20 September 2012

EMA/641505/2012

Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Eliquis

apixaban

Procedure No.: EMEA/H/C/002148/X/04/G

Note

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

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List of abbreviations

ACC	American College of Cardiology
ACS	acute coronary syndrome
ADR	adverse drug reaction
AE	adverse event
AF	atrial fibrillation
AHA	American Heart Association
ALP	alkaline phosphatase
ALS	amyotrophic lateral sclerosis
ALT	alanine aminotransferase
aPTT	activated partial thromboplastin time
ASA	acetylsalicylic acid (aspirin)
AUC	area under the concentration curve
AUC(INF)	area under the concentration-time curve to infinity
BID	twice daily
CAD	coronary artery disease
CDP	clinical development plan
CI	confidence interval
CLcr	creatinine clearance
CLT	total body clearance
CLT/F	apparent clearance
Cmax	maximum plasma concentration
CrCL	creatinine clearance
CNS	central nervous system
CRNM	clinically relevant non-major
CSR	Clinical Study Report
CT	computed tomography
CV	cardiovascular
CYP	cytochrome P450
DMC	Data Monitoring Committee
DAT	Dual antiplatelet therapy
DVT	deep vein thrombosis
EMA	European Medicines Agency
E-R	exposure-response
ESC	European Society of Cardiology
EU	European Union
FDA	Food and Drug Administration
FXa	factor Xa
GBS	Guillain-Barre syndrome
GI	gastrointestinal
GUSTO	Global Utilization of Streptokinase and t-PA for Occluded Coronary Arteries Trial
HR	hazard ratio
INR	International Normalized Ratio
ICH	International Conference on Harmonisation
ISTH	International Society on Thrombosis and Hemostasis
IV	intravenous(ly)
LFT	liver function test
LMWH	low molecular weight heparin
LTOLE	long-term open-label extension
LVEF	left ventricular ejection fraction
MHLW	Japan's Ministry of Health, Labor, and Welfare
MI	myocardial infarction
MRI	magnetic resonance image
NDA	New Drug Application
NHS	National Health Service
NI	non-inferiority
NNT	numbers needed to treat
NSAID	non-steroidal anti-inflammatory drug
PD	pharmacodynamic(s)

PE	pulmonary embolism
PIP	Pediatric Investigation Plan
PK	pharmacokinetic(s)
PO	oral(ly)
POC	point-of-care
PPK	population pharmacokinetics
PT	prothrombin time
QD	once daily
RR	risk reduction
RRR	relative risk reduction
SA	Scientific Advice
SAE	serious adverse event
SAP	statistical analysis plan
SCE	Summary of Clinical Efficacy
SCS	Summary of Clinical Safety
SE	systemic embolism
SPAF	stroke prevention in atrial fibrillation
TBili	total bilirubin
TIA	transient ischemic attack
TIMI	Thrombolysis in Myocardial Infarction
THR	total hip replacement
TKR	total knee replacement
TTR	time in therapeutic range
ULN	upper limit of normal
UK	United Kingdom
US	United States
Vc/F	apparent volume of distribution of the central compartment
VKA	vitamin K antagonist
VTE	venous thromboembolism
VTEp	venous thromboembolism prevention

1. Background information on the procedure

1.1. Submission of the dossier

Pursuant to Article 7.2(b) of Commission Regulation (EC) No 1234/2008, Bristol-Myers Squibb/Pfizer EEIG submitted to the European Medicines Agency on 30 September 2011 an application for a group of variations consisting of an Extension of the Marketing Authorisation, one Type II variation and one Type IB variation.

The extension of the Marketing Authorisation for the above mentioned medicinal product concerns a new strength: 5 mg.

Within Type II variation the MAH has also applied for an update of the SmPC to include a new indication for the new strength (5 mg) and for previously approved 2.5 mg strength:

Prevention of stroke and systemic embolism in adult patients with nonvalvular atrial fibrillation (NVAF) with one or more risk factors, including those unsuitable for vitamin K antagonists (VKA).

ELIQUIS also reduced the risk of major bleedings and death when compared to warfarin."

The variations submitted in the group are the following:

Variation(s) requested		**Type**
B.II.e.5	Change in pack size of the finished product	IB

Addition of a new pack size for Eliquis 2.5mg film-coated tablets of 168 film coated tablets (12 blisters of 14 film-coated tablets each).

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

Update of the SmPC to include a new indication for the new strength (5 mg) and for 2.5 mg strength: Prevention of stroke and systemic embolism in adult patients with nonvalvular atrial fibrillation (NVAF) with one or more risk factors, including those unsuitable for vitamin K antagonists (VKA).

ELIQUIS also reduced the risk of major bleedings and death when compared to warfarin."

Information on Paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/210/2011 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the P/210/2011 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Not applicable.

Additional Data/Market exclusivity

Not applicable.

Scientific Advice

The MAH received Scientific Advice from the CHMP on 15 December 2005 and 18 October 2006. The Scientific Advice pertained to clinical aspects of the dossier.

Licensing status

Eliquis has been given a Marketing Authorisation in the EU on 18 May 2011.

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 30 September 2011.
- The procedure started on 19 October 2011.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 03 January 2012 .The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 04 January 2012.
- During the meeting on 16 February 2012, 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 20 February 2012.
- During the meeting on 15 March 2012, the CHMP agreed on the updated consolidated List of Questions to be sent to the applicant. The final updated consolidated List of Questions was sent to the applicant on 16 March 2012.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 18 May 2012.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 29 June 2012.
- During the CHMP meeting on 19 July 2012 the CHMP agreed on a list of outstanding issues to be addressed in writing by the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 20 August 2012.
- During the meeting on 20 September 2012, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for an extension associated with a grouped variation on 20 September 2012.

2. Scientific discussion

2.1. Introduction

Atrial fibrillation (AF) is the most common cardiac arrhythmia, accounting for approximately one third of hospitalizations attributed to cardiac rhythm disturbances. During AF, electrical impulse propagation in the atria is disorganized and chaotic, with ineffective mechanical contraction. This results in remodelling of atrial anatomy, stasis of blood and activation of prothrombotic blood constituents, leading to the formation of thrombus or clot. Fragments of clot can dislodge from such thrombi and

embolize to the brain to cause a stroke, or enter the systemic circulation and occlude the arterial circulation of an organ or limb to produce a systolic embolism (SE). An estimated 2.6 million people in North America and 4.5 million people in Europe have AF, with increasing prevalence in older age.

