths and PE

Study CV185035. There were 5 deaths in the apixaban group and 2 deaths in the enoxaparin group during the entire study duration; the cause of death is as follows:

Apixaban
- Intended Treatment Period: 3 deaths (1 VTE-related, 1 due to abdominal compartment syndrome, and 1 due to colonic neoplasm)
- Intended Follow-up Period: 2 deaths (1 due to ileal perforation and 1 due to pancreatic cancer)

Enoxaparin
- Intended Treatment Period: 1 death (fat embolism)
- Intended Follow-up Period: 1 death (stroke).

The number of observed PE events (fatal and non-fatal) was smaller for the apixaban group (3) than the enoxaparin group (9) during the Intended Treatment and Follow-up Periods.

The one case of VTE-related death reported in the apixaban during the intended treatment period concerns a 73 years old Asian male. The patient died on day 9 with PE as the adjudicated cause of death. No diagnostic procedures were performed due to the rapidity of the subject's demise. No autopsy was performed. Per protocol all deaths including this one are adjudicated independently. The adjudication committee ruled this as a VTE-related death, since acute PE could not be excluded and the subject is included in the primary analysis. In the CSR, the efficacy listing reports the result of adjudication and therefore includes this subject as having had a VTE-related death; the listing of SAEs with outcome of death reports the SAE that led to death per investigator assessment and therefore includes this subject as having had a non-VTE related cause of death.

Study CV185047. There were 3 deaths in the apixaban group and 1 death in the enoxaparin group during the entire study duration; the cause of death is as follows:

Apixaban.

- Intended Treatment Period: 2 deaths (1 VTE-related and 1 due to hepatitis, hyponatremia, aspiration of vomitus, and atrial fibrillation)
- Intended Follow-up Period: 1 death (VTE-related)

Enoxaparin.

- Intended Treatment Period: none
- Intended Follow-up Period: 1 death (major bleed [retroperitoneal]).

The number of observed PE events (fatal and non-fatal) was higher for the apixaban group (7) than the enoxaparin group (1) for the Intended Treatment and Follow-up Periods. However, the small number of events does not allow for a meaningful assessment of the effect of apixaban relative to enoxaparin on PE alone.

The one case of VTE-related death reported in the apixaban group during the intended treatment period concerns a 64 years old white female with history of ischemic heart disease, congestive heart failure (CHF), and hypertension. She received her first dose of apixaban the day after surgery. The day after, she was diagnosed with cardio-pulmonary arrest with unsuccessful cardiopulmonary resuscitation. The autopsy revealed a right pulmonary artery embolism and a right lower extremity DVT. The subject had been fully compliant with study medication prior to the event.

The one case of VTE-related death reported in the apixaban group during the intended follow-up period concerns an 85 years old white female, with PE as the adjudicated cause of death. The subject died at home approximately 1 month after her last dose of study medication. No autopsy was performed.

In the **THR** (CV185035) study, results of the main secondary endpoints are mainly driven by the favorable results of proximal DVT (7 vs 20 cases in the apixaban and enoxaparin respectively). There is a numerical reduction in the events of non-fatal PE (2 vs 5 in the apixaban and enoxaparin respectively) but there was also one case of VTE-related death in the apixaban arm. Furthermore, in the follow-up period, PE and symptomatic proximal DVT were still recorded in numerically higher numbers in the enoxaparin (4 and 3 cases respectively) compared to none in the apixaban group. Considering the clinical importance of these endpoints, the benefit of apixaban in THR is considered demonstrated.

In the **TKR** (CV185047) study, analysis of the clinically significant endpoints represented in major VTE confirmed apixaban superiority, with the benefit mainly driven by the lower incidence of proximal DVT events (0.76% and 2.17% respectively). There is a numerically higher incidence of **PE** in the apixaban group (3 vs 0 respectively) in addition to one VTE-related death versus no events with enoxaparin. Results of the follow-up period show one extra case of VTE-related death, 2 cases of PE and 2 cases of symptomatic proximal VTE, versus 0, 1 and 1 case for enoxaparin respectively.

The duration of administration of apixaban in the TKR studies is in line with that used in other studies and in the relevant CHMP guideline. These recommendations are based on several clinical reviews investigating the benefit/risk of extended thromboprophylaxis in different orthopedic surgeries. In one meta-analysis, it was shown that patients who underwent THR tended to derive greater protection from symptomatic VTE using extended thromboprophylaxis (pooled OR, 0.33; 95% CI, 0.19 to 0.56; NNT, 62) than patients who underwent TKR (pooled OR, 0.74; 95% CI, 0.26 to 2.15; NNT, 250). Accordingly, the ACCP guideline (Geerts et al., 2008) clearly recommends the extension of thromboprophylaxis beyond 10 days and up to 35 days after surgery in cases of THR (Grade 1A). However for patients undergoing TKR, the evidence of recommendation for the same extended duration is graded 2B.

In study CV185047, an equal number of patients (n=4) with PE were observed during each of the treatment periods and the follow-up periods (4:0 and 3:1 in the apixaban and enoxaparin groups respectively). The figures do not support that the duration of apixaban thromboprophylaxis was too short compared to enoxaparin. In summary, based on data from the apixaban dossier, it appears that the duration of administration of apixaban was adequate compared to enoxaparin for the recruited patients in these studies.

The missing or non-evaluable venograms rate recorded in the studies are on the higher limit recorded in previous studies, but are within the assumed rate in the statistical plan. Missing venograms were mainly due to subject refusal, however, another category "others" accounting for 13% of the missing cases was observed. The most frequent reason was due to discontinuation from the study or due to a

medical event (i.e. an adverse event not specified to be related to VTE, bleeding, stroke, or myocardial infarction). Importantly, these reasons appear balanced between the treatment groups.

Sensitivity analysis of the primary efficacy endpoints supports the robustness of the results. However, for the superiority of the secondary endpoints, sensitivity analysis is less robust, which can be attributed to the few events, as noted by the applicant. Subgroup analysis generally supported the overall results.

Supportive study

Study CV185034 was the first conducted phase III study in the indication of VTEp in the TKR. It follows the general design and endpoints of the previously presented pivotal studies, but can be considered only as supportive taking into account that the comparator enoxaparin was administered in a different dose regimen than that employed in EU. That is a dose of 30 mg BID starting 12-24 hours post-surgery, whereas in EU, it is administered as 40 mg QD with the first dose administered before surgery. So actually in this study, almost double the dose of enoxaparin is administered.

Results. The observed event rate for the primary efficacy endpoint for apixaban 2.5 mg BID (8.99%) was similar to that of enoxaparin 30 mg BID (8.85%) (Table E9). The study did not achieve the pre-defined statistical criteria for NI based on the CI for RR (RR = 1.02 with 95% CI of 0.78 to 1.32). The pre-specified NI criterion was based on meeting two conditions: (1) the upper bound of the 95% CI for the RR must not have exceeded 1.25 and (2) the upper bound of the 95% CI for the difference between event rates must not have exceeded 5.6%.

Table E9: Summary of Primary Efficacy Endpoint (Composite of All VTE/All-cause Death) During the Intended Treatment Period - Primary Efficacy Population

	Apix 2.5 mg BID	Enox 30 mg q12h
CV185034 (KNEE, ENOX 30 MG Q12H, PHASE 3)		
All VTE/ALL-CAUSE DEATH, n/N	104/ 1157	100/ 1130
EVENT RATE (%)	8.99	8.85
95% CI	(7.47, 10.79)	(7.33, 10.66)
RELATIVE RISK (APIX/ENOX)	1.02	
95% CI	(0.78, 1.32)	
ADJ. RISK DIFFERENCE (%) (APIX-ENOX)	0.11	
95% CI	(-2.22, 2.44)	
TWO-SIDED P-VALUE	0.8850	

The applicant attributes this inability to show NI of apixaban to enoxaparin to the unexpectedly low event rate of enoxaparin. The sample size of the study was based on an event rate of total VTE/all cause death around 16% (reported in the phase II study CV185010 table E2), whereas the currently reported rate in the study was 8.85%. The applicant argues that this was the lowest recorded event rate for enoxaparin. This argument is accepted as in the study RE.MOBILIZE comparing dabigatran to enoxaparin 30 mg BID, results of enoxaparin on total VTE/all cause death were reported to be 25.3%, were higher than that reported in either TKR studies currently presented. Admittedly the standard of care could have improved through the time, but does not account alone for such a decrease in event rates.

The observed event rate for the ***key secondary efficacy endpoint*** was higher for apixaban (2.05%) than enoxaparin 30 mg BID (1.64%), but was not significant (p-value = 0.44)(table E10).

Table E10: Key Secondary Efficacy Endpoints During the Intended Treatment Period

	Apix 2.5 mg BID	Enox 30 mg q12h
CV185034 (KNEE, ENOX 30 MG Q12H, PHASE 3)		
PROXIMAL DVT/NON-FATAL PE/All-CAUSE DEATH, n/N *	26/ 1269	20/ 1216
EVENT RATE (%)	2.05	1.64
95% CI	(1.39, 3.01)	(1.06, 2.55)
RELATIVE RISK (APIX/ENOX)	1.25	
95% CI	(0.70, 2.23)	
ADJ. RISK DIFFERENCE (%) (APIX-ENOX)	0.36	
95% CI	(-0.68, 1.40)	
TWO-SIDED P-VALUE	0.4443	

This difference in the event rates was driven by the difference in PEs (16 on apixaban and 7 on enoxaparin 30 mg BID)(table E11).

Table E11: Summary of Individual Components of Primary and Key Secondary Efficacy Endpoints with Onset During the Intended Treatment Period.

	Apix 2.5 mg BID	Enox 30mg q12h
ALL-CAUSE DEATH, n/N *	3/ 1599	3/ 1596
EVENT RATE (%)	0.19	0.19
VTE-RELATED DEATH, n/N *	2/ 1599	0/ 1596
EVENT RATE (%)	0.13	0.00
NON-FATAL PE, n/N *	14/ 1599	7/ 1596
EVENT RATE (%)	0.88	0.44
PROXIMAL DVT, n/N ***	9/ 1254	11/ 1207
EVENT RATE (%)	0.72	0.91
SYMPTOMATIC DISTAL DVT, n/N	1/ 1599	6/ 1596
EVENT RATE (%)	0.06	0.38

An opposite trend was observed during the 60-day Intended Follow-up Period (1 [0.06%] for apixaban and 5 [0.32%] for enoxaparin).

It should be noted that these are numerical increases and should be considered with caution. Of note, data submitted in previous regulatory submissions for other products, in the RE-MOBILIZE study, the approved dose of dabigatran was associated with 6 cases of PE (1%) versus 0 cases for the lower dose and 5 cases (0.7%) with enoxaparin. Also one case of VTE-related death was reported with dabigatran (0.2%) versus no cases reported with the lower dose or enoxaparin.

The applicant submitted a thorough analysis investigating the possible contributing factors to this higher incidence of PE in the apixaban group. The applicant did not specifically address the issue of duration of hospitalization. It can be agreed with the applicant that for the investigated risk factors in patient characteristics none can be identified that could be specifically attributed to this higher incidence of PE. The applicant did not specifically address the issue of duration of hospitalization. There was a higher incidence of total VTE reported in Russia/Ukraine which was attributed to the longer hospitalization period in these countries. However, this explanation can not hold when comparing the hospitalization period between studies CV185047 (mean 11 days) and showing a lower incidence of VTE events, compared to study CV185034 (mean 6 days). So, it can be concluded that duration of hospitalization does not per se play a major role in the incidence of VTE events.Regarding geographic location and medical practice, it can be agreed with the applicant that a higher diagnostic workup in US/Canada may have contributed to the higher reported incidence of PE in study CV185034 as shown in the table below.

Assessment of Ascertainment Bias for PE - Randomized Subjects (Pooled CV185035, CV185047, CV185034 and CV185010)

	Suspected PE/Randomized	CI/Suspected PE	Confirmed PE/Randomized
CANADA	59/ 1861 (3.17)	38/ 59 (64.41)	20/ 1861 (1.07)
USA	39/ 1938 (2.01)	31/ 39 (79.49)	12/ 1938 (0.62)
NORTH AMERICA	98/ 3799 (2.58)	69/ 98 (70.41)	32/ 3799 (0.84)
EUROPE (EXCLUDING RUSSIA AND UKRAINE)	26/ 4213 (0.62)	15/ 26 (57.69)	10/ 4213 (0.24)
REST OF WORLD	17/ 3959 (0.43)	7/ 17 (41.18)	10/ 3959 (0.25)

However, this can not explain the imbalance noticed between the apixaban and enoxaparin arms, as it is a randomized study. In addition, the applicant brought forward a hypothesis that these early cases of PE could have been cases of fat emboli misdiagnosed as PE. This hypothesis is not supported, as these cases are supposedly adjudicated and the diagnosis is not solely based on the radiological findings.

Deaths: There were 3 deaths in the apixaban group and 6 deaths in the enoxaparin group during the entire study duration; the cause of death is as follows:

Apixaban

- Intended Treatment Period: 3 deaths (2 VTE-related, 1 due to myocardial infarction)
- Intended Follow-up Period: none

Enoxaparin

- Intended Treatment Period: 3 deaths (1 bleeding, 1 atrial fibrillation, and 1 due to unknown cause)
- Intended Follow-up Period: 3 deaths (2 VTE-related and 1 due to myocardial infarction).

The first case of VTE-related death concerns a 65 years old white female without history of cardiovascular disease randomized to apixaban 2.5mg BID. She had no apparent VTE risk factors other than the current orthopedic procedure. On the day after surgery, three hours after the first dose of study drug, she became hypotensive, hypoxemic and required mechanical respiratory support. She was diagnosed with cardiac arrest. Resuscitative measures were unsuccessful. An autopsy was performed and it revealed a PE.