Apart from the symptoms associated with AF, it is the strong association of AF with stroke that is a major source of both mortality and of major morbidity. The risk of stroke is increased >5-fold in patients with AF; this risk increases with age. More than 15% of all strokes are due to AF and such strokes are more severe than strokes not associated with AF. Strokes in patients with AF are associated with a 70% increase in mortality, a 20% increase in the length of hospital stay, and a 40% decrease in the rate of return to home because of more severe functional impairment. The outcome of such cardioembolic strokes is poor, with a mortality rate of 25% at 30 days and 50% at 1 year. Current guidelines recommend stroke prevention treatment for patients with either AF or atrial flutter, whether paroxysmal or chronic, who have at least one (CHADS2)[1] risk factor. Bleeding is the major safety concern associated with current therapies for stroke prevention in AF. When considering appropriate therapy, clinicians must weigh the benefits of preventing a potentially devastating outcome, such as stroke, with the risk of serious haemorrhage. Unfortunately, the risk of stroke and of haemorrhage tends to rise in parallel, so that those patients most at risk for stroke are also at increased risk for bleeding. Because of the concern of bleeding associated with the coumarin derivatives, acetylsalicylic acid (ASA) and other agents have been studied as alternatives. However a meta-analysis and review of these data by Hart and colleagues[2] concluded that anti-platelet therapies reduced stroke in AF patients by a modest 20%, and were associated with lower rates of major bleeding than warfarin. Nonetheless, warfarin reduced stroke by ~40% when compared with anti-platelet agents, but because of the large variability of stroke risk in this population, there is still a recognised unmet need for antithrombotic agents that are more efficacious than ASA and that are safer or more easily administered than adjusted-dose warfarin.

The ACC/AHA/ESC 2006 Guidelines for the Management of Patients with Atrial Fibrillation recommended that patients with a CHADS2 score of 2 or more be treated with warfarin (International Normalized Ratio [INR] 2.0 to 3.0). For those with a CHADS2 score of 1, recommended treatment was either ASA (81 to 325 mg daily) or warfarin (INR 2.0 to 3.0). The American College of Chest Physicians published practice guidelines in 2008 that were in substantial agreement with the ACC/AHA/ESC 2006 guidelines, but with a preference of warfarin over ASA for patients whose CHADS2 score was 1. The most recent ESC “Guidelines for the management of AF” (2010) used a slightly different risk factor score (CHA2DS2-VASC) that includes female gender, vascular disease and age 65 to 74 as risk factors. Using this approach, they recommended oral anticoagulation with either warfarin/VKA or dabigatran for those whose score was 2 or greater. For those whose score was 1, ASA (75 to 325 mg daily) was acceptable, but oral anticoagulation (as defined above) was preferred. The recently published 2011 ACCF/AHA/HRS Focused Update on the Management of Patients with Atrial Fibrillation (Updating the 2006 Guideline) added the recommendation that “the addition of clopidogrel to ASA to reduce the risk of major vascular events, including stroke, might be considered in patients with AF in whom oral anticoagulation with warfarin is considered unsuitable due to patient preference or the physician’s assessment of the patient’s ability to safely sustain anticoagulation”. In the 2012 focused update of the ESC Guidelines for the management of atrial fibrillation (published during the assessment), the use of

[1] CHADS2: cardiac failure, hypertension, age, diabetes, stroke (doubled)
[2] Hart RG, Pearce LA, Aguilar MI. Meta-analysis: antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation. Ann Intern Med. 2007; 146: 857- 867.

the CHA2DS2-VASc score was considered better at identifying 'truly low-risk' patients with AF and is as good as—and possibly better than—scores such as CHADS2 in identifying patients who develop stroke and thromboembolism. This guideline currently recommends in patients with a CHA2DS2-VASc score ≥2, OAC therapy with VKA or the new oral anticoagulant agents [dabigatran (anti-thrombin) or rivoroxaban (anti Xa)], unless contraindicated. In patients with a CHA2DS2-VASc score of 1, OAC therapy with VKA or the new oral anticoagulant agents should be considered based upon an assessment of the risk of bleeding complications and patient preferences.

Eliquis 2.5 mg film-coated tablets have been approved in the European Union for the prevention of venous thromboembolic events (VTE) in adult patients who have undergone elective hip or knee replacement surgery through centralised procedure on 18th May 2011. Currently an Extension Application is submitted for the addition of Eliquis 5 mg film-coated tablets in order to support a new proposed indication, grouped with a type II variation to add the newly proposed indication and a type IB variation to add a pack size of 168 tablets for Eliquis 2.5 mg film-coated tablets.

In the Extension Application the MAH cross reference to quality, non-clinical and pharmacokinetic data submitted previously for Eliquis 2.5 mg film-coated tablets. Therefore in this assessment report only the newly provided quality, non-clinical and pharmacokinetic data for the 5 mg strength have been discussed.

Apixaban (BMS-562247) is an orally active, direct, selective inhibitor of the 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. As the common mediator of both extrinsic and intrinsic activation of coagulation, FXa is the sole physiological mediator of thrombin formation. Thrombin, through its actions on fibrin formation and platelet activation, is a key mediator of thrombosis in both the venous and arterial circulation. Inhibition of thrombin generation, therefore, produces antithrombotic effects under a variety of pathological conditions. Accordingly, apixaban is being developed for the prevention and treatment of a wide range of thrombotic diseases.

2.2. Quality aspects

2.2.1. Introduction

Eliquis 5 mg film-coated tablet contains 5 mg of apixaban active substance. The tablet is a pink, oval shaped, biconvex film-coated tablets with "894" debossed on one side and "5" on the other side. It is presented in PVC/PVDC blisters of 14, 20, 56, 60, 100, 168 or 200 film-coated tablets in cartons.

The full list of ingredients is defined in section 6.1 of the SmPC.

2.2.2. Active Substance

The active substance manufacturing process, controls and manufacturing sites have already been approved in conjunction with the 2.5 mg tablets, EU/1/11/691/001-005 and no new information is added. Therefore it is acceptable that no further assessment or discussion concerning the drug substance has been provided in the context of the present line extension application.

It is noted that for the calculation of safe levels of impurities in this dossier a maximum daily dose 10 mg has been considered, covering both the recommended oral dose of 2.5 mg twice daily and also the maximum daily dose for Eliquis 5 mg for the new indication.

2.2.3. Finished Medicinal Product

Pharmaceutical Development

It is noted that with the present Line Extension application quality information that is specific to 5 mg strength was provided including application of two NIR methods to perform on-line (pre-blending) and at-line (tabletting) testing of Eliquis 5 mg uncoated (core) tablets for assay (potency) and content uniformity in support of the RTRT at the two finished product manufacturing sites, Humacao, Puerto Rico, USA and Mount Vernon, Indiana, USA. It is also noted that with the recent Type II variation EMEA/H/C/002148/II/003/G the initially proposed NIR method for releasing apixaban tablets 2.5 mg (real time release testing, RTRT) at both finished product manufacturing sites was registered. In view of the common granulate for both strengths, all principles also apply for the new 5 mg strength.