The second case concerns a 66 years old white male, with PE as the adjudicated cause of death. Prior to the first dose of study medication, the subject became diaphoretic, short of breath, and hypotensive and was given volume resuscitation. The study drug was administered more than 24 hours after surgery. The PE event occurred the day after surgery (Day 1) and was confirmed by lung scan. The patient developed cardiopulmonary arrest and death occurred later the same day. No autopsy was performed.

Two cases of death were reported with enoxaparin during the intended follow-up period.
One subject was a 72-year-old white female randomized to enoxaparin 30 mg q12h. She had a medical history of hypertension and a prior cerebrovascular accident and had BMI of 36 kg/m2. On study Day 1 (the day after surgery) she experienced hypoxemia, hypotension and respiratory difficulties leading to cardio-respiratory arrest. Blinded study drug was discontinued after this SAE. She was successfully resuscitated but had multiple complications including hypoxic encephalopathy and urosepsis. These complications led to a prolonged hospital course resulting in her death on Day 41. An autopsy was not done. The case was adjudicated as a VTE-related death since PE could not be excluded. The clinical presentation prior to death could also have been caused by other conditions such as fat embolism or cardiac arrest due to another cause.
The other subject was a 78-year-old white female without significant cardiovascular disease history. She experienced a cardio respiratory arrest on study Day 1 (the day after surgery). Blinded study drug was discontinued after this SAE. During the event, she was hypotensive, hypoxemic and required endotracheal intubation due to respiratory failure. The etiology of the event was attributed to a PE, confirmed by spiral CT scan. The subject remained hospitalized. Her clinical course was complicated by septic shock, aspiration pneumonia, acute respiratory distress syndrome (ARDS), and acute renal failure (ARF). On Day 21, the subject had a second PE and died of its complications. The case was adjudicated per protocol and a VTE event resulting in death was confirmed.

Summary of main studies

The two 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).

Summary of Efficacy for trial ADVANCE-2 (CV185047)

Title: A Phase 3, Randomized, Double-blind, Active-controlled (Enoxaparin 40 mg QD),Parallel group, Multi-center Study to Evaluate the Safety and Efficacy of Apixaban in Subjects Undergoing Elective Total Knee Replacement Surgery				
Study identifier	CV185047			
Design	randomized, double-blind, double-dummy, parallel-group			
	Duration of main phase:	12 ± 2 days		
	Duration of Run-in phase:	not applicable		
	Duration of Extension phase:	not applicable		
Hypothesis	Apixaban 2.5 mg orally twice daily (BID) is non-inferior to subcutaneous enoxaparin 40 mg once daily (QD) in reducing the event rate on the composite endpoint of venous thromboembolic (VTE) events (asymptomatic and symptomatic deep vein thrombosis [DVT] and non-fatal pulmonary embolism [PE]) and all-cause death through Day 12 of double-blind treatment in subjects undergoing elective unilateral or same day bilateral total knee replacement surgery.			
Treatments groups	Apixaban	Oral apixaban, 2.5 mg BID, beginning 12-24 hours after surgery; subcutaneous placebo, once daily beginning 12 ± 3 hours before surgery; duration 12 ± 2 days after surgery; 1528 randomized		
	Enoxaparin	Subcutaneous enoxaparin, 40 mg QD, beginning 12 ± 3 hours before surgery; oral placebo, BID, beginning 12-24 hours after surgery; duration 12 ± 2 days after surgery; 1529 randomized		
Endpoints and definitions	Primary endpoint	All VTE and death	Composite of adjudicated asymptomatic and symptomatic DVT, non-fatal PE (All VTE) and all cause death through Day 12 of double-blind treatment.	
	Secondary endpoint	Major VTE	Composite of adjudicated proximal DVT, non-fatal PE and VTE-related death through Day 12 of double-blind treatment.	
	Other endpoints	Efficacy components	Components of the primary and key secondary efficacy endpoints and composites of individual components.	
	Safety endpoints	Bleeding	Major bleeding, Clinically relevant non-major bleeding, and the composite of Major or clinically relevant non-major bleeding.	
Database lock	05-Mar-2009			

Results and Analysis

Analysis description	**Primary Analysis**			
Analysis population and time point description	Primary efficacy population consisted of all randomized subjects who had an adjudicated and evaluable bilateral venogram performed through the Day 12 visit, or had an asymptomatic or symptomatic DVT or PE through Day 12 that is confirmed by adjudication, or died due to any cause through Day 12.			
Descriptive statistics and estimate variability	Treatment group	Apixaban	Enoxaparin	
	Number of subject	976	997	
	Primary endpoint (rate)	15.06	24.37	
	95% CI	(12.95, 17.46)	(21.81, 27.14)	
Effect estimate per comparison	Primary endpoint	Comparison groups	Apixaban vs. enoxaparin	
		Relative risk	0.62	
		95% CI	(0.51, 0.74)	
		P-value for non-inferiority*	< 0.0001	
		P-value for superiority*	< 0.0001	
Notes	* denotes two-sided p-value			
Analysis description	**Major VTE**			
Analysis population and time point description	Key secondary efficacy population consisted of all randomized subjects who had an adjudicated and evaluable proximal bilateral venogram performed through the Day 12 visit, or had an asymptomatic or symptomatic proximal DVT or non-fatal PE through Day 12 that is confirmed by adjudication, or had a VTE-related death through Day 12.			
Descriptive statistics and estimate variability	Treatment group	Apixaban	Enoxaparin	
	Number of subject	1195	1199	
	Major VTE (rate)	1.09	2.17	

	95% CI	(0.62, 1.88)	(1.47, 3.18)	
Effect estimate per comparison	Major VTE	Comparison groups	Apixaban vs. enoxaparin	
		Relative risk	0.50	
		95% CI	(0.26, 0.97)	
		P-value for non-inferiority*	0.0006	
		P-value for superiority*	0.0373	
Notes	* denotes two-sided p-value			
Analysis description	**All VTE/VTE-related death**			
Analysis population and time point description	Analysis performed on all randomized subjects who had an adjudicated and evaluable bilateral venogram performed through the Day 12 visit, or had an asymptomatic or symptomatic DVT or PE through Day 12 that is confirmed by adjudication, or had a VTE-related death through Day 12.			
Descriptive statistics and estimate variability	Treatment group	Apixaban	Enoxaparin	
	Number of subject	975	997	
	All VTE/VTE-related death (rate)	14.97	24.37	
	95% CI	(12.87, 17.37)	(21.81, 27.14)	
Analysis description	**Major VTE/all-cause death**			
Analysis population and time point description	Analysis performed on all randomized subjects who had an adjudicated and evaluable proximal bilateral venogram performed through the Day 12 visit, or had an asymptomatic or symptomatic proximal DVT or non-fatal PE through Day 12 that is confirmed by adjudication, or died due to any cause through Day 12.			
Descriptive statistics and estimate variability	Treatment group	Apixaban	Enoxaparin	
	Number of subject	1196	1199	
	Major VTE/all-cause death (rate)	1.17	2.17	
	95% CI	(0.68, 1.98)	(1.47, 3.18)	
Analysis description	**Asymptomatic or symptomatic distal DVT**			
Analysis population and time point description	Analysis performed on all randomized subjects who had an adjudicated and evaluable distal bilateral venogram performed through the Day 12 visit, or had an asymptomatic or symptomatic distal DVT through Day 12 that is confirmed by adjudication.			
Descriptive statistics and estimate variability	Treatment group	Apixaban	Enoxaparin	
	Number of subject	978	1000	
	Distal DVT (rate)	14.52	23.90	
	95% CI	(12.45, 16.88)	(21.36, 26.65)	
Analysis description	**Asymptomatic or symptomatic proximal DVT**			
Analysis population and time point description	Analysis performed on all randomized subjects who had an adjudicated and evaluable proximal bilateral venogram performed through the Day 12 visit, or had an asymptomatic or symptomatic proximal DVT through Day 12 that is confirmed by adjudication.			
Descriptive statistics and estimate variability	Treatment group	Apixaban	Enoxaparin	
	Number of subject	1192	1199	
	Proximal DVT(rate)	0.76	2.17	
	95% CI	(0.38, 1.46)	(1.47, 3.18)	
Analysis description	**Other Efficacy Components: Non-fatal PE, VTE-related deaths, and all-cause death**			
Analysis population and time point description	Analysis performed on all randomized subjects. Timepoint through Day 12.			
	Treatment group	Apixaban	Enoxaparin	
	Number of subject	1528	1529	
	Non-fatal PE(rate)	0.20	0.00	
	95% CI	(0.04, 0.61)	(0.00, 0.31)	
	VTE-related death(rate)	0.07	0.00	
	95% CI	(0.00, 0.42)	(0.00, 0.31)	
	All-cause death (rate)	0.13	0.00	
	95% CI	(0.01, 0.52)	(0.00, 0.31)	
Analysis description	**Major Bleeding**			
Analysis population and time point description	Analysis performed on all randomized subjects who received at least one dose of blinded study medication for bleeding events from time of first dose of study medication through two days after the last dose of study medication.			

Descriptive statistics and estimate variability	Treatment group	Apixaban	Enoxaparin	
	Number of subject	1501	1508	
	Major bleeding rate	0.60	0.93	
	95% CI	(0.30, 1.16)	(0.54, 1.57)	
Effect estimate per comparison	Major Bleeding	Comparison groups	Apixaban vs. enoxaparin	
		Adjusted difference of Event Rates (APIX-ENOX) (%)	-0.33	
		95% CI	(-0.95, 0.29)	
		P-value*	0.3014	
Notes	* denotes two-sided p-value All bleeding criteria included surgical site bleeding. Includes bleeding events that occurred before the first dose of oral study medication.			
Analysis description	**Composite of Major or Clinically Relevant Non-major Bleeding**			
Analysis population and time point description	Analysis performed on all randomized subjects who received at least one dose of blinded study medication for bleeding events from time of first dose of study medication through two days after the last dose of study medication.			
Descriptive statistics and estimate variability	Treatment group	Apixaban	Enoxaparin	
	Number of subject	1501	1508	
	Clinically relevant non-major bleeding rate	3.53	4.77	
	95% CI	(2.71, 4.60)	(3.81, 5.98)	
Effect estimate per comparison	Major or clinically relevant non-major bleeding	Comparison groups	Apixaban vs. enoxaparin	
		Adjusted difference of Event Rates (APIX-ENOX) (%)	-1.24	
		95% CI	(-2.66, 0.18)	
		P-value*	0.0881	
Notes	* denotes two-sided p-value All bleeding criteria included surgical site bleeding. Includes bleeding events that occurred before the first dose of oral study medication.			
Analysis description	**Clinically Relevant Non-major Bleeding**			
Analysis population and time point description	Analysis performed on all randomized subjects who received at least one dose of blinded study medication for bleeding events from time of first dose of study medication through two days after the last dose of study medication.			
Descriptive statistics and estimate variability	Treatment group	Apixaban	Enoxaparin	
	Number of subject	1501	1508	
	Clinically relevant non-major bleeding rate	2.93	3.85	
	95% CI	(2.19, 3.93)	(2.98, 4.95)	
Effect estimate per comparison	Major or clinically relevant non-major bleeding	Comparison groups	Apixaban vs. enoxaparin	
		Adjusted difference of Event Rates (APIX-ENOX) (%)	-0.91	
		95% CI	(-2.20, 0.38)	
		P-value*	0.1668	
Notes	* denotes two-sided p-value All bleeding criteria included surgical site bleeding. Includes bleeding events that occurred before the first dose of oral study medication.			

Summary of Efficacy for trial ADVANCE-3 (CV185035)

Title: A Phase 3, Randomized, Double-blind, Active-controlled, Parallel-group, Multi-center Study to Evaluate the Safety and Efficacy of Apixaban in Subjects Undergoing Elective Total Hip Replacement Surgery (The Advance-3 Study Apixaban Dosed Orally Versus AntiCoagulation with Injectable Enoxaparin to Prevent Venous Thromboembolism)		
Study identifier	CV185035	
Design	randomized, double-blind, double-dummy, parallel-group	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	35 ± 3 days not applicable not applicable

Hypothesis	Apixaban 2.5 mg twice daily (BID) is non-inferior to enoxaparin 40 mg once daily (QD) in reducing the composite endpoint of venous thromboembolic (VTE) events (asymptomatic and symptomatic deep vein thrombosis [DVT] and non-fatal pulmonary embolism [PE]) and all-cause death during 35 days of double-blind treatment in subjects undergoing elective total hip replacement surgery.		
Treatments groups	Treatments groups		Treatments groups
	Apixaban		Oral apixaban, 2.5 mg BID, beginning 12-24 hours after surgery; subcutaneous placebo, once daily beginning 12 ± 3 hours before surgery; duration 35 ± 3 days after surgery; 2708 randomized
	Enoxaparin		Subcutaneous enoxaparin, 40 mg QD, beginning 12 ± 3 hours before surgery; oral placebo, BID, beginning 12-24 hours after surgery; duration 35 ± 3 days after surgery; 2699 randomized
Endpoints and definitions	Primary endpoint	All VTE and death	Composite of adjudicated asymptomatic and symptomatic DVT, non-fatal PE (All VTE) and all cause death through Day 35 of double-blind treatment.
	Secondary endpoint	Major VTE	Composite of adjudicated proximal DVT, non-fatal PE and VTE-related death through Day 35 of double-blind treatment.
	Other endpoints	Efficacy components	Components of the primary and key secondary efficacy endpoints and composites of individual components.
	Safety endpoints	Bleeding	Major bleeding, Clinically relevant non-major bleeding, and the composite of Major or clinically relevant non-major bleeding.
Database lock	20-Oct-2009		

Results and Analysis

Analysis description	**Primary Analysis**			
Analysis population and time point description	Primary efficacy population consisted of all randomized subjects who had an adjudicated and evaluable bilateral venogram performed through the Day 35 visit, or had an asymptomatic or symptomatic DVT or PE through Day 35 that is confirmed by adjudication, or died due to any cause through Day 35.			
Descriptive statistics and estimate variability	Treatment group	Apixaban	Enoxaparin	
	Number of subject	1949	1917	
	Primary endpoint (rate)	1.39	3.86	
	95% CI	(0.95, 2.02)	(3.08, 4.83)	
Effect estimate per comparison	Primary endpoint	Comparison groups	Apixaban vs. enoxaparin	
		Relative risk	0.36	
		95% CI	(0.22, 0.54)	
		P-value for non-inferiority*	< 0.0001	
		P-value for superiority*	< 0.0001	
Notes	* denotes two-sided p-value			
Analysis description	**Major VTE**			
Analysis population and time point description	Key secondary efficacy population consisted of all randomized subjects who had an adjudicated and evaluable proximal bilateral venogram performed through the Day 35 visit, or had an asymptomatic or symptomatic proximal DVT or non-fatal PE through Day 35 that is confirmed by adjudication, or had a VTE-related death through Day 35.			
Descriptive statistics and estimate variability	Treatment group	Apixaban	Enoxaparin	
	Number of subject	2199	2195	
	Major VTE (rate)	0.45	1.14	
	95% CI	(0.24, 0.85)	(0.77, 1.69)	
Effect estimate per comparison	Major VTE	Comparison groups	Apixaban vs. enoxaparin	
		Relative risk	0.40	
		95% CI	(0.15, 0.80)	
		P-value for non-inferiority*	0.0001	
		P-value for superiority*	0.0107	
Notes	* denotes two-sided p-value			
Analysis description	**All VTE/VTE-related death**			
Analysis population and time point description	Analysis performed on all randomized subjects who had an adjudicated and evaluable bilateral venogram performed through the Day 35 visit, or had an asymptomatic or symptomatic DVT or PE through Day 35 that is confirmed by adjudication, or had a VTE-related death through Day 35.			