Eliquis tablets formulation and manufacturing process were designed to produce tablets with rapid disintegration and dissolution characteristics ensuring consistent and acceptable bioavailability. Apixaban is non-ionisable; 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, thus, it is classified as a Class III (high solubility/low permeability) compound as per the Biopharmaceutical Classification System (BCS).

Information on different strengths that were used in the early stages of the clinical development had already been presented at the time of the initial application form the 2.5 mg strength. The currently approved marketing application for apixaban 2.5 mg tablet included all the relevant information on formulation and process development of apixaban 5 mg tablet as supporting information.

Of all the strengths initially used, the 2.5 mg and 5 mg were selected for Phase 3 studies and commercialisation. The 2.5 mg tablet have been authorised for the prevention of venous thromboembolism (VTE). The 5 mg strength is intended for the new indication applied together with this application. Both 2.5 and 5 mg tablets are manufactured from a common granulate and proportional tablet weight (tablet core). The only difference is concerning the coating agent colour. The excipients used are well known. The concentrations are usual for an immediate release tablet formulation and can be considered safe in the proposed concentrations.

Pharmaceutical development of the finished product contains QbD elements.

The formulation and manufacturing development have been evaluated through the use of design of experiments and risk assessment respectively to identify the critical product quality attributes and critical process parameters.

The product critical quality attributes identified were appearance, assay, content uniformity and dissolution. The active substance particle size was determined as CQA as well in view of the low content of apixaban in the tablet.

Proven acceptable ranges (PARs) for the film coated tablet composition with regards to the disintegrant, surfactant and lubricant. In addition PARs have been established for the pre-blending, roller compaction and compression steps of the manufacturing process.

The quality of the product is further assured by the comprehensive control strategy defined for the manufacture of Eliquis tablet including process analytical technology (PAT) NIR, as well as conventional tests, to control the in-process manufacture.

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 pre-blending, a quantitative on-line NIR method was developed to monitor the mixing profile during the pre-blending unit operation and to determine the blending endpoint. For this new

strength the same NIR method used at the pre-blending applies since the 5mg tablets are manufactured from an identical blend to that of the existing tablet strength.

Holding times have been established and the results generated for three batches demonstrate that they did not negatively impact the product quality attributes.

No additional process development was conducted for the film-coating process step as typical coating procedures are followed.

An at-line NIR method, coupled with tablet weight monitoring throughout the compression run, is also applied on the tabletting step to control the content uniformity of the uncoated tablets. Tablets from various batches were tested in order to demonstrate the use of the at-line FT-NIR spectroscopy method for testing the 5 mg core tablets and the application of the large-N sample sizes. The results show a low %RSD with a very small number of units outside 85.0 – 115.5%. The comparison of the results against the reference method (HPLC) demonstrates an overall good correlation. It has been observed that NIR method could show artificially inflated assay results due to the presence of localised concentrations of apixaban, suggesting agglomerates formation during pre-blending. To mitigate this risk, a screen milling step was added to the commercial manufacturing process to further ensure a uniform blend. The application of the at-line NIR testing of the core tablets allows for more tablets to be tested compared to the traditional methods specified in the harmonised pharmacopoeial specification for uniformity of dosage units. The proposed alternative approach to the uniformity of dosage units test (EP - 2.9.40) has been scientifically establish and set acceptance criteria for content uniformity where large-N samples are tested. The proposed test is based on a one-tiered counting system and applying an appropriate quality level for tablets outside the set Label Claim (LC). The content uniformity (CU) results of 13 batches of 2.5-mg and 18 batches of 5-mg Eliquis tablets, manufactured at commercial scale at both sites, underline that the applied approach including NIR blend control and Large-N content uniformity testing on the tablet cores ensure manufacture of tablets showing a high content uniformity determined on tablets representative for the whole batch. NIR assay data on several batches of the 2.5-mg and 5-mg tablets manufactured at commercial scale are provided to demonstrate the suitability of the NIR methods developed for both strengths and thus there is no need for parallel testing.

The proposed control of content uniformity testing in both the blend as well the compression stage of manufacture is considered adequate and herewith acceptable.

The NIR models maintenance is a GMP issue. Nevertheless, it is expected that changes outside of the scope of the NIRS procedure will be submitted via an appropriate variation.

This grouped application that includes the line extension also includes a Type IB variation to add a new pack size of 168 film-coated tablets (12 blisters of 14 film-coated tablets each) for Eliquis 2.5 mg film-coated tablets.

Adventitious agents

Lactose used in the manufacture of tablets is of animal origin (bovine milk). Statements from the suppliers and finished product manufacturer in relation to the quality of lactose confirm 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 was described in the original submission and comprises the following main steps: blending, granulation, blending, tabletting, film-coating and packaging. A flow-chart including in-process controls is provided.

The validation strategy consisted of manufacture of three consecutive commercial scale batches of Eliquis 5 mg coated tablets at the Humacao site. The in-process controls that were monitored during the execution of the validation exercise were: pre-blend active substance homogeneity, roller compaction ribbon density and ribbon thickness, tablet core weight and hardness and coated tablet weight gain. In addition to the in-process controls, for the validation batches the final blend uniformity was determined by NIR. All validation results were in accordance with the set acceptance criteria. Finally, batch analysis results on the coated tablets according to the release specifications are listed for two coating loads sampled at each three locations. All results met the set requirements.

The process validation protocol for Eliquis 5 mg tablets at the new site (BMS Mount Vernon) at the proposed scale is also considered adequate.

It can be concluded that the validation is satisfactory, all the in-process control criteria were met, all the validation testing complied with the pre-established acceptance criteria, and the release testing of the batches were in compliance with the predetermined specifications and quality attributes.

Due to the use of NIR (as PAT) and RTR for the manufacturing of the drug product, the proposed finished product manufacturing site (Mount Vernon, USA) will be inspected post-approval in the scope of the planned re-inspection.

Product specification

The same drug product specifications are applied for the 5 mg tablets as finalized in Type II variation procedure EMEA/H/C/00002148/II/0003/G for the 2.5 mg tablets.