Descriptive statistics and estimate variability	Treatment group	Apixaban	Enoxaparin	
	Number of subject	1947	1916	
	All VTE/VTE-related death (rate)	1.28	3.81	
	95% CI	(0.86, 1.90)	(3.04, 4.77)	
Analysis description	**Major VTE/all-cause death**			
Analysis population and time point description	Analysis performed on all randomized subjects who had an adjudicated and evaluable proximal bilateral venogram performed through the Day 35 visit, or had an asymptomatic or symptomatic proximal DVT or non-fatal PE through Day 35 that is confirmed by adjudication, or died due to any cause through Day 35.			
Descriptive statistics and estimate variability	Treatment group	Apixaban	Enoxaparin	
	Number of subject	2201	2196	
	Major VTE/all-cause death (rate)	0.55	1.18	
	95% CI	(0.30, 0.97)	(0.80, 1.74)	
Analysis description	**Asymptomatic or symptomatic distal DVT**			
Analysis population and time point description	Analysis performed on all randomized subjects who had an adjudicated and evaluable distal bilateral venogram performed through the Day 35 visit, or had an asymptomatic or symptomatic distal DVT through Day 35 that is confirmed by adjudication.			
Descriptive statistics and estimate variability	Treatment group	Apixaban	Enoxaparin	
	Number of subject	1951	1908	
	Distal DVT (rate)	1.03	2.99	
	95% CI	(0.66, 1.59)	(2.31, 3.86)	
Analysis description	**Asymptomatic or symptomatic proximal DVT**			
Analysis population and time point description	Analysis performed on all randomized subjects who had an adjudicated and evaluable proximal bilateral venogram performed through the Day 35 visit, or had an asymptomatic or symptomatic proximal DVT through Day 35 that is confirmed by adjudication.			
Descriptive statistics and estimate variability	Treatment group	Apixaban	Enoxaparin	
	Number of subject	2196	2190	
	Proximal DVT(rate)	0.32	0.91	
	95% CI	(0.14, 0.68)	(0.59, 1.42)	
Analysis description	**Other Efficacy Components: Non-fatal PE, VTE-related deaths, and all-cause death**			
Analysis population and time point description	Analysis performed on all randomized subjects. Timepoint through Day 35.			
	Treatment group	Apixaban	Enoxaparin	
	Number of subject	2708	2699	
	Non-fatal PE(rate)	0.07	0.19	
	95% CI	(0.00, 0.29)	(0.07, 0.45)	
	VTE-related death (rate)	0.04	0.00	
	95% CI	(0.00, 0.24)	(0.00, 0.18)	
	All-cause death (rate)	0.11	0.04	
	95% CI	(0.02, 0.35)	(0.00, 0.24)	
Analysis description	**Major Bleeding**			
Analysis population and time point description	Analysis performed on all randomized subjects who received at least one dose of blinded study medication for bleeding events from time of first dose of study medication through two days after the last dose of study medication.			
Descriptive statistics and estimate variability	Treatment group	Apixaban	Enoxaparin	
	Number of subject	2673	2659	
	Major bleeding rate	0.82	0.68	
	95% CI	(0.54, 1.25)	(0.42, 1.08)	

Effect estimate per comparison	Major Bleeding	Comparison groups	Apixaban vs. enoxaparin
		Adjusted difference of Event Rates (APIX-ENOX) (%)	0.15
		95% CI	(-0.33, 0.64)
		P-value*	0.54
Notes	* denotes two-sided p-value All bleeding criteria included surgical site bleeding. Includes bleeding events that occurred before the first dose of oral study medication.		

Analysis description	**Composite of Major or Clinically Relevant Non-major Bleeding**			
Analysis population and time point description	Analysis performed on all randomized subjects who received at least one dose of blinded study medication for bleeding events from time of first dose of study medication through two days after the last dose of study medication.			
Descriptive statistics and estimate variability	Treatment group	Apixaban	Enoxaparin	
	Number of subject	2673	2659	
	Major or clinically relevant non-major bleeding rate	4.83	5.04	
	95% CI	(4.08, 5.71)	(4.27, 5.94)	
Effect estimate per comparison	Major or clinically relevant non-major bleeding	Comparison groups	Apixaban vs. enoxaparin	
		Adjusted difference of Event Rates (APIX-ENOX) (%)	-0.21	
		95% CI	(-1.38, 0.95)	
		P-value*	0.72	
Notes	* denotes two-sided p-value All bleeding criteria included surgical site bleeding. Includes bleeding events that occurred before the first dose of oral study medication.			
Analysis description	**Clinically Relevant Non-major Bleeding**			
Analysis population and time point description	Analysis performed on all randomized subjects who received at least one dose of blinded study medication for bleeding events from time of first dose of study medication through two days after the last dose of study medication.			
Descriptive statistics and estimate variability	Treatment group	Apixaban	Enoxaparin	
	Number of subject	2673	2659	
	Clinically relevant non-major bleeding rate	4.08	4.51	
	95% CI	(3.39, 4.90)	(3.79, 5.38)	
Effect estimate per comparison	Major or clinically relevant non-major bleeding	Comparison groups	Apixaban vs. enoxaparin	
		Adjusted difference of Event Rates (APIX-ENOX) (%)	-0.44	
		95% CI	(-1.53, 0.66)	
		P-value*	0.43	
Notes	* denotes two-sided p-value All bleeding criteria included surgical site bleeding. Includes bleeding events that occurred before the first dose of oral study medication.			

2.5.3. Discussion on clinical efficacy

Venous thromboembolism VTE is a common cause of morbidity and mortality following total hip replacement or total knee replacement surgeries. These events, which include distal deep venous thrombosis DVT, proximal DVT, clinical pulmonary embolism PE, and fatal PE, occur in 40%-80%, 10%-20%, 4%-10%, and 0.2%-5% of patients, respectively, when thromboprophylaxis is not used (Geerts et al., 2008).[1]

PE is not the only serious consequence of DVT. Any episode of DVT significantly increases the risk of further VTE, and may also lead to a post-thrombotic syndrome that includes venous ulceration, debilitating pain, and intractable edema.

Most clots that cause PE originate in the large veins of the legs. This is supported by the effectiveness of vena cava filters in the reduction of the incidence of PE in patients who have had recurrent VTE, but have contraindications for anticoagulation. PE is difficult to diagnose, expensive to treat, and often fatal. Therefore, the prevention of DVT represents the best strategy to decrease the morbidity and mortality of PE.

The most effective methods for prevention of VTEp involve the use of anticoagulants in patients at risk. Several of the clinical situations that result in the highest risk of VTE are transient, such as those associated with major orthopedic or other surgeries or hospitalization for acute medical illnesses. For these situations, guidelines recommend short-term VTE prophylaxis that is most often achieved with parenteral anticoagulants. These agents include heparin, low molecular weight heparins (LMWHs), and fondaparinux.

The most commonly used agents for VTEp are still the parenteral agents. These can be associated with local injection site hematomas. In addition, heparin and LMWH carry a low, but serious, risk of

[1] Geerts WH, Bergqvist D, Pineo GF, et al. Prevention of venous thromboembolism: American College of Chest Physicians evidence-based clinical.

thrombocytopenia. By their very nature, parenteral agents are less likely to be used properly after hospital discharge than simple PO regimens. Thus, there exists an unmet medical need for safe and effective agents that can be administered PO. In the setting of orthopaedic surgery, not all patients currently receive appropriate thromboprophylaxis because surgeons are concerned about the bleeding risks of available agents.

Choice of Endpoints

The chosen primary endpoint of the pivotal studies is not in line with the current CHMP guideline (CPMP/EWP/707/98 Rev.1 corr), whereas the key secondary endpoint is in fact the recommended primary endpoint in the CHMP guideline. All-cause death can also be part of the primary endpoint. It should be noted that the relevant CHMP guideline has itself undergone several changes in the past few years. The last revisions were meant to restrict the primary efficacy endpoint to the more clinically relevant DVT that is the proximal variety only (symptomatic or asymptomatic). However, this was later changed to the possibility to include distal symptomatic DVT as well. Thus, whereas the chosen primary endpoint can be considered too liberal as it includes asymptomatic distal DVT, the chosen secondary endpoint is conservative, as it excludes symptomatic distal DVT and asymptomatic distal DVT.

According to the applicant, aiming to show non-inferiority to enoxaparin based on the incidence of major VTE endpoint (excluding all distal DVT) would require large studies.

Statistical methods

In study CV185035, initial sample size calculations over estimated the event rates (3.85% and 5.5% for apixaban and enoxaparin). Based on the results of the dabigatran studies, these estimations appeared realistic (event rates recorded of around 5%), though overestimated compared to rivaroxaban (1.1% to 3.7% respectively). A blinded event rate estimation of study CV185035 showed lower events rates, which necessitated increasing study sample size to provide adequate power for NI. This is accepted, as the estimation was blinded and was not made to detect efficacy. An estimated event rate of around 1% for secondary endpoints appears to be on the lower side (dabigatran study had an event rate of around 4%, while rivaroxaban had a range from 0.2% to 2%). The justification of the choice of the NI margin for both the primary endpoint and the main secondary endpoint is acceptable clinically.

In study CV185047, sample size calculations were based on event rates reported in study CV185010 (16% and 11 % for enoxaparin and apixaban respectively), which eventually appear to have been under-estimated (24% and 15 % respectively).

The NI margin for the primary endpoint in the TKR studies appears appropriate. Setting a NI with another criterion based on the absolute risk difference is also conservative considering the possible difference in the event rates. Calculation of NI margin of 1.5 for the major secondary endpoint also appears clinically relevant and it is in line with that previously accepted for rivaroxaban.

Efficacy results shown in the THR (CV185035) study are mainly driven by the favorable results of clinically relevant endpoint. There is a numerical reduction in the events of non-fatal PE but there was also one case of VTE-related death in the apixaban arm. Furthermore, in the follow-up period PE and symptomatic proximal DVT were still recorded in numerically higher number in the enoxaparin compared to none in the apixaban group.

Benefit in VTE-p TKR is mainly based on study CV185047. Analysis of the clinically significant endpoints represented in major VTE confirmed apixaban superiority, with the benefit mainly driven by the lower incidence of proximal DVT events (0.76% and 2.17% respectively). However, this was associated with more numbers of PE cases in the apixaban group (n=4, with one fatal in intended treatment period and 3 in the intended follow-up period) compared to the enoxaparin group (0 in intended treatment period and 1 in the intended follow-up period). Thorough analysis of these cases did not show that any specific patient characteristic could have contributed to this higher incidence. The later initiation of either apixaban or enoxaparin was shown to be associated with a higher probability of total VTE, but not major VTE, but no robust conclusions can be made about the optimal timing of initiation; which should best be individualized. The posology also appears optimal.

In the supportive TKR study CV185034, the incidence of PE was even higher in the apixaban group. The only relevant explanation given about the higher threshold of clinical suspicion in US/Canada can only explain the higher diagnosis of PE in this study, but can not explain the higher incidence of PE in the apixaban group as it is a randomized study.