The release and shelf-life specifications include tests and limits for appearance (visual), identification (Raman, IR, HPLC, at release only), assay (by approved Real Time Release testing (NIR and tablet weight) or HPLC if tested), uniformity of dosage units/ content uniformity (by approved Real Time Release testing (NIR) or HPLC if tested, HPLC at release), disintegration (Ph. Eur., at release only), impurities/degradants (HPLC, stability only), dissolution (HPLC, stability only) and microbial limit test (Ph. Eur., not routinely).

A correlation between the particle size of the drug substance and dissolution rate of apixaban has been established. Based on this relationship, the specification for the particle size of the drug substance is proposed as a surrogate for dissolution testing and therefore the specification does not include a test for dissolution.

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.

Furthermore, due to microbial tests results of the long-term stability batches and low water activity of Eliquis film-coated tablets, the tablets are not susceptible to microbial growth. Batches are proposed to be tested on a skip-lot basis (one lot once a year or every ten batches, whichever is sooner) for microbial contamination.

Batch analysis data for Eliquis 5 mg tablets were available from two production scale batches from Mount Vernon site and three production scale batches from BMS Humacao site. The tablets have been analysed according to both conventional finished product tests (HPLC assay, HPLC content uniformity) and RTRT tests (based on core tablets, NIR assay and NIR content uniformity). In addition results from a large number of batches from both strengths were also presented. Based on the comparative results it has been demonstrated that the applied RTR tests could replace the conventional finished product tests based on HPLC.

All results on other parameters like disintegration, dissolution and impurities were satisfactory and meeting the set requirements. No differences between the two manufacturing sites could be observed.

The assay results obtained by HPLC (film-coated tablets) and by NIR (uncoated core tablets, large (N) – 150 to 160) are very similar.

The dissolution results are satisfactory and the levels found for the impurities are very low.

The batch analysis data demonstrate that the manufacturing process, both at the Humacao as well as the Mount Vernon site, is well under control.

Stability of the product

Three batches of active substance were used to prepare three batches of Eliquis 5 mg film-coated tablet. All batches were made using a site and process representative of the proposed commercial process. The stability protocol includes testing for all three batches packaged in PVC/PVDC blisters and HDPE bottles. The PVC/PVDC blister represents the worst case for water and oxygen permeation. Therefore, the results from this package represent the worst case for microbial counts and are applicable to all packages. The tablets have been stored for 36 months under three long term conditions (5°C, 25°C/60%RH and 30°C/75% RH) and for 6 months under accelerated 40°C/75%RH. Appearance, HPLC identification (only initially), KF water content, dissolution + HPLC/UV detection, HPLC assay, HPLC impurity/degradants, microbial limit tests (including specified organisms), hardness and disintegration. During the 36 months studies in PVC/PVDC blisters or HDPE bottles at the 3 long term conditions and after 6 months accelerated study, no changes for appearance, assay, impurities, dissolution, hardness, disintegration, and microbial content have been seen. A slight increase in water content values was observed for the tablets packaged in PVC/PVDC blisters. However, there was no impact on any other attributes.

In addition, one batch was packaged in an in-process bulk container and tested after storage at 30°C/65%RH through 6 months.

Stress study

Stress conditions (50°C), photostability, freeze-thaw cycling and bulk stability studies have been performed. One batch of apixaban tablets, for each package type, was exposed to the stress condition of 50°C. One batch of tablets placed in a single layer in an open petri dish was exposed to 25°C/60%RH for 12 months or 40°C/75%RH for 6 months. One batch of tablets in the 60-count HDPE bottle was exposed to seven freeze-thaw cycles. Photostability studies were conducted as per ICH Q1B. In addition, one batch of tablets (equivalent to 10% of the anticipated amount packaged for commercial manufacturing) placed in an in-process bulk container was also placed on stability at 30°C/65%RH through 6 months.

The product when stored in PVC/PVDC blisters or HDPE bottles for 3 months at 50°C was stable with essentially no change from initial observed in potency, impurities, hardness, disintegration time, appearance, or dissolution. The freeze/thaw cycling, open-dish, and high-temperature stress studies

support shipping of the product through normal distribution channels. Based on the photostability data collected the product is considered not sensitive to light.

The overall stability results support the proposed shelf-life and storage conditions.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

The quality of Eliquis 5 mg 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 substances has been presented in a satisfactory manner. The quality of the active substances 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. Since the new 5 mg strength is manufactured from the same identical blend, the already established PARs apply also for 5 mg tablets. The same PAT tools (NIR) are used for the monitoring of the pre-blending step for both strengths.

RTRT is proposed for the assay and content uniformity of the tablets. The NIR method together with tablet weight is used for this purpose has been approved for the 2.5 mg strength. The method has been satisfactorily validated for the new strength at both the proposed manufacturing sites. The results of tests carried out indicate 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.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. The design space is considered sufficiently validated for the proposed batch size range at both the proposed manufacturing sites. The proposed RTRT for content uniformity and assay is accepted and has been sufficiently supported by data and validation studies.

Stability tests indicate that the product under ICH guidelines conditions is chemically stable for the proposed shelf life.

2.2.6. Recommendations for future quality development

Not applicable.

2.3. Non-clinical aspects

2.3.1. Pharmacology

No new pharmacology studies were provided within current application to support the extension of indications. Since both indications, new and the previously approved one, are based on the same pharmacodynamic mechanism, the CHMP was of the opinion that there is no need for additional pharmacology data. Therefore, the reference is made to the assessment of initial marketing authorisation application (MAA) for Eliquis 2.5 mg film-coated tablets and only new information is discussed in the current report.

2.3.2. Pharmacokinetics

The only new information provided consists of two (non-GLP) *in vitro* studies showing an inhibiting effect of diltiazem on digoxin efflux in Caco- 2 cells and in porcine kidney-derived LLC-PK_1 cell monolayers. Based on these data it can be concluded that diltiazem is an inhibitor of P-gp.