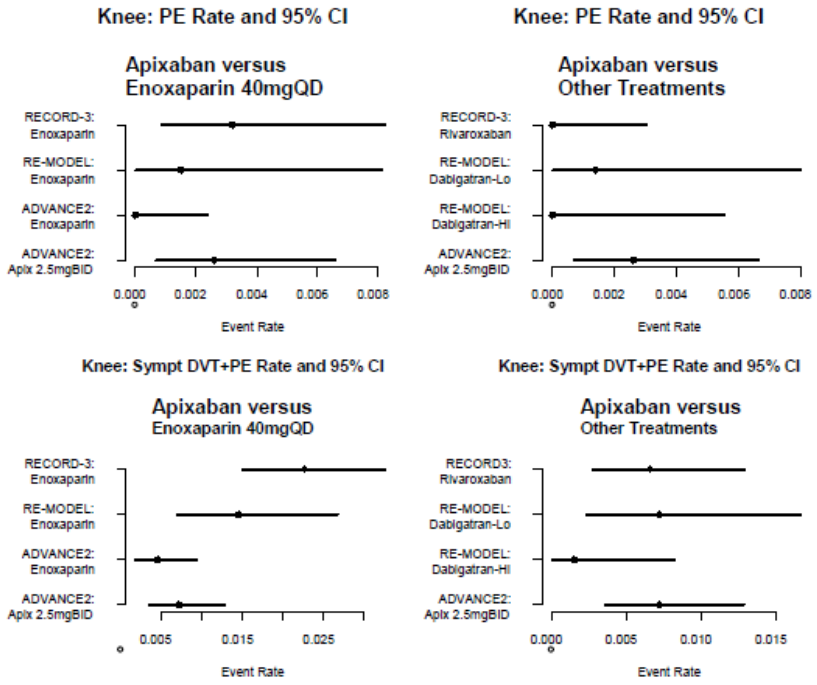
By historical comparisons with the results of recently approved anti-coagulants, it could be observed that apixaban had higher incidences of PE and VT-related death. Enoxaparin on the other hand faired the best in the apixaban studies. This supports that these PE were chance findings.

Summary of Pulmonary Embolism and Venous Thromboembolism-related Death in Phase 3 TKR Studies: apixaban, rivaroxaban and dabigatran.

	Enoxaparin 40 mg QD		Enoxaparin 30 mg q12h	
Apixaban 2.5 mg BID	CV185047 (ADVANCE-2)		CV185034 (ADVANCE-1)	
	Enoxaparin	Apixaban	Enoxaparin	Apixaban
PE [a]	0/1529 (0%)	4/1528 (0.26%)	7/1596 (0.44%)	16/1599 (1.00%)
VTE-related Death [b]	0/1529 (0%)	1/1528 (0.07%)	0/1596 (0%)	2/1599 (0.13%)
Rivaroxaban 10 mg QD	RECORD-3		RECORD-4	
	Enoxaparin	Rivaroxaban	Enoxaparin	Rivaroxaban
PE	6/1277 (0.47%)	0/1254 (0%)	11/1564 (0.70%)	5/1584 (0.32%)
VTE-related Death	2/1277 (0.16%)	0/1254 (0%)	3/1564 (0.19%)	1/1584 (0.06%)
Dabigatran (pooled) 220 and 150 mg QD	RE-MODEL		RE-MOBILIZE	
	Enoxaparin	Dabigatran	Enoxaparin	Dabigatran
PE	1/699 (0.14%)	2/1401(0.14%)	5/876 (0.57%)	7/1739 (0.40%)
VTE-related Death	1/699 (0.14%)	1/1401 (0.07%)	0/876 (0%)	1/1739 (0.06%)

Source: Lassen et al 2008, Eriksson et al 2007, EPAR for Pradaxa, Turpie et al 2009, and Ginsberg et al 2009
Note: Denominators to calculate percentages are the number of subjects randomized in each treatment group.
a PE includes non-fatal PEs and VTE-related deaths (i.e., deaths for which PE is the cause, PE cannot be excluded as a cause, or unexplained deaths).
b VTE-related death includes deaths for which PE is the cause, PE cannot be excluded as a cause, or unexplained deaths.

Event Rates for PE and Symptomatic VTE During the Intended Treatment Period in Recent TKR Pivotal Trials with the EU Regimen of Enoxaparin as Comparator



In support that the higher PE incidence in the US study can be coincidental is that there was no associated higher incidence of all DVT in the apixaban group compared to enoxaparin (7.8% vs 8.2% respectively). Also the incidence of PE in the enoxaparin arm in the US study was higher (n=7; 0.44 %) than that in the EU study (0). In summary, apixaban results in VTE-related deaths in TKR are numerically higher compared historically to other anti-coagulants, whereas the results of enoxaparin are comparatively better.

Patient population
The pivotal studies excluded patients with severe renal impairment; this limited clinical experience is reflected in the SmPC. Based on PK data, the expected increase in exposure is not associated with an increased risk of bleeding.

The excluded patients in the VTEp clinical program (patients with ALT/AST > 2x ULN or total bilirubin ≥ 1.5 x ULN) are reflected in the SmPC and eliquis should be used with caution in this population together with the need to measure ALT before apixaban administration.

Time of administration
Timing of initiation of apixaban administration which is more delayed compared to other oral agents was further investigated. Using a cut off of 18 hours from surgery, results show that the incidence rate of major VTE/all cause death is slightly lower in patients administered apixaban less than 18 hours after surgery (1.07%) compared to those administered apixaban more than 18 hours after surgery (1.21%). This difference is even more marked in the enoxaparin group (0.91% vs 2.65%) and even more exaggerated if incidence of all VTE is considered. Based on another analytical approach, it is shown that time from surgery to dose of apixaban was a significant independent predictor of the risk for All VTE and that for every additional hour from surgery to dose the odds of having All VTE increase by a factor of 1.027. This argues on one hand for the early use of the anticoagulant. On the other hand, the same analysis also showed that time from surgery to dose was not a significant predictor of the risk for major VTE/all-cause death which is the most relevant endpoint. This analysis applies for both apixaban and enoxaparin, therefore, can not explain the observed imbalance in PE. In the current ACCP guideline (Geerts et al., 2008), the advantages of pre-operative initiation of anti-coagulant therapy is even debated (current EU enoxaparin regimen). The applicant submitted further analysis of the VTE events in patients administered apixaban earlier than 12 hours after surgery. However, the numbers of these patients are too limited to draw any conclusions. Overall, these results support the general recommendations of initiating apixaban 12-24 hours after surgery. However considering the wide time frame of 12-24 hours and the potential impact between the benefits of delayed initiation (less bleeding) and the risks (thrombosis), it is considered useful to alert the physicians that the exact time of initiation should be individualized. This is implemented in the SmPC.

2.5.4. Conclusions on the clinical efficacy

The benefit of apixaban in VTEp in patients undergoing THR and TKR is considered acceptable. No explanation can be given for the higher incidence of PE reported in the TKR studies, even after thorough analysis of possible patient characteristics or posology that could have contributed to this observation. Based on the current data analysis and compared to results of other anti-coagulants, it can be concluded that these PE were probably chance finding and they are mentioned in the SmPC section.

2.6. Clinical safety

Available safety information related to apixaban 2.5 mg BID in the indication of VTEp is based mainly on studies CV185035, CV185047, CV185034 and CV185010 (VTEp). Reference will also be made in certain sections to the available safety data from apixaban investigated in other indications (VTE treatment, secondary prevention in ACS, VTEp in metastatic cancer patients and AF). Exposure of patients in the ongoing studies CV185030, CV185048 and CV185036 is 14,456 (apixaban/warfarin), 4,592 (apixaban/aspirin) and 3382 (apixaban/enoxaparin) in the indications stroke-p in AF for the first 2 studies and VTEp in medically ill subjects in the third study respectively is high. Although this can add valuable safety information, its value is limited as the data is blinded.

Patient exposure

The total number of subjects who received at least one dose of any double-blind study drug in the four VTEp studies was 12,742. Of these, 11,828 subjects received apixaban 2.5 mg BID (5,924) or enoxaparin 40 mg QD (4,167) or enoxaparin 30 mg BID (1,737). This exposure is considered adequate to characterize the safety profile of apixaban in this indication. The extent of exposure was similar in the apixaban and enoxaparin groups, both in the overall population and within subgroups. There were no treatment differences judged to be clinically relevant to the safety comparisons.
The duration of exposure was bimodal due to the different target treatment durations by operative site (12 days for TKR and 35 days for THR). Approximately half of the subjects (46%) received study drug for 10 to 14 days, as per protocol for the 12-day studies in TKR, while 38% received study drug for 32 to 38 days, as per protocol for the 35-day study in THR.

Pooled data for all 4 studies, as well as for the pivotal studies is presented. Pooling of the 4 studies is considered acceptable considering that the same dose of apixaban was used. However, for comparative purposes with enoxaparin, such pooling may not always be appropriate considering that in the two

pivotal studies, enoxaparin was administered as 40 mg QD, and as 30 mg BID in the other studies. For brevity, only selected data will be presented.

Adverse events

In the four pooled VTEp studies, the frequency of common AEs (reported for > 1% of subjects in either treatment group) was similar in the apixaban and enoxaparin groups (apixaban 3812 [64%], enoxaparin 3936 [66.7%]) (Table S3). AEs reported for > 5% of subjects in the apixaban group were nausea (13.9% vs 15.5%), constipation (10.7% vs 12%), pyrexia (7.9% vs 8.2%), procedural pain (7.8% vs 8.1%), vomiting (6.7% vs 7.9%), peripheral edema (6.3% vs 6.5%), hypotension (5.7% for both), and dizziness (5.4% vs 4.7%) reported in the apixaban and enoxaparin groups respectively. The overall frequency of common AEs with onset during the follow-up period was similar in the apixaban and enoxaparin groups (897 [15.5%] and 913 [15.9%], respectively) in the 4 pooled studies, as well as in the 2 pivotal studies (apixaban 485 [12.0%], enoxaparin 492 [12.2%]).

***Treatment-related adverse events TRAEs**:* In the four pooled VTEp studies, the overall frequency of drug-related AEs TRAEs with onset during the treatment period was similar for the apixaban and enoxaparin groups (1051 [17.7%] and 1122 [19.0%], respectively) (table S3). The following drug-related AEs were reported for > 1% of subjects in both treatment groups: nausea, DVT, peripheral edema, pyrexia, contusion, and post-operative anemia.

Table S3: Summary of Related Adverse Events with Onset During the Treatment Period - Treated Subjects (Pooled CV185010, CV185034, CV185035 and CV185047)

System Organ Class (e) Preferred Term (e)	Apix 2.5mg BID N = 5924	Enox N = 5904
TOTAL SUBJECTS WITH AN EVENT	1051 (17.7)	1122 (19.0)
GASTROINTESTINAL DISORDERS	266 (4.5)	305 (5.2)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	263 (4.4)	255 (4.3)
VASCULAR DISORDERS	228 (3.8)	261 (4.4)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	227 (3.8)	255 (4.3)
INVESTIGATIONS	224 (3.8)	269 (4.6)

Serious adverse event/deaths/other significant events

Serious Adverse Events: The overall frequency of SAEs with onset during the treatment period and the follow-up period in the four pooled VTEp studies was similar in the apixaban and enoxaparin groups (392 [6.6%] and 396 [6.7%], respectively in the treatment period and in the follow-up period: 46 [0.8%] and 49 [0.9%]) respectively). No SAE was reported for > 1% of subjects in either treatment group.
During the treatment period, event numbers and rates of SAEs of DVT and PE in the apixaban vs. enoxaparin groups in each of the individual studies were as follows:

- CV185035: DVT 8 (0.3%) vs. 18 (0.7%); PE 3 (0.1%) vs. 7 (0.3%)
- CV185047: DVT 11 (0.7%) vs. 22 (1.5%); PE 5 (0.3%) vs. 1 (< 0.1%)
- CV185034: DVT 6 (0.4%) vs. 10 (0.6%); PE 19 (1.2%) vs. 9 (0.6%)
- CV185010: DVT 3 (1.9%) vs. 3 (2.0%); PE 2 (1.3%) vs. 2 (1.3%).

During the follow-up period, serious events of DVT and PE were reported for 2 (< 0.1%) subjects in the apixaban group and 8 [0.1%] subjects in the enoxaparin group. SAEs of DVT with onset during the follow-up period were reported for none of the subjects in the apixaban group and 5 (< 0.1%) subjects in the enoxaparin group. SAEs of PE with onset during the follow-up period were reported for 2 (< 0.1%) subjects in the apixaban group and 3 (< 0.1%) subjects in the enoxaparin group.
These SAE are previously discussed under efficacy.

Deaths: Overall event rates for deaths in the pooled analysis of the four studies were low in both treatment groups with only numerical differences between treatment groups during the treatment period (apixaban 10/5924 [0.17%], enoxaparin 7/5904 [0.12%]). The event rates for death in the

apixaban group are consistent with rates reported during the treatment period in published reports of enoxaparin-controlled joint replacement studies (ranging from 0 to 0.3%).

SAEs of PE with the outcome of death were reported by the investigators for 5 (0.08%) subjects in the apixaban group and 1 (0.02%) subject in the enoxaparin group (table S4). Of these deaths, 4 events in the apixaban group and 1 event in the enoxaparin group were confirmed by adjudication. These events are tabulated in table S4, but were earlier discussed under efficacy.

Table S4: Subjects with Serious Adverse Events of Pulmonary Embolism with the Outcome of Death During the Treatment Period (CV185035, CV185047, CV185034, and CV185010)

Protocol/Patient Identifier Age/Gender/Race	Serious Adverse Event (PT) / Study Day of Event Onset[b] /Inv. Causality	Investigator Cause of Death[a] (or Verbatim Term for SAE)	Adjudicated Cause of Death	Comments[b]
		Apixaban 2.5 mg BID		
CV185047				
CV185047-129-1750 (64/F/W)	PE / 4 / Unrelated	Phlebothrombosis of the right shin and severe PE	PE	Events occurred after the subject fell on Day 4. An autopsy revealed thromboembolism of the pulmonary artery, and thrombophlebitis of the right shin and right gonarthrosis.
CV185034				
CV185034-74-3540 (65/F/W)	PE / 1 / Unlikely related	Verbatim term: PE	PE	The subject completed TKR surgery, received 1 dose of apixaban, and died while in bed on Day 1. PE was confirmed by autopsy.
CV185034-151-1124 (66/M/W)	PE / 1 / Unrelated	Pulmonary embolus	PE	Prior to the first dose of study medication, the subject became diaphoretic, short of breath, and hypotensive and was given volume resuscitation. Surgery was completed on 16-Jul-2007 at 09:20. Study drug was administered at 10:07 on 17-Jul-2009 more than 24 hours after surgery. PE with onset at 09:35 on 17-Jul-2007 (Day 1) was confirmed by lung scan. The patient developed cardiopulmonary arrest and death occurred at 16:54 on 17-Jul-2007. No autopsy was performed.
CV185010				
CV185010-3-4 76/M/B/AfAm	PE / 8 / Possibly related	Verbatim term: Bilateral pulmonary thromboemboli	PE	The subject died from cardiac arrest on Day 9. An autopsy revealed bilateral pulmonary artery blood clots highly suspicious for acute pulmonary emboli, cardiomegaly, minimal coronary artery atherosclerosis, mild hepatomegaly. No consolidation or tumor was identified.
CV185010				
CV185010-175-4 80/F/W	Acute MI / 5 / Unlikely related PE/ 18 / Unlikely related	Verbatim terms: acute MI; pulmonary embolization	Not associated with VTE or bleeding	On Day 5, the subject experienced acute very severe MI, and study drug was discontinued. Severe PE, was diagnosed on Day 18 and was ongoing at the time of death, which occurred 7 days later. The investigator reported that death was a sequel to acute MI. No autopsy was performed.
		Enoxaparin		
CV185034				
CV185034-150-453 (78/F/W)	PE / 21 / Unrelated	PE	PE	The subject experienced PE on Day 1, approximately 4 hours after receiving the first dose of study medication. She died on Day 21. No autopsy was performed.