2.3.3. Toxicology

The final report was provided of the definitive juvenile rat toxicology study (GLP) which was ongoing at the time of the assessment of the initial MAA for Eliquis. In this study, cross-fostered rat pups were treated from postnatal day (PND) 4 to PND 94. Tested doses were 0, 10, 50 and 600 mg/kg/day. Subgroups were sacrificed on PND 10 (toxicokinetics), PND21 (coagulation testing), PND 94 (toxicokinetics), on PND 21 and 87 (organ weights, serum chemistry, hematology, coagulation, urinalysis, necropsy, histopathology), or after a recovery period of 1 month (after production of an F2 generation, organ weights, coagulation, serum chemistry [males], testis histopathology). No apixaban-related toxicity or changes of F1-generation fertility or mating indices were observed. Apixaban-related effects were limited to mild prolongations of PT and aPTT values that were not adverse and were recoverable. The no-observed-adverse-effect-level (NOAEL) was 600 mg/kg/day (AUC during PND 21 to 87 respectively 25 and 9 times human AUC at 5 mg BID) changes. Toxicokinetic data showed decreasing exposure from PND 10 to 87, presumably due to developmental changes (Tmax on PND 10 was about 2-3 times the Tmax on PND 21). Taking into account the additional information, the CHMP agreed not to consider the findings from this study as drug related for the following reasons: all other toxicity signs observed in the reproductive/developmental studies are related to apixaban's action on coagulation, i.e. its pharmacodynamic mechanism of action. From other toxicity studies provided (repeated dose studies, fertility studies, juvenile toxicity studies) there was no evidence of any effects on parameters which could be related to female fertility. Based on the overall data set now available the observed slightly decreased mating and fertility indices in offspring of pre/post-natally treated rats is unlikely to be an apixaban-related effect. Based on this conclusion, the CHMP agreed on the amendments of the SmPC text of sections 5.3 and 4.6.

2.3.4. Environmental risk assessment

A full ERA has already been presented and evaluated for Eliquis 2.5 mg tablets at the time of the initial MAA. At that time a complete dossier was submitted, meeting the requirements of the EMA guideline on ERA. The ERA concluded that no risk to the environment was anticipated following the use of Eliquis 2.5 mg tablets. In the current procedure the same, complete ERA dossier has been submitted. Due to the added indication, the environmental exposure is expected to increase. The MAH submitted a revised ERA, which was evaluated with respect to the PEC calculations and the result of the revised risk quotients.

Apixaban (BMS-562247) is a selective, reversible inhibitor of the coagulation factor Xa (FXa). Its log K_{ow} is 1.2 (shake flask), water solubility 38-60 mg/L at 25°C and its K_{oc} 12.2 L/kg (HPLC method; log K_{oc} = 1.09). Apixaban is not readily biodegradable. In a water/sediment simulation study (OECD 308), half life values of 31.5-41.7 d were found for the water phase and 100-182 d for the whole system, all determined at 20±2°C. The toxicity data are summarized below. Inhibition of activated sludge respiration: EC50 > 1000 mg/L and hence NOEC > 1000 mg/L. Aquatic species: green alga *P. subcapitata*, 3 d NOEC 3.6 mg/L (growth rate); crustacean *D. magna*, 21 d NOEC 9.6 mg/L (reproduction); fish *P. Promelas*, 32 d NOEC ≥ 10 mg/L (E.L.S. test, hatching success, percentage of embryos producing live normal larvae at hatch, survival at test termination, and larval growth (total

length and dry weight)). Sediment dwelling organism, midge *C. riparius*, 28 d NOEC 417 mg/kg$_{dw}$ (emergence and development rate; result normalised to 10% o.c.). Using a refined F_{pen} of 0.01 (57% metabolism), PEC$_{surface\ water}$ was 0.0285 µg/L. No risk following the use of apixaban was anticipated for the sewage treatment plant, surface water, groundwater and sediment. The PBT (Persistent, Bioaccumulative, Toxic) assessment is summarized below. Apixaban does not meet the screening criterion for B, since log K_{ow} is < 4.5. Based on the OECD 308 study and the resulting whole system half life values of 100-182 at 20°C, the P criterion is met. Based on the aquatic toxicity data submitted, the substance is not T.

In conclusion, apixaban was considered by the CHMP not PBT, nor vPvB (very persistent, very bioaccumulative).

Table 1 ERA table of endpoints

Substance (INN/Invented Name): apixaban					
CAS-number (if available): 503612-47-3					
PBT screening		Result			**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD107	1.2			not B
PBT-assessment					
Parameter	**Result relevant for conclusion**				**Conclusion**
Bioaccumulation	log K_{ow}	1.2			not B
	BCF	not triggered			
Persistence	ready biodegradability	not readily biodegradable			
	DT50$_{water}$	31.5-41.7 d at 20°C			
	DT50$_{whole\ system}$	100-182 d at 20°C			P
Toxicity	NOEC or CMR	> 1 mg/L, not CMR			not T
PBT-statement :	The compound is not considered not PBT nor vPvB				
Phase I					
Calculation	**Value**	**Unit**			**Conclusion**
PEC$_{surface\ water}$	0.050	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			determined at 20±2°C
Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test/ *Pseudokirchneriella subcapitata*	OECD 201	NOEC	3.6 x 10^3	µg/L	
Daphnia sp. Reproduction Test	OECD 211	NOEC	9.6 x 10^3	µg/L	
Fish, Early Life Stage Toxicity Test/ *Pimephales promelas*	OECD 210	NOEC	≥ 10 x 10^3	µg/L	
Activated Sludge, Respiration Inhibition Test	OECD 209	NOEC EC50	>1.0 x 10^6 >1.0 x 10^6	µg/L	
Phase IIb Studies					
Sediment dwelling organism / *C. riparius*	OECD 218	NOEC	≥ 100	mg/kg	

2.3.5. Discussion on non-clinical aspects

The MAH submitted supplemental data related to: (1) potential pharmacokinetic interactions with diltiazem and (2) the final report of an ongoing juvenile toxicity study. The evidence was provided that diltiazem inhibits P-gp.

No evidence of juvenile toxicity was found at systemic exposure of 9 – 25 times human exposure (based on data from adults). Since chronic use of apixaban was already assessed in the initial MAA of

apixaban, no new data were considered necessary by the CHMP to support the extension of the treatment duration that was approved within current application. The doses used in the non-clinical toxicity studies provided in the initial dossier resulted in sufficiently high exposure compared to clinical exposure. The MAH provided updated overview of exposure factors, based on the new clinical dose of 5 mg BID.

The CHMP agreed not to consider the findings from this study as drug related for the following reasons: all other toxicity signs observed in the reproductive/developmental studies are related to apixaban's action on coagulation, i.e. its pharmacodynamic mechanism of action. From other toxicity studies provided (repeated dose studies, fertility studies, juvenile toxicity studies) there was no evidence of any effects on parameters which could be related to female fertility. Based on the overall data provided the CHMP believed, that the observed slightly decreased mating and fertility indices in off-spring of pre/postnatally treated rats was unlikely to be an apixaban-related effect. As a consequence, sections 4.6 and 5.3 of the SmPC were modified. In addition, the juvenile toxicity study was added to section 5.3 of the SmPC.

In addition, an updated ERA was provided within current line extension application in which the new indication was covered.

2.3.6. Conclusion on the non-clinical aspects

From a non-clinical view, Eliquis 5 mg tablets were considered approvable by the CHMP. Cross reference was made to the information in the assessment of the initial MAA for Eliquis 2.5 mg film-coated tablets. Based on the additional juvenile toxicity data, the CHMP proposed amendments to sections 4.6 and 5.3. of the SmPC.

2.4. Clinical aspects

2.4.1. Introduction

Apixaban is a novel, orally active, selective, direct, reversible inhibitor of the coagulation factor Xa (FXa), developed as an anticoagulant. Factor Xa plays a pivotal role in the coagulation cascade because it sits at the junction of the intrinsic and extrinsic pathways of the coagulation system. Inhibition of FXa is expected to exert anticoagulant and antithrombotic effects by decreasing the conversion of prothrombin to active thrombin, thereby diminishing thrombin-mediated activation of the coagulation process, including fibrin formation and platelet activation.

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.

A request for GCP inspection had been adopted for the following clinical study CV 185030 (ARISTOTLE). The outcome of this inspection was submitted and assessed. No critical findings were observed in three inspected sites. In conclusion the CHMP agreed with the inspectors that based on the inspections conducted in three different sites the conduct of the main clinical study ARISTOTLE is considered to be GCP compliant.

During the assessment of the current application an issue was raised concerning possible errors in medication dispensing. Analysis of a sample of labels (around 20% of dispensed labels) showed that these occurred within values that could be expected in major trials. Sensitivity analyses further

confirmed the robustness of the data. In the analysed sample of labels, illegible labels (after dispensing) were read using bar code readers. No medication errors were discovered in most of these labels. This further confirms the limited rate of medication errors previously calculated in ARISTOTLE (0.03%). There was also some concern whether monitoring activities were vigilant enough to detect the identified medication errors. The MAH submitted the monitoring plan implemented in ARISTOTLE, describing its frequency and the main activities including source data verification and drug accountability. The submitted analysis shows that most of the incorrect medication containers dispensed (46/50) were detected by monitoring visits or data queries. Also corrective actions were taken. Although no reference standard for comparison is available, the submitted analysis and narratives are reassuring. In addition, the EMA inspections of three of the trial sites support that the study was GCP compliant.

Additional concerns were raised with regards to the integrity of the interactive voice response system (IVRS), which specified each container to be dispensed to the patient, and on discrepancies between the trial database and the data collected on the eCRF. In response, the MAH clearly explained that the identified discrepancies were isolated events and not part of systematic error. With regard to the IVRS, the MAH explained in sufficient detail the pre-defined procedures employed in case manual changes are implemented, the reason such changes were implemented, and the audit trail of such changes. The submitted data indicate that these changes were necessary, well documented and not interfering with the integrity of the data or the safety of the trial subjects. This response was considered acceptable by the CHMP.

- Tabular overview of clinical studies

Table 2 Tabular listing of clinical studies with apixaban submitted within current application

Study Number	Objectives	Study Design	Type of Subjects	Dosage, Route	Duration of Treatment	Number of Treated Subjects	Study Status, Type of Report
Completed Studies							
CV185029	To assess the oral bioavailability of apixaban solution formulation (Treatment B, 10 mg as 25 mL x 0.4 mg/mL) relative to apixaban Phase 3 tablets (Treatment A, 10 mg as 2 x 5 mg tablets) in healthy subjects	Phase 1, Open-label, randomized, 2-period, 2-treatment, crossover study	Healthy	Treatment A: apixaban 10 mg (2 x 5mg tablets) / Oral; Treatment B: apixaban 10 mg (25 mL x 0.4 mg/mL) / Oral Solution	Apixaban tablets - single dose; Apixaban OS - single dose (4 day washout period)	14	Completed, Full CSR

Table 2 Tabular listing of clinical studies with apixaban submitted within current application

Study Number	Objectives	Study Design	Type of Subjects	Dosage, Route	Duration of Treatment	Number of Treated Subjects	Study Status, Type of Report
CV185074	To assess the multiple-dose pharmacokinetics (PK) of apixaban and rivaroxaban following oral administration in healthy subjects and to compare plasma concentration peak to trough ratio (Cmax/Cmin) of rivaroxaban to apixaban following oral administration in healthy subjects	Phase 1 Open-label, randomized, 2-period, 2-treatment, crossover study	Healthy	Treatment A: Rivaroxaban 10 mg QD Treatment B: Apixaban 2.5 mg Q12h	Trt A: 4 days Trt B: 4 days	14	Completed, Full CSR
CV185104	The primary objective was to assess the effect of activated charcoal on the pharmacokinetics of apixaban, when administered 2 hours or 6 hours following the dose of apixaban in healthy subjects. The secondary objective was to assess the safety of apixaban when administered with and without activated charcoal.	Phase 1, Open-label, 3-treatment, 3-period, randomized, crossover study	Healthy	Apixaban 20 mg (4 x 5 mg tablets) with 50 g activated charcoal and 96 g sorbitol, single dose / Oral	Single dose (4 day washout period)	18	Completed Full CSR

Table 2 Tabular listing of clinical studies with apixaban submitted within current application

Study Number	Objectives	Study Design	Type of Subjects	Dosage, Route	Duration of Treatment	Number of Treated Subjects	Study Status, Type of Report
CV185066	To characterize the in vitro PD activity of apixaban in blood obtained from pediatric subjects (neonates through adolescents) and cord blood as compared to blood obtained from adult subjects	Non-therapeutic, in vitro study	Healthy	Not applicable, non-therapeutic study	Not applicable, non-therapeutic study	Not applicable, non-therapeutic study	Completed, Full CSR
CV185067 (B0661003)	To assess (safety endpoint) the effect of 2 doses of apixaban (2.5 mg BID and 5.0 mg BID) versus warfarin on the composite endpoint of major and CRNM bleeding during the Treatment Period.	Phase 2b, randomized, double-blind (apixaban), open-label comparator (warfarin)	non-valvular atrial fibrillation (in Japan)	Oral apixaban: 2.5 mg bid 5.0 mg bid Warfarin given per label requirements as per standard of care.	12 weeks	2.5 mg BID: 72 5.0 mg BID: 71 warfarin: 75	Completed, Full CSR

Table 2 Tabular listing of clinical studies with apixaban submitted within current application