Death related to other causes. Eleven subjects (apixaban 5, enoxaparin 6) had non-VTE related SAEs with the outcome of death with onset during the treatment period (Table S5).

Table S5: Subjects with Non-VTE-related Serious Adverse Events with the Outcome of Death During the Treatment Period (CV185035, CV185047, CV185034, and CV185010)

Protocol/Patient Identifier Age/Gender/Race	Serious Adverse Event (PT) / Study Day of Event Onset[b] / Inv. Causality	Investigator Cause of Death[a] (or Verbatim Term for SAE)	Adjudicated Cause of Death	Comments[b]
		Apixaban 2.5 mg BID		
CV185035				
CV185035-25-3828 (69/F/W)	Abdominal compartment syndrome / 7 / Unlikely related	Abdominal compartmental syndrome, which led to multi-system organ failure	Not associated with VTE or bleeding	The subject had severe discomfort and diaphoresis on Day 6, and was assessed as having symptoms consistent with acute abdominal pain with suspected ischemic bowel. An exploratory laparotomy showed a large amount of serous fluid, normal stomach and duodenum, viable bowels and no areas of focal infarction. There were no complications during surgery, and the estimated blood loss was minimal. She was diagnosed with very severe abdominal compartment syndrome, for which the specific etiology was not identified. She remained critically ill with hypotension and died on Day 7. No autopsy was performed.
CV185035-57-3453 (83/F/W)	Colon neoplasm / 17 / Unrelated	Pulmonary and circulation failure, which were connected to surgery	Not associated with VTE or bleeding	Pulmonary and circulation failure occurred during surgery for tumor resection.
CV185035-158-1958 (73/M/A)	Cardiopulmonary failure / 9 / Unrelated	Cardiorespiratory failure, with pulmonary or cerebral embolic phenomenon suspected as the cause	PE	No diagnostic procedures were performed due to the rapidity of the subject's demise. No autopsy was performed.
CV185047				
CV185047-201-936 (66/M/A)	Hepatitis / 7 Hyponatremia / 10 Metabolic acidosis/ 12 Respiratory acidosis / 12 Atrial fibrillation / 13 All unrelated	Respiratory failure due to metabolic acidosis, respiratory acidosis, hyponatremia, and atrial fibrillation	Not associated with VTE or bleeding	On Day 7, the subject had a fever, developed icterus, and was diagnosed with severe hepatitis and jaundice. Study medication was discontinued. ALT and AST were > 3 x ULN and his total bilirubin was > 2 x ULN. Severe metabolic acidosis and respiratory acidosis developed after the subject aspirated vomitus on Day 13. The subject died on Day 14. No autopsy was performed. A detailed narrative is provided in Section 2.1.6.2.
CV185034				
CV185034-52-829 (64/F/W)	Intestinal obstruction/ 6 / Unlikely related Multi-organ failure/ 6 / Unrelated Septic shock / 6 / Unrelated MI / 7 /Unrelated	Septic shock	Not associated with VTE or bleeding	The subject developed multi-organ failure following surgery to treat intestinal obstruction and septic shock. No autopsy was performed.
		Enoxaparin		
CV185035				
CV185035-2-750 (76/F/B-AfAm)	Cerebrovascular accident / 49 / Unrelated	Verbatim term: Acute stroke	Not associated with VTE or bleeding	The subject completed THR surgery Day 2 and had elevated AST and ALT on Day 3, which resolved on Day 11. The subject experienced acute stroke and died on Day 49. A CT scan showed a left occipital lobe stroke. No autopsy was performed.
		Enoxaparin		
CV185035-163-1616 (44/F/W)	Fat embolism / 1 / Unlikely related	Verbatim term: Fat embolism	Not associated with VTE or bleeding	The subject received 1 dose, the last, on Day 1, which was given pre-surgery. The subject died the same day following surgery. Clinical manifestations of respiratory failure were absent prior to surgery. The autopsy report noted fat embolis of the terminal branches of the pulmonary arteries. Bronchial asthma and obesity were considered primary diseases that "further aggravated consequences of cardiopulmonary failure."
CV185034				
CV185034-52-672 (75/M/W)	Atrial fibrillation / 10 / Unrelated Heart rate decreased / 16 / Unrelated	Verbatim terms: Atrial fibrillation, low heart rate	Not associated with VTE or bleeding	The subject received the last dose on Day 11. On Day 9, he was treated with digoxin to control tachycardia. He was hospitalized with very severe atrial fibrillation on Day 10. Dizziness, malaise, loss of consciousness, and low heart rate of 34 beats per minute were reported on Day 16. He

				developed cardiopulmonary arrest and died on Day 17. No autopsy was performed.
CV185034-59-3553 (70/M/W)	MI / 4 / Possibly related	Verbatim term: MI	Not associated with VTE or bleeding	The subject received the last dose on Day 5. On Day 5, he experienced chest pain, generalized weakness, syncope, and cardiac failure. He died on Day 6. The cause of death was reported as MI. No EKG, enzyme, or autopsy was performed.
		Enoxaparin		
CV185034-124-1431 (76/F/W)	Hemorrhage intracranial / 5 / Unlikely related	Verbatim term: Right sided intracranial hemorrhage	Bleeding	The subject received the last dose on Day 4. The post-surgery course from (Day 2 to 5 post-dose), included bleeding into the post-operative knee, confusion, left-sided weakness, difficulty standing and speaking, urinary incontinence, vomiting, and unresponsiveness. Very severe intracranial hemorrhage was diagnosed on Day 5. The subject died on Day 6. No autopsy was performed.
CV185034-143-1576 (67/M/W)	Death / 4 / Unlikely related	Verbatim term: No obvious cause of death	Not associated with VTE or bleeding	The subject received the last dose on Day 3. He was found dead in bed on Day 4. An autopsy was performed and ruled out PE.

During the follow-up period, SAEs with the outcome of death with onset during the follow-up period were reported for 3 (0.05%) subjects in the apixaban group, and 2 (0.03%) subjects in the enoxaparin group (table S6).

Table S6: Subjects with Serious Adverse Events with the Outcome of Death During the Follow-up Period (CV185035, CV185047, CV185034, and CV185010)

Protocol/Patient Identifier Age/Gender/Race	Serious Adverse Event (PT) / Study Day of Event Onset/ Inv. Causality	Investigator Cause of Death[a] (or Verbatim Term for SAE)	Adjudicated Cause of Death	Comments[b]
		Apixaban 2.5 mg BID		
CV185035				
CV185035-13-4934 (76/M/W)	Colon cancer / 72 / Unrelated	Verbatim term: Obstructive colon cancer and suspected metastases to the liver	Not associated with VTE or bleeding	Computed tomography on Day 61 confirmed cancer of the pancreas and showed possible metastases to liver. A final diagnosis was Grade III carcinoma of the colon, with obstruction and possible liver metastases. The subject refused chemotherapy. He died on Day 87. No autopsy was performed.
CV185035-177-4000 (66/M/W)	Myocarditis / 47 / Unrelated	Verbatim term: Secondary myocarditis	Not associated with VTE or bleeding	The subject was hospitalized on Day 10 for perforation of the cecum. Study drug was discontinued. His post-operative course was complicated by sepsis, pneumonia, respiratory failure, and acute tubular necrosis with renal failure requiring dialysis. On Day 47, he was found dead in bed. Autopsy found bilateral subphrenic abscesses, myocarditis, pulmonary edema, gastric ulcer, and acute tubulointerstitial nephropathy.
CV185047				
CV185047-1-2467 (85/F/W)	MI / 45 / Unrelated PE / 45 / Unrelated	Verbatim term: Suspected MI, suspected PE	PE	The subject died at home approximately 1 month after her last dose of study medication. No autopsy was performed
		Enoxaparin		
CV185047				
CV185047-102-464 (80/F/W)	Death / 40 / Unrelated	Verbatim term: Retroperitoneal bleeding	Bleeding	The autopsy report noted the subject had been taking Marcumar (VKA). Autopsy revealed a large retroperitoneal hematoma which was noted as the cause of death.
CV185034				
CV185034-96-2645 (72/F/W)	Cardiorespiratory arrest / 41 / Unlikely related	Verbatim term: Cardiorespiratory arrest	PE	On Day 1, the subject experienced a cardiac and respiratory arrest (both very severe), which were considered resolved on Day 2. On Day 5, she developed very severe hypoxicoischemic encephalopathy (Glasgow scale 6). On Day 6, she developed severe urosepsis. The subject died on Day 41 after experiencing very severe cardiac and respiratory arrest with onset on Day 41. No autopsy was performed.

For other causes of death, the rate appears comparable between the treatment groups. Of these cases, 2 cases are considered relevant to the assessment of the benefit risk of apixaban. This includes one case of hepatitis, discussed below. The other 2 cases occurred in the enoxaparin group secondary to bleeding. The first case concerns a case of intracranial hemorrhage reported during the treatment period (TKR study: CV185034), the other concerns a case of retroperitoneal bleeding observed during the follow-up period (TKR study: CV185047).

Other Significant Adverse Events. Bleeding

Bleeding was the primary safety endpoint in all four VTEp studies and includes:
- adjudicated major bleeding (adapted from International Society on Thrombosis and Hemostasis [ISTH] guidelines)
- composite of adjudicated major bleeding (per ISTH guidelines) and clinically relevant non-major CRNM bleeding
- all bleeding endpoints (adjudicated or reported by the investigator).

All acute clinically overt bleeding events were submitted for adjudication by an independent, expert panel of physicians. Bleeding endpoints were the same for all three Phase 3 studies and defined as follows:

Major Bleeding:

- A decrease in hemoglobin of ≥ 2 g/dL over a 24-hour period
- A transfusion of ≥ 2 units of packed red blood cells
- Bleeding that occurred in at least 1 of the following critical sites: intracranial, intra spinal, intraocular (within the corpus of the eye; thus, a conjunctival bleed was not an intraocular bleed), pericardial, an operated joint and required re-operation or intervention, intramuscular with compartment syndrome, or retroperitoneal
- Bleeding that was fatal

Clinically-relevant Non-major (CRNM) Bleeding:

- Acute clinically-overt bleeding
- Did not satisfy additional criteria required for the bleeding event to be defined as a major bleeding event and met at least 1 of the following criteria:
  - Epistaxis (nose bleed): Subject sought medical attention from a physician, Subject visited an emergency room, bleeding required an intervention (e.g., nasal pack) or single bleeding episode persisted for ≥ 5 minutes
  - GI bleed: Vomit containing frank blood or coffee ground material that tested positive for blood, endoscopically-confirmed bleeding, or frank blood per rectum or melenic stools
  - Hematuria: Overt, spontaneous bleeding or bleeding (bloody urine) persisted for ≥ 24 hours after instrumentation
  - Bruising/ecchymosis: Any bruise that was assessed as "unusual" (e.g., greater than expected following surgery)
  - Expectoration of blood or blood-stained sputum
  - Hematoma: Overt blood collection associated with the surgical wound or the presence of a hematoma was demonstrated radiographically, e.g., ultrasound, CT, MRI, and a drop in hemoglobin was present with no external evidence of bleeding

The definition of major bleeding is acceptable. The following table (S7) summarizes the bleeding endpoints during the treatment period of the 3 phase III studies.