Study Number	Objectives	Study Design	Type of Subjects	Dosage, Route	Duration of Treatment	Number of Treated Subjects	Study Status, Type of Report
CV185030	To determine if apixaban is noninferior to warfarin (INR target range 2.0 3.0) in the combined endpoint of stroke (ischemic or hemorrhagic) and systemic embolism, in subjects with AF and at least one additional risk factor for stroke	Phase 3, active (warfarin)-controlled, randomized, multi-national, multi-center, double-blind, double-dummy, parallel group study	Non-valvular atrial fibrillation	5 mg (2.5 mg for select subjects with a higher risk of bleeding) BID apixaban/ Oral Warfarin with INR therapeutic range 2.0 to 3.0/ Oral	2.1 years average[a]	18,140	Completed, Full CSR
CV185048	To determine if apixaban is superior to aspirin for preventing the composite outcome of stroke or systemic embolism in patients with AF and at least one additional risk factor for stroke who have failed or are unsuitable for vitamin K antagonist therapy.	Phase 3 randomized, multi-national, multi-center, double-blind, double-dummy, parallel-arm	Non-valvular atrial fibrillation	5 mg (2.5 mg for select subjects with a higher risk of bleeding) BID apixaban/ Oral Aspirin 81 to 324 mg QD / Oral	1.6 years average[a]	5578	Double-Blind Phase: Completed, Full CSR; Open-Label Phase: Ongoing

Table 2 Tabular listing of clinical studies with apixaban submitted within current application

Study Number	Objectives	Study Design	Type of Subjects	Dosage, Route	Duration of Treatment	Number of Treated Subjects	Study Status, Type of Report
CV185068	To determine if apixaban is superior to placebo for preventing the composite of cardiovascular death, myocardial infarction, or ischemic stroke, in subjects with a recent acute coronary syndrome (ACS).	Phase 3, randomized, placebo-controlled, parallel group study	Recent ACS and at least 2 additional risk factors for recurrent ischemic events	Oral apixaban 2.5 (for patients with CrCl< 40 mL/min) or 5 mg BID placebo	Apixaban 27 weeks Placebo 28 weeks	Apixaban 3672 Placebo 1508	Completed, Full CSR

[a]This is an event-driven trial. Treatment duration is estimation.

ACS = Acute Coronary Syndrome; AF = atrial fibrillation; BID = twice daily; CrCl = creatinine clearance; CRNM = clinically relevant non-major; CSR = clinical study report; DR = dry granulation; DVT = deep vein thrombosis; GI = gastrointestinal; INR = international normalized ratio; IV = intravenous; LMWH = low molecular weight heparin; PD = pharmacodynamic; PE = pulmonary embolism; PK = pharmacokinetic; PO = by mouth; QD = once daily; SC = subcutaneous; TIA = transient ischemia attack; VKA = vitamin k antagonist; VTE = venous thromboembolism

2.4.2. Pharmacokinetics

The pharmacokinetic data submitted within initial MAA were considered sufficient for the authorisation of the 5 mg tablet, as the pharmacokinetics of both tablets were intensively investigated in the submitted phase I-III studies. All studies in the initial MAA were relevant for both strengths, and the 2.5 and 5 mg tablets showed dose proportionality. Therefore, reference is made to the information assessed within the initial MAA of Eliquis 2.5 mg film-coated tablets and only new information will be discussed.

For the current application the MAH submitted 2 additional PK studies (study CV185029 and CV185074) and updated the (pop-pk) pharmacokinetic analysis with data of newly performed phase 2/3 studies which employed sparse sampling.

Newly submitted pharmacokinetic studies

The following pharmacology studies including population pharmacokinetics are new in this application compared to the initial application of the 2.5 mg strength.

Study **CV185029** was designed to evaluate the relative bioavailability (BA) of the apixaban Phase 3 tablet (2.5 mg) and an oral solution formulation. This study provides additional data showing that the extent of absorption of apixaban from the tablet and solution formulation is comparable.

The results of this study did not contribute specifically for the application of the 5mg tablet, but merely confirmed the observations already made with regard to the absorption profile of apixaban tablets, as Study CV185029 showed that absorption seems not to be dissolution-rate dependent.

Study **CV185074** provided an additional assessment of apixaban multiple dose PK following administration of 2.5 mg BID in healthy subjects. This study also allowed a relative assessment of apixaban PK and rivaroxaban PK within the same individual. The results of the study are used to update figure PK16 (assessment report) and in the tables below, however they are not separately discussed. The results are completely in line with previous pk results for multiple dose administration of 2.5 mg BD apixaban in healthy subjects.

The tables below (Table 3 and 4) are updated with data from studies **CV185029** and **CV185074**. The single- and multiple dose pharmacokinetics parameters estimates of apixaban are not changed after including these studies.

Table 3 Apixaban Oral Single-Dose PK Parameter Values Following Administration of 2.5-, 5- and 10-mg Apixaban Doses

Dose (n)	Cmax (ng/mL) Geom. Mean (%CV)	Tmax (h) Median (min, max)	AUC(INF)[a] (ng*h/mL) Geom. Mean (%CV)	T-HALF (h) Mean (SD)	CLR (mL/min) Mean (SD)	F (%) Geom. Mean %CV)
Solution 10 mg (n = 13)	287 (30)	2.0 (1.0, 4.0)	2855 (21)	13.8 (6.1)	-	-
Tablet,10 mg (n = 214)	185 (39)	3.0 (0.5, 8.0)	1924[b] (32)	12.4[b] (5.6)	15.1[c] (6.0)	49[d] (24)

AUC(0-T) is not listed since it accounted for >93% of AUC(INF) across the dose full range

n= 212,

n= 20

n= 80

Table 4 Apixaban Oral Steady-State PK Parameters Following Administration of 2.5-, 5-, and 10-mg BID Apixaban Doses

Dose BID (n)	Cmax (ng/mL) Geom. Mean (%CV)	Cmin (ng/mL) Geom. Mean (%CV)	Tmax (h) Median (min, max)	AUC(TAU) (ng*h/mL) Geom. Mean (%CV)	T-HALF (h) Mean (SD)	CLR (mL/min) Mean (SD)	AI Mean (SD)
2.5 mg (n= 25)	77.2 (25)	18.5 (20)	2.0 (1.0, 9.0)	527.9 (23.5)	8.48 (2.2)	15.7 (5.6)	1.53 (0.31)
5 mg (n= 12)	162.3 (27)	55.9 (19)	4.0 (2.0, 4.0)	1276.4 (23)	10.9 (3.8)	17.8[b] (4.7)	1.83 (0.36)
10 mg (n= 24)	341.2 (28)	105.7 (39)	4.0 (2.0, 4.0)	2647.9 (28)	10.1 (3.9)	18.4 (6.2)	1.76 (0.38)

AUC(TAU) represents AUC for the dosing interval, 0-12 h post dose, following the morning dose.

n = 6

n=11

n=18

Dose proportionality and time dependencies

The summary of clinical pharmacology data submitted to support the registration of for venous thromboembolism prevention (VTEp) indication remains largely unchanged, even with the additional new data from the **CV185029** study. As such, the interpretation of these findings remains consistent with that presented in the Clinical pharmacology Summary (CPS) for VTEp indication. Loss of proportionality at doses ≥25 mg has little, if any, clinical impact for this indication.