Table S7: Summary of Bleeding Endpoints During the Treatment Period - Treated Subjects (CV185035, CV185047 and CV185034)

	(CV185035)		(CV185047)		(CV185034)	
	Apix 2.5 mg BID N=2673	Enox 40 mg QD N=2659	Apix 2.5 mg BID N=1501	Enox 40 mg QD N=1508	Apix 2.5 mg BID N=1596	Enox 30 mg Q12h N=1588
MAJOR BLEEDING, N	22	18	9	14	11	22
EVENT RATE (%)	0.82	0.68	0.60	0.93	0.69	1.39
95% CI	(0.54, 1.25)	(0.42, 1.08)	(0.30, 1.16)	(0.54, 1.57)	(0.37, 1.25)	(0.91, 2.11)
DIFF OF EVENT RATES (APIX-ENOX) (%)	0.15		-0.33		-0.81	
95% CI	(-0.33, 0.64)		(-0.95, 0.29)		(-1.49, -0.14)	
TWO-SIDED P-VALUE (%)	0.54		0.3014		0.0583	
CLINICALLY RELEVANT NON-MAJOR BLEEDING, N	109	120	44	58	35	47
EVENT RATE (%)	4.08	4.51	2.93	3.85	2.19	2.96
95% CI	(3.39, 4.90)	(3.79, 5.38)	(2.19, 3.93)	(2.96, 4.95)	(1.58, 3.05)	(2.23, 3.93)
DIFF OF EVENT RATES (APIX-ENOX) (%)	-0.44		-0.91		-0.77	
95% CI	(-1.53, 0.66)		(-2.20, 0.38)		(-1.87, 0.33)	
TWO-SIDED P-VALUE (%)	0.43		0.1668		0.1709	
MAJOR OR CLINICALLY RELEVANT NON-MAJOR BLEEDING, N	129	134	53	72	46	68
EVENT RATE (%)	4.83	5.04	3.53	4.77	2.88	4.28
95% CI	(4.08, 5.71)	(4.27, 5.94)	(2.71, 4.60)	(3.81, 5.98)	(2.16, 3.84)	(3.39, 5.41)
DIFF OF EVENT RATES (APIX-ENOX) (%)	-0.21		-1.24		-1.46	
95% CI	(-1.38, 0.95)		(-2.66, 0.18)		(-2.75, -0.17)	
TWO-SIDED P-VALUE (%)	0.72		0.0881		0.0338	
ANY BLEEDING, N	313	334	104	126		
EVENT RATE (%)	11.71	12.56	6.93	8.36	85	108
95% CI	(10.55, 12.99)	(11.36, 13.88)	(5.75, 8.34)	(7.06, 9.87)	5.33	6.80
					(4.33, 6.55)	(5.66, 8.16)
DIFF OF EVENT RATES (APIX-ENOX) (%)	-0.85		-1.39			
95% CI	(-2.61, 0.90)		(-3.29, 0.51)		-1.52	
TWO-SIDED P-VALUE (%)	0.34		0.1412		(-3.18, 0.13)	
					0.0816	

No major bleeding events occurred in the apixaban 2.5 mg BID group or enoxaparin group in the Phase 2 study CV185010.

There was a comparable risk of bleeding during both the treatment and follow-up periods in the two pivotal studies CV185035/ CV185047 between apixaban and enoxaparin administered in the lower dose of 40 mg QD. Regarding major bleeding, in the THR study, major bleeding events were slightly higher in the apixaban group (0.82%) than the enoxaparin group (0.68%), in the TKR study, the opposite trend was observed (apixaban 0.6% and enoxaparin 0.98%).
In study CV185034, in which enoxaparin was administered as 30 mg BID, the rates of major bleeding and the rates of the composite endpoint of major plus clinically relevant non-major bleeding were lower for apixaban than enoxaparin. For the major bleeding endpoint the 95% CI for the difference in event rates is <0 but the p-value is > 5%. This is due to the fact that different statistics were used to calculate the 95% CI and the p-value. The Mantel-Haenszel test stratified by type of surgery was used to calculate the p-value. The inverse variance or harmonic means method was used to calculate the 95% CI for the difference in event rates. These methods were pre-specified in the statistical methodology section.

Two fatal bleeding cases were reported in the enoxaparin group as discussed above. The bleeding profile of apixaban appears to be better compared to enoxaparin in the TKR studies. Analysis of causes of major bleeding in the three main studies revealed that most of the cases could be attributed to decrease in haemoglobin and transfusion of ≥ 2 units of packed red blood cells. Importantly bleeding hemarthrosis in operated joint resulting in re-operation or intervention was a rare event, with comparable incidence between apixaban and enoxaparin.

There is no general need to monitor apixaban. Routine monitoring is not considered feasible because both the efficacy and bleeding response curves are shallow across the range of exposures following 2.5 mg BID dosing. In addition, only one dose was investigated in the clinical studies and no dose adjustments are currently recommended in case of higher exposures. In cases of suspected overdose

or emergency surgery the commercially available Rotachrom anti-FXa assay may be useful to monitor bleeding.

During the assessment preliminary safety information of the Appraise II study was submitted. Clarification of the relevance of the safety bleeding events in Appraise II to the currently proposed indications was requested.
APPRAISE II was designed to investigate the efficacy and safety of Apixaban 5 mg BID compared to placebo in patients with Acute Coronary Syndrome (ACS). Most patients (~80%) were administered apixaban on top of both ASA and clopidogrel. The study was prematurely stopped because of a higher bleeding risk observed in the Apixaban arm compared to the placebo arm (any bleeding of 17.4% vs. 7.6%).
The bleeding risk difference was less noticeable in patients administered mono-antiplatelet therapy (9.7% vs 4.8%) and more in patients on dual anti-platelet therapy (19.4% vs. 9.3%). The additive effect of the three different agents on the bleeding risk is anticipated, but the exaggerated differences compared to the placebo support the decision to stop the study, especially because apixaban would usually be prescribed on top of the other agents in the ACS indication.
The submitted preliminary data identified three factors that in particular increase this bleeding risk: age of the subjects (>65 years), creatinine clearance (CrCL) at baseline (< 60 ml/min), and type of antiplatelet therapy.
It can be agreed with the applicant that the general results of APPRAISE 2 may not be directly relevant to the currently assessed application for VTEp, considering the doses used (5 mg BID vs 2.5 mg BID respectively). Also dual anti-platelet therapy administration is not expected to be as extensive, in the current indication.
However, particularly relevant to the VTEp indication are the patients administered apixaban 2.5 mg BID because of reduced renal impairment (Cr CL < 40 ml/min). The presented analysis included Cr Cl with a cut-off <60 ml/min as a risk factor for increased bleeding; it is not clear in how many of these patients dose reductions were implemented and whether this had actually minimized the risk of bleeding. For clarity, only patients administered 2.5 mg BID are relevant to the current indication; for the group with identified higher risk= Cr Cl <60 ml/min and those with Cr Cl between 40-60 ml/min did not have dose reductions and accordingly not directly relevant to the VTEp indication. However, the clinical experience in the VTEp studies in patients with severe renal impairment is limited.

In addition, as there is a much higher bleeding risk in patients >65 years administered apixaban (20.7% vs 9.6% in placebo), it could have been informative to know if there was an associated renal impairment in these patients and if dose reductions were accordingly implemented. This analysis is recommended when final results of the APPRAISE II study will be submitted.
Current results from this application indicate that elderly patients are a particularly high risk subpopulation, although it should be emphasized that this risk is mostly shown when co-administered with other anti-platelet agents. This high risk population is reflected in the current SMPC.
It can be agreed with the applicant that monitoring anti-Xa activity would not have helped prevent the bleeding events in the study as this bleeding risk is a pharmacodynamic interaction; anti-Xa activity is not expected to be increased or to be able to predict a higher risk.

AEs of special Interest: Liver safety, MI, stroke, thrombocytopenia, and neurologic AEs.

Liver Safety. Thirteen cases of concurrent elevations of ALT > 3 x Upper Limit Normal (ULN) and total bilirubin > 2 x ULN are reported in the 4 placebo-controlled studies. Of the 8 cases reported with apixaban, causality was assessed as possible only in 2 cases (in another case, causality is not available). In two cases (including the one with causality not available) treatment was continued. In the third case, the outcome was fatal. The causality of the drug in this fatal case is possible, but the contribution of other concomitantly administered drugs can not be excluded.

In the 5 patients with reported SAE related to LFT, 4 were reported with apixaban, of which 3 causality is assessed as possible. One is the case of death reported above. In the second case, already an SAE of Grade II elevation of liver enzymes was reported prior to apixaban administration and no treatment was required. This precludes a firm conclusion regarding the relationship between further elevation of LFT and apixaban administration. The LFT elevations were reversible. In the third case, the possible cause of the LFT elevation is not clear; the causation by apixaban can not be excluded either. However, there was no concomitant bilirubin elevation; apixaban was not discontinued and the case was reversible without treatment.
Hepatic safety data from 4 completed clinical studies in other indications (n=2547) showed a single case of concurrent elevations of ALT > 3 x ULN and total bilirubin > 2 x ULN reported with apixaban 20 mg QD group in study CV185027. This subject had underlying pancreatic cancer and a stent in the

common bile duct developed severe bacteremia leading to treatment interruption. Later apixaban was restarted and LFT decreased to within normal ranges while the subject was still on study drug.
Blinded data from ongoing studies were also submitted (14,456 subjects have received apixaban 2.5 mg BID or warfarin for a mean of 41.3 weeks and 4,592 subjects received blinded apixaban 5 mg BID or aspirin for a mean of 31.4 weeks). Although of limited value as data is blinded the large patient exposure may still help in identifying potential toxicity.

Concerns were raised regarding an apparent imbalance in the pooled results of the European studies ADVANCE-2 and ADVANCE-3 for total bilirubin BRB > 2xULN and also for the combination of AT >3xULN plus BRB > 2xULN (data based on the published clinical studies):

- BRB > 2xULN: Apixaban 1.02% (42 of 4136) vs. Enoxaparin 0.51% (21 of 4126); RR = 2.00 (95%CI: 1.19 to 3.35).
- AT >3xULN plus BRB > 2xULN: Apixaban 0.31% (13 of 4136) vs. Enoxaparin 0.12% (5 of 4126); RR = 2.59 (95%CI: 0.96 to 6.98).

The North-American ADVANCE-1 study showed the opposite trend in favour of apixaban. Only pooled data on AT >3xULN plus BRB > 2xULN were submitted without any discussion on the different rate of bilirubin elevations in the European and North-American studies. The main problem of pooling the safety data is that one can fail to detect heterogeneity in clinically important events between different trials that could be of clinical relevance.
Clarification regarding this heterogeneity between the European studies (2-fold increase in bilirubin elevations x2ULN) and the North-American study (no increase) was further requested with clarification regarding baseline characteristics (i.e.: age, gender, race, renal or hepatic function) or pattern of concomitant medications or surgical/anaesthetic procedures that could explain the apparent higher risk of bilirubin elevations with apixaban in the European studies ADVANCE-2 and 3 compared with the North-American study ADVANCE-1.
The submitted analysis shows that the observed imbalance was mainly an artifact due to the counting of cases of elevated LFT even before apixaban was administered.

Regarding the hepatotoxic potential of apixaban, the Hy's law which is the most acceptable method to identify drug induced liver damage was used. This identifies three criteria: a 3 fold or greater increase in ALT/AST compared to control drug or placebo, accompanied with elevations in TOTAL BRB to >2xULN, without initial findings of cholestasis and after excluding other causes that could increase LFT. Based on these criteria, it can be concluded that there is no imbalance between apixaban and enoxaparin in the EU or the North American studies, during the post-surgery period and follow-up period: 3 vs 4 cases and 1 vs 1 respectively, whereas in the North American study, only one case was reported with enoxaparin.
Additionally, applying Hy's law to clinical studies conducted with apixaban in other indications: CV185048 (exposure ~ 2700 patients to apixaban) and CV185023 (exposure ~ 1000 patients to apixaban), point to the same conclusions. In conclusion, it is considered that the above data do not support a hepatotoxic potential for apixaban.

Upon CHMP request, the applicant submitted also the narrative of the case: CV185030-836-9443, which is still blinded and no conclusions can be inferred. The applicant has committed to submit the information on the study medication of this patient as soon as it becomes available. (see letter of Undertaking).

Based on the above, the SmPC clearly identifies the limitations of the clinical studies and the recruited populations. As requested by the CHMP, the applicant included "transient elevation of liver tests" as an Identified Risk in the RMP, and will closely monitor "hepatotoxicity" in the post marketing period.

Regarding the risk of rebound thrombosis, during the treatment period, the incidence of MI appears balanced in the studies between the treatment groups. However, specifically in study CV185035, more cases of MI were observed in the apixaban group compared to enoxaparin during the treatment period (5 vs 3) and follow-up period (4 vs 1). However, there is no increase in MI during the Follow-up Period as compared to the Treatment Period for apixaban in this study CV185035 (4 MI and 5 MIs respectively) or in the combined CV185035, CV185047, CV185034 studies (7 MIs in the Treatment Period vs 5 in the Follow-up). The absence of an increase in MI during the Follow-up Period (which is a longer observation period) indicates that there is no evidence of either a rebound effect of anticoagulant discontinuation or the removal of effective antithrombotic therapy during a persisting sate of hypercoagulability. Accordingly, this is probably a chance finding. Results of Study CV185023 (a phase II study in patients with ACS) also provide reassuring data, as apixaban was even shown to reduce the risk of coronary artery thrombotic events.
The risk of stroke or thrombocytopenia appears comparable between apixaban and enoxaparin.

Neurologic AEs
Clinical neurological events became events of interest for apixaban after SAE reports were received for 1 case of amyotrophic lateral sclerosis (ALS) and 1 case of Guillain-Barre syndrome (GBS) in the apixaban arm in a Phase 2 study for VTE prevention. Since then additional four cases of GBS and two cases of ALS have been reported in the programme with an exposure amounting to around 50,000 patients (apixaban/placebo/comparator). All cases of ALS had disease onset before starting study drug. Although the causality of apixaban to the reported cases of GBS and ALS did not appear likely (assessment confirmed by external neurology consultants), applicant was requested to unblind the cases reported with GBS or ALS in the ongoing development program of apixaban to allow adequate assessment of the benefit-risk balance.

The cases of GBS and ALS were distributed in both arms; there is no class alert or structural association between Factor Xa inhibitors and neurological disorders; the preclinical safety assessment did not show any evidence of toxicity in central or peripheral nervous system; therefore there is no evidence that these cases are associated to the study treatment and the cases more likely occurred at random. All the same, enhanced surveillance is ongoing across the Phase 3 apixaban clinical program for neurological adverse events, and the applicant will have to provide cumulative reviews of GBS and ALS cases in PSURs.

Safety in special populations

No clinically relevant differences were noted in the event rates for bleeding between apixaban and enoxaparin groups within subgroups in the 2 pivotal studies. Neither intrinsic factors (age, gender, weight, BMI, level of renal impairment, number of risk factors for VTE, or type of surgery [unilateral or bilateral THR or TKR]), nor extrinsic factors (geographic region) appeared to have an impact on the bleeding profile of apixaban relative to enoxaparin observed overall in these studies.

Results from studies in other indications (study CV185068 in ACS) showed an increased bleeding risk in patients co-administered apixaban, ASA and clopidogrel. This risk was more in elderly patients >65 years and patients with CrCL> 60 ml/min. Most of the recruited patients were White (~86%) or Asian (~10%). Additional discussion on the efficacy and safety in different races groups was provided and did not raise any concerns. However since this is limited information from other ethnic groups (black ~ 2%); no firm conclusions about efficacy and safety in these groups can be drawn.

Safety related to drug-drug interactions and other interactions

Post-operative utilization of NSAIDs in the main studies ranged from 52% till 71% and of ASA from 5.5% till 17.6%, comparable to previous studies in THR and TKR. Results suggest a comparable bleeding risk of co-administration of apixaban compared to enoxaparin, sometimes even more favourable. Regarding the combined administration of aspirin, clopidogrel and apixaban, the available PK data did not show a relevant increase in template bleeding time, platelet aggregation, or clotting tests (PT, INR, and aPTT) compared to administration of these antiplatelet agents without apixaban. However, results from clinical experience in phase II and III studies in ACS patientsshow that a higher bleeding risk in such patients can not be excluded. The use of apixaban also is not recommended in patients receiving concomittant systemic treatment with strong inhibitors of both CYP3A4 and P-gp. These interactions are reported in the SmPC.

Discontinuation due to AES

The rate of discontinuation due to AEs from the clinical studies was comparable between the treatment groups in the 4 studies (apixaban 200 [3.4%], enoxaparin 217 [3.7%]). DVT (apixaban 20 [0.3%], enoxaparin 25 [0.4%]) and PE (apixaban 23 [0.4%], enoxaparin 14 [0.2%]) were the most common AEs leading to discontinuation.

Post marketing experience

N/A

2.6.1. Discussion on clinical safety

Exposure is considered adequate to characterize the safety profile of apixaban in this indication (n=5,924). The duration of exposure is also in line with the specified guidelines.

Overall, results indicate that the adverse events and the treatment related adverse events profile of apixaban are comparable to that of enoxaparin.

The overall frequency of serious adverse events with onset during the treatment period and the follow-up period in the four pooled VTEp studies was similar in the apixaban and enoxaparin groups. No SAE was reported for > 1% of subjects in either treatment group. The most frequently reported SAEs in both groups were DVT and PE, which are further discussed under efficacy.

Overall event rates for deaths were low in both treatment groups with only numerical differences between treatment groups during the treatment period. The event rates for death in the apixaban group are consistent with rates reported during the treatment period in published reports of enoxaparin-controlled joint replacement studies (ranging from 0 to 0.3%).

Adjudicated cases of PE and fatal PE are discussed under efficacy. Death related to other causes with onset during the treatment period or the follow-up periods was reported in comparable distribution between apixaban and enoxaparin groups.

The bleeding profile of apixaban in both THR and TKR is considered acceptable. There was a numerical increase in major bleeding in the apixaban arm in the THR and the opposite trend in the TKR study. Compared to the higher dose of enoxaparin, a trend of lower risk of major bleeding was observed in favor of apixaban and a significant reduction in the risk of the composite of major/(clinically relevant non major (CRNM) bleeding. Two fatal bleeding cases were reported in the enoxaparin group.

Current clinical data do not support a hepatotoxic potential of apixaban. There is numerical increase of LFT compared to enoxaparin, and causality was assessed as possible in 2 cases, one of them was fatal. The causality of the drug in this fatal case is possible, but the contribution of other concomitantly administered drugs can not be excluded. Data from 4 completed clinical studies in other indications (n=2547) revealed another case of elevated LFT, which could be confounded by multiple co-morbidities. Blinded data from ongoing studies suggest that apixaban is unlikely to be hepatotoxic. Clarification was provided regarding imbalance between EU and US studies which did not support a hepatotoxic potential for apixaban at present. The SmPC clearly identifies the limitations of the clinical studies and the recruited populations. Furthermore, "Transient elevation of liver tests" are included as an Identified Risk in the RMP and "hepatotoxicity" will be closely monitored in the post marketing period.

No clinically meaningful differences were noted in the frequencies of clinical laboratory test results for the apixaban and enoxaparin groups in any of the analysis periods.

No clinically relevant differences were noted in the event rates for bleeding between apixaban and enoxaparin groups within patients subgroups. There is limited experience in patients with severe renal impairment which is reflected in the SmPC. Analysis based on different degrees of hepatic impairment is not submitted as some parameters of the Child-Pugh scale were not measured as baseline. A cautionary remark is included about the exclusion of patients with elevated liver enzymes, and the need to perform ALT prior to administration for adequate risk management. Based on PK data, bleeding parameters appear not be significantly affected in patients concomitantly administered apixaban and other drugs especially platelet aggregation inhibitors and NSAIDs. However, clinical experience is different and is reflected in the SmPC.

Preliminary results from study CV185048 (stroke prevention in AF patients) which was prematurely discontinued because of efficacy were submitted upon CHMP request. The event rates for bleeding are higher for apixaban than ASA but these are based on a pool analysis of mixed doses of apixiban (5 mg BID and 2.5BID) and ASA (81, 162, 243 or 324 mg QD).

Additional information received from cases of GBS and ALS did not show evidence of neurotoxicity since they were equally distributed in both arms and additional predisposing risk factors for GBS/ALS in the underlying medical/surgical conditions were present. There is no class alert or structural association between Factor Xa inhibitors and neurological disorders and the preclinical safety assessment did not show any evidence of central or peripheral neurotoxicity.

2.6.2. Conclusions on clinical safety

Safety profile of apixaban in VTE-p in THR and TKR appears to be comparable to that of enoxaparin, with a bleeding profile that appears favourable compared to the higher dose of enoxaparin.
The most frequent observed adverse reactions are anaemia, haemorrhage, nausea and contusion.

Based on the current clinical and pre-clinical data, the hepatotoxic potential of apixaban is not supported. Because "Transient elevation of liver tests" were reported, this is included as an Identified Risk in the RMP and "hepatotoxicity" will be closely monitored in the post marketing period.

The SmPC clearly identifies the limitations of the clinical studies and the recruited populations:
ELIQUIS is contraindicated in patients with hepatic disease associated with coagulopathy and clinically relevant bleeding risk (see section 4.3).
It is not recommended in patients with severe hepatic impairment (see sections 4.4. and 5.2).

It should be used with caution in patients with mild or moderate hepatic impairment (Child Pugh A or B). No dose adjustment is required in patients with mild or moderate hepatic impairment (see sections 4.4 and 5.2).

Patients with elevated liver enzymes (ALT/AST >2 x ULN) or total bilirubin ≥1.5 x ULN were excluded in clinical trials. Therefore Eliquis should be used with caution in this population (see sections 4.4 and 5.2). ALT should be measured as part of the standard pre-operative evaluation (see section 4.4).

2.7. Pharmacovigilance

Detailed description of the pharmacovigilance system

The applicant has provided documents that set out a detailed description of the system of pharmacovigilance.

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements and provides adequate evidence that the Applicant has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the European Union or in a third country.

Risk Management Plan

The applicant submitted a risk management plan as part of the marketing authorisation. Planned pharmacovigilance activities for each important safety concern are summarised in Table below:

Summary of the Risk Management Plan for Apixaban

Safety concern	Proposed pharmacovigilance activities	Proposed risk minimisation activities
Identified Risks		
Bleeding	Routine PV including blinded adjudication of bleeding events in pivotal clinical trials	The risk of bleeding will be communicated in the following 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 hemorrhagic complications: • guidance for administration of apixaban in high risk groups such as the elderly, renally impaired and subjects with hepatic impairment in section 4.2 • Contraindication for patients with hepatic disease associated with coagulopathy and clinically relevant

		bleeding risk in section 4.3 • Warning in section 4.4 • Use with caution in elderly patients co-administered apixaban with acetylsalicylic acid in section 4.4. • Information regarding interaction with other medicinal products affecting hemostasis in section 4.5 • Listed as ADR in section 4.8
Transient elevation of liver test	Routine PV including: Supplemental case report forms for liver events of interest as needed Ad hoc reporter contact for individual severe liver events as needed	Communication of elevated liver tests in appropriate product literature • Information regarding patients with elevated liver enzymes in section 4.2 • Warning in section 4.4 • Listed in section 4.8 • Further information in section 5.2
Potential Risks: None		
Missing Information		
Pregnancy and lactation	Routine PV including pregnancy outcome follow up	Communication of pregnancy and lactation treatment recommendation and requirements is in product information • Indicating that no human data is available in section 4.6
Non-Caucasian and non-Asian ethnicity	Routine PV	There is limited clinical experience of non-Caucasian and non Asian ethnic groups in the VTEp studies with apixaban. No risk minimization activity is currently required.
Pediatric population	Routine PV Additional information from PIP	Communication of indication in product information • The recommendation limiting use to adults will be described in section 4.1 • Indicating that no data below age 18 is available in section 4.2
Severe renal or hepatic impairment	Routine PV	Communication of severe renal or hepatic impairment risks, contraindication, cautions in product information • Information in section 4.2 • Contraindication in patients with hepatic disease associated with coagulopathy in section 4.3 • Warning in section 4.4 • Further information in section 5.2
Potential for off-label use	Routine PV Drug utilization study	Communication of target indication in product information • Clarifying the target patient population in section 4.1 • Warning in section 4.4

The applicant has committed to provide the actual exposure data (e.g. numbers of patients with different underlying cardiac conditions in the atrial fibrillation studies) as soon as these are available, together with a summary of relevant safety information for this population in the RMP. The RMP should also be updated with this information when it becomes available.

Five cases of Guillain-Barre syndrome (GBS) were reported. The assessment of these cases concluded that they were not related to the given medication. The applicant has committed to closely monitor cases of GBS in the PSURs.

Safety Specification

Non-clinical and clinical safety specifications
Nonclinical toxicity studies demonstrated no consistent adverse findings across species. Moreover, no safety concerns for apixaban were identified in safety pharmacology assessments of cardiovascular, neurological, or respiratory functions, and apixaban was not phototoxic *in vitro*. Apixaban was not genotoxic *in vitro* or *in vivo* and did not impair fertility or early embryonic developments in rats directly dosed with apixaban.

Identified clinical safety specifications consist of the risk of bleeding and the risk of interactions between apixaban and various CYP 3A4 and P-gp inhibitors. Potential clinical safety specifications consist of the risk of transient elevation of liver tests, risk of interactions between apixaban and antiplatelet and anticoagulants, risk of off-label use, misuse and overdose.

Several issues were identified as important missing information: subpopulations in paediatrics; pregnancy and/or lactating women; severe hepatic or renal impairment populations; and hip fracture surgery or other non elective orthopedic procedures.

Pharmacovigilance Plan

The applicant will undertake continuous monitoring for safety signals and proposes routine and enhanced pharmacovigilance practices. The risk on bleeding, interactions, transient elevation of liver tests, on overdose, and the missing information concerning paediatrics, pregnancy, patients with severe hepatic or renal impairment are considered covered by the proposed SmPC in the respective sections.

The Applicant states that additional pharmacovigilance activities are planned which include:

- Pivotal Clinical Trials: (a) Independent DMC oversight on all ongoing phase 3 clinical studies; expedited follow up of selected liver cases and supplemental case report forms to obtain more detailed information and assessment in clinical studies regarding liver events of interest, as needed; (b) frequent aggregate reviews on events of special interest and specific algorithms followed for monitoring LFT elevations; (c) external blinded adjudication for bleeding events, (d) external blinded hepatologist panel assessment for targeted hepatic events in ongoing and future pivotal clinical studies as needed and (e) periodic update to health authorities of hepatologist assessments.
- Post Marketing: (a) Targeted questions for spontaneous reports of liver events; for specific cases of severe liver events (e.g. fulminant hepatitis, liver failure, hepatic encephalopathy and hepatic necrosis), based upon medical judgment, an ad-hoc follow-up will be performed with local PV telephone contact and/or more intensive follow-up as needed; (b) frequent aggregate reviews on events of special interest; (c) a drug utilization study is planned to assess potential for off-label use; (d) a Paediatric Investigational Plan (PIP) has been approved for investigation of VTE prevention in children with central venous catheter or cardiac disease.

Evaluation of the need for a Risk Minimisation plan

The CHMP, having considered the data submitted in the application, is of the opinion that no additional risk minimisation activities are required beyond those included in the product information.

Additional information will be available from ongoing and planned studies, combined with information from ongoing pharmacovigilance activities. Potential product labelling and risk minimization activities will be reviewed and recommended if appropriate

User consultation

A readability test has been submitted with the day 121 response. The results of User Testing demonstrated that at least 90% of the participants were able to find each point of information. It also showed that at least 90% of those participants were able to understand the information.

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

2.8. BENEFIT RISK ASSESSMENT

Benefits

Beneficial effects

In Total Hip Replacement (THR) study (CV185035), apixaban demonstrated a significant superiority to enoxaparin for the primary efficacy endpoint (composite endpoint of all VTE/all-cause death). The point estimate was 1.39% vs. 3.86%; p < 0.0001, relative risk reduction [RRR]: 64% - 95% CI = 0.22, 0.54). More importantly, this superiority was demonstrated also on major VTE (proximal DVT, non-fatal PE and VTE-related death). Reported event rates were 0.45% vs. 1.14%; p=0.0107, RRR: 60% - 95% CI = 0.15, 0.80. Results of the main secondary endpoints are mainly driven by the favorable results of proximal DVT (7 vs 20 cases in the apixaban and enoxaparin groups respectively). There is a reduction in the events of non-fatal PE (apixaban(2) and enoxaparin(5)) but there was one case of VTE-related death in the apixaban arm. In the follow-up period, PE and symptomatic proximal DVT were recorded in higher numbers in the enoxaparin (4 and 3 cases respectively) compared to none in the apixaban group. A benefit of apixaban in THR over the standard comparator was considered adequately proven.

In Total Knee Replacement (TKR) study **(**CV185047), superiority of apixaban was also shown over enoxaparin in the primary endpoint (15.06% vs. 24.37%; 2-sided p-value <0.0001, RRR: 38%; 95% CI = 0.51, 0.74) as well as the secondary endpoint (1.09% vs. 2.17%; p-value=0.0373, RRR: 50% - 95% CI = 0.26, 0.97). This superiority is not only driven by the incidence of distal DVTs (14.52 % and 23.9% respectively), but also the clinically relevant proximal DVT events (0.76% and 2.17% respectively).

Uncertainty in the knowledge about the beneficial effects

The superiority demonstrated by apixaban over enoxaparin in TKR was associated with an increase in PE (3 vs 0 respectively) and one VTE-related death versus no events with enoxaparin. Results of the follow-up period show one additional case of VTE-related death, 2 cases of PE and 2 cases of symptomatic proximal VTE in apixaban arm versus 0, one and one case for enoxaparin respectively.

In the TKR supportive US study, in which enoxaparin was administered as 30 mg BID, non-inferiority of apixaban against enoxaparin was not reached. Importantly, here also an increase in PE in the apixaban group (n=14; 0.88%) was observed compared to the enoxaparin group (n=7; 0.44%).

There was an increase in VTE-related deaths in the apixaban arm in TKR (1 and 2 cases in the EU and US studies respectively) compared to none with enoxaparin. Three major issues were explored as possible contributory factors to the higher incidence of events above described: patient characteristics, timing of initiation of apixaban and the posology. Patient characteristics (risk factors, compliance, co-administration of other drugs) were balanced and where not considered by the CHMP as influential. Geographical location/medical practice probably had an effect on the higher incidence of PE reported in the US/Canada study compared to the EU study, but could not explain the higher incidence of PE in the apixaban compared to enoxaparin in the same study. Duration of hospital stay was also longer in the EU study than in the US, with better results in the EU study, precluding the duration of hospital stay to be of importance in the current assessment. The duration of thromboprophylaxis used in the TKR studies are in line with previously performed studies and CHMP guideline. However, in some patients an extension of prophylaxis beyond 14 days could have been beneficial to prevent the cases of PE reported in the follow up period. This is also in line with the most recent ACCP guideline (2008) and applies also to all other antithrombotics. The time of initiation of apixaban is more delayed than other anti-coagulants. Presented data suggest that for both apixaban and enoxaparin delayed initiation of administration is associated with higher risk for total VTE, but not major VTE. The advantages of delayed initiation should probably be individually balanced against the VTE risk per agent used.

In conclusion, the CHMP was of the opinion that this increase of PE events was probably chance findings. This can be further supported by the observation that this increase of PE was isolated, without a comparable increase in the incidence of DVT. This is not a likely event, considering that most PE events originate from the leg veins. In addition, the reported incidence of PE in the enoxaparin arm in the EU study was lower (0.07%) than the US study (0.44%), which is counterintuitive, considering the doses of enoxaparin used.

Risks

Unfavourable effects

Available safety information related to apixaban 2.5 mg BID in the indication of VTEp was considered adequate (n=5,924) to characterize the safety profile of apixaban in this indication. The duration of exposure is also relevant to the indication.
Overall, results indicate that the adverse events and treatment emergent adverse events profile of apixaban was similar to that of enoxaparin.
The overall frequency of SAEs with onset during the treatment period and the follow-up period in the four pooled VTEp studies was similar in the apixaban and enoxaparin groups (392 [6.6%] and 396 [6.7%], respectively in the treatment period and in the follow-up period: 46 [0.8%] and 49 [0.9%] respectively. No SAE was reported for > 1% of subjects in either treatment group. The most frequently reported serious adverse events were deep vein thrombosis and pulmonary embolism.

Overall event rates for deaths were low in both treatment groups with only numerical differences between treatment groups during the treatment period (apixaban 10/5924 [0.17%], enoxaparin 7/5904 [0.12%]). The event rates for death in the apixaban group were consistent with rates reported during the treatment period in published reports of enoxaparin-controlled joint replacement studies (ranging from 0 to 0.3%).

Fatal PE was reported by the investigators for 5 (0.08%) subjects in the apixaban group and 1 (0.02%) subject in the enoxaparin group. Of these deaths, 4 events in the apixaban group and 1 event in the enoxaparin group were confirmed by adjudication.

The rate of death related to other causes was comparable between the treatment groups during the treatment period (apixaban 5, enoxaparin 6) and the follow-up period [apixaban 3 and enoxaparin 2].

There was a comparable risk of bleeding during both the treatment and the follow-up periods in the two pivotal studies between apixaban and enoxaparin administered in the lower dose of 40 mg QD, with major bleeding events slightly higher in the apixaban group in the THR study (0.82% vs 0.68%) and slightly lower in the TKR (0.6% vs 0.98%). In study CV185034, in which enoxaparin was administered as 30 mg BID a trend of lower risk of major bleeding was observed in favor of apixaban (adjusted difference of event rates -0.81%; p: 0.0533) and a significant reduction in the risk of the composite of major/clinically relevant non major bleeding (-1.46%; p=0.0338). Two fatal bleeding cases were reported in the enoxaparin group. The bleeding profile of apixaban appears to be better compared to enoxaparin in the TKR studies.

No clinically meaningful differences were noted in the frequencies of clinical laboratory test results for the apixaban and enoxaparin groups in any of the analysis periods.

No clinically relevant differences were noted in the event rates for bleeding between apixaban and enoxaparin groups within patients subgroups. Results suggest a comparable bleeding risk of co-administration of apixaban with NSAIDs compared to enoxaparin, sometimes even more favourable.

The rate of discontinuation due to AEs from the clinical studies was comparable between the treatment groups in the 4 studies (apixaban 200 [3.4%], enoxaparin 217 [3.7%]), with DVT and PE as the most common AEs leading to discontinuation.

Uncertainty in the knowledge about the unfavourable effects

Analysis of clinical and pre-clinical data did not support a hepatotoxic potential of apixaban. Actual representation of patients with different degrees of hepatic impairment in the current studies was not known, but patients with elevated liver enzymes were excluded in the clinical trials. This was clearly identified in the SmPC together with the need to measure ALT before administration. The incidence of

concurrent elevations of ALT > 3 x ULN and total bilirubin > 2 x ULN was numerically higher with apixaban (n=8) than that reported with enoxaparin (n=5), and causality was assessed as possible in 2 apixaban cases, one of them was fatal. The causality of the drug in this fatal case was possible, but the contribution of other concomitantly administered drugs could not be excluded. Data from four completed clinical studies in other indications (n=2547) revealed one case of ALT > 3 x ULN and total bilirubin > 2 x ULN, which can be confounded by multiple co-morbidities. Blinded data from ongoing studies suggested that apixaban is unlikely to be hepatotoxic.
"Transient elevation of liver tests" was included as an Identified Risk in the RMP, and "hepatotoxicity" will be closely monitored in the post marketing period.

Apixaban, clopidogrel and ASA were co-administered in clinical studies in patients with ACS. Results show an increased bleeding risk in these patients, particularly in elderly patients and patients with CrCl < 60 ml/min. These risks were reflected in the SmPC.

Routine monitoring of apixaban is not needed. However, in cases of overdose or emergency surgery, the commercially available Rotachrom assay can be used. This was reflected in the SmPC.

Further safety data from the completed/ongoing studies should be submitted to facilitate the assessment of the safety profile of apixaban.

Balance

Importance of favourable and unfavourable effects

In the indication of VTEp in THR, apixaban showed favourable results that were considered by the CHMP both statistically significant as well as clinically relevant compared to enoxaparin.

The risk of bleeding was considered comparable to that of enoxaparin, with a slightly higher number of major bleedings

In the indication VTEp in TKR, apixaban also showed favourable results against enoxaparin in the pivotal study. In the supportive study, non-inferiority NI against enoxaparin was not achieved. The favourable results in the pivotal study were considered more relevant to the EU population, in particular taking into account the dose of enoxaparin used.

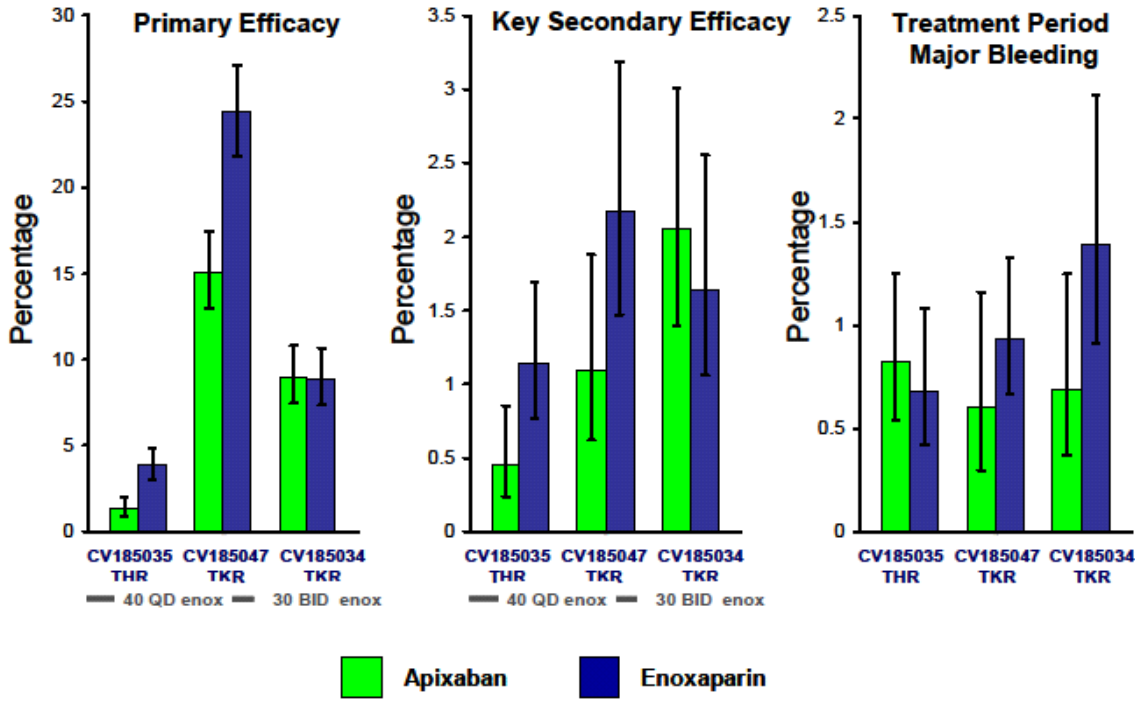
The higher incidence of PE and to a lesser extent VTE-related death in the apixaban group, could not be explained based on the explored patient characteristics or apixaban posology. Based on the current knowledge and compared to other studies, this higher PE incidence was considered by the CHMP to be probably a chance finding.

Bleeding risk appeared to be comparable if not better than enoxaparin. In the pivotal study, there were fewer major bleeding events in the apixaban group compared to enoxaparin.

Benefit-risk balance

Based on the above data, the beneficial effects of apixaban outweigh the unfavourable results in VTEp in both THR and TKR. Apixaban administration was associated with better efficacy in terms of superior reduction of the clinically relevant events of VTE compared with enoxaparin. This was accompanied with a comparable bleeding risk (main results are depicted in the figure below).

Apixaban Primary Efficacy, Key Secondary Efficacy, and Major Bleeding Event Rates in Subjects Undergoing Orthopedic Surgery (THR or TKR)



In case of VTEp in TKR, more cases of PE and fatal PE were recorded in the apixaban group. Further analysis did not show that patient characteristics or apixaban posology could have significantly contributed to these cases. Comparing the current results with those of other anti-coagulants, from previously conducted studies, this higher PE incidence could be considered by the CHMP to be a chance finding and this was reflected in the SmPC. Time of initiation of apixaban is delayed compared to other agents, which probably ensures a better bleeding profile, however this advice could be better individualized.
Current data did not point to a hepatotoxic potential for apixaban. Safety data from the ongoing studies should be submitted to facilitate further assessment of the safety profile for apixaban.

2.8.1. Discussion on the benefit-risk balance

Based on the above data, the beneficial effects of apixaban outweigh the unfavourable results in VTEp in both THR and TKR. Better efficacy in terms of superior reduction of the clinically relevant events of VTE compared with enoxaparin was demonstrated together with a comparable bleeding risk.
Time of initiation of apixaban is delayed compared to other agents, which probably ensures a better bleeding profile, however this advice could be better individualized.

In case of VTEp in TKR, more cases of PE and fatal PE were recorded in the apixaban group although not significantly attributed either to patient characteristics or apixaban posology. Comparing the current results with those of other anti-coagulants, this higher PE incidence was considered by the CHMP to be probably a chance finding and is reflected in the SmPC.
The SmPC currently contains adequate warnings for subgroups who may have higher risk for bleeding due to PK or PD interactions, in particular patients administered strong inhibitors of both CYP3A4 and P-gp, or platelet inhibitors, patients with moderate and severe renal impairment and elderly patients.
Safety data from the ongoing studies should be submitted to facilitate further assessment of the safety profile of apixaban.

In conclusion, the CHMP considered that the benefit/risk of apixaban is positive for the prevention of venous thromboembolic events (VTE) in adult patients who have undergone elective hip or knee replacement surgery".

2.8.2. Risk management plan

A risk management plan was submitted. The CHMP, having considered the data submitted, was of the opinion that no additional risk minimisation activities were required beyond those included in the product information.

2.9. Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered by consensus that the risk-benefit balance of Eliquis in the prevention of VTE in adult patients who have undergone elective hip or knee replacement surgery was favourable and therefore recommended the granting of the marketing authorisation.

2.10. Other conditions

N/A