POP-PK update and update intrinsic factors

The MAH used sparse sampling in several newly submitted phase 2 and 3 trials (study CV185030, CV185067, CV185070, and CV185023). A POP-PK analysis was conducted with this new data. Results of this analysis indicated that, 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 healthy Phase 1 subjects and patients with AF. In addition, patient status accounted for a small, 14% reduction in apixaban CL/F.

Higher apixaban exposures, up to approximately 30%, were observed for intrinsic factors such as age, gender, race, or low body weight (≤ 50 kg). Subjects with AF who are at a potentially greater risk of bleeding (defined as those who meet at least 2 of the following 3 criteria: age ≥ 80 yrs, body weight ≤ 60 kg, or serum creatinine ≥ 1.5 mg/dL) may require a lower dose of apixaban (i.e., 2.5 mg BID). It was shown in phase 3 trials that exposures in the subjects who met the dose reduction criteria and received 2.5 mg BID was slightly lower (~25%) than that of AF subjects treated with apixaban 5 mg BID (daily median AUCss values of 2703 ng*hr/mL versus 3603 ng*hr/mL, respectively). Therefore, this advice of dose reduction is incorporated in section 4.2 of the SmPC.

Other important PK updates

Additionally the MAH included in the clinical overview information with regard to possible genetic polymorphism. The MAH confirmed and the CHMP agreed that genetic polymorphism resulting in clinical significant differences in metabolic clearance of apixaban is not likely.

2.4.3. Pharmacodynamics

Pharmacodynamic data presented during the original application to support the VTEp indication are also applicable to the current indication.

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. As the common mediator of both extrinsic and intrinsic activation of coagulation FXa is the sole physiological mediator of thrombin formation. Thrombin, through its actions on fibrin formation and platelet activation, is a key mediator of thrombosis in both the venous and arterial circulation. Inhibition of thrombin generation, therefore, produces antithrombotic effects under a variety of pathological conditions. PD effects of apixaban include inhibitory effects on FXa activity and *ex vivo* thrombin generation as well as the prolongation of clotting tests such as PT/INR, aPTT, and mPT.

Primary pharmacology

For this application, the MAH included one new pharmacodynamic Study ***CV185066*** which provided an assessment of apixaban PD in paediatric and adult plasma utilizing 2 different anti-Xa assays. Presented data show that the Rotachrom chromogenic (RCC) anti-Xa (AXA) assay is not affected by intrinsic factor X levels. Although apixaban does not require routine monitoring of exposure, the Rotachrom anti-Xa assay may be useful in situations where knowledge of apixaban exposure may help to inform clinicians when taking decisions. However its use was not implemented in the clinical program limiting any recommendation regarding its applicability.

Based on PKK and exposure-response ER modelling from the pivotal study CV185030 (ARISTOTLE), AXA activity and apixaban plasma concentration are shown to be highly correlated within and above concentrations achieved following administration of apixaban 2.5 mg and 5 mg BID in AF patients. This is in line with data provided in the original MAA for subjects receiving 2.5 mg BID for VTEp indication. The model predicts a tight correlation between higher exposure and bleeding, but a lesser correlation between higher exposure and efficacy, in the form of prevention of stroke.

Secondary pharmacology

No new data since initial MAA were provided.

2.4.4. Discussion on clinical pharmacology

Pharmacokinetic and pharmacodynamic data presented during the original application for the VTEp indication are also relevant for the current application. New data further support the utility of Rotachrom anti-Xa assay, however, there was limited utilization of this assay in the phase 3 studies.

2.4.5. Conclusions on clinical pharmacology

The initial MAA included sufficient pharmacokinetic data to support the marketing authorisation of the 5 mg tablet. The PD properties of apixaban are adequately characterized and are in line with those of a direct FXa inhibitor. The Rotachrom anti-Xa assay was not used for decision-making in the clinical program limiting any recommendation regarding its applicability.

2.5. Clinical efficacy

Overview of the two new phase 3 studies to support the proposed indication are included in table E1. The phase 2 study CV185067 is discussed under Safety.

Table E1 Overview of phase 3 clinical studies in AF

Study No. Study Phase # of sites Regions	Subject Population Study Design	Study Start Enrollment Status Target Randomized	Number Randomized Duration	Gender M/F (%) Age Mean (min, max)	Primary and Other Key Endpoints / Objectives and Testing Strategy
CV185030 Phase 3 1053 sites enrolled subjects 1034 sites randomized subjects North America, Europe, Latin America, Asia/Pacific	Subjects (both warfarin-naïve and warfarin-experienced) with AF and at least one additional risk factor for stroke Randomized, acrive-controlled, double-blind, double-dummy, parallel-group study	19-Dec-2006 Complete Randomized Target: 18,000 subjects (9,000 in each group)	Apixaban: 9,120 Warfarin: 9,081 Event driven: The Double-blind Treatment Period was to be completed after approximately 448 subjects had a primary efficacy endpoint. The mean extent of exposure to double-blind study drug was 1.7 years for subjects in both treatment groups.	Apixaban: 64.5/35.5 69.1 (21, 95) Warfarin: 65/35 69.0 (19, 97)	Primary: stroke (hemorrhagic, ischemic or of unspecified type) or SE. Key Secondary: ISTH major bleeding; all-cause death Objectives and Testing: NI for stroke/SE, followed by superiority for stroke/SE, followed by superiority for ISTH major bleeding, followed by superiority for all-cause death
CV185048 Phase 3 526 North America, Europe, Latin America, Asia/Pacific	Subjects with AF and at least one additional risk factor for stroke, who failed (Demonstrated VKA unsuitable) or were expected to be unsuitable for VKA treatment (Expected VKA unsuitable) Randomized, double-blind, double-dummy, parallel-group study.	31-Aug-2007 Double-blind Complete Randomized Target: 5600 subjects (2800 in each group) Open-label Ongoing	Apixaban: 2807 ASA: 2791 Event driven: The Double-blind Treatment Period was to be completed after at least 226 subjects had a primary efficacy endpoint. The mean extent of exposure to double-blind study drug was 1.1 years for subjects in both treatment groups.	Apixaban: 59.1/40.9 69.7 (48, 95) ASA: 57.9/42.1 70.0 (49, 100)	Primary: stroke (hemorrhagic, ischemic or of unspecified type) or SE Key Secondary: major vascular events (stroke, SE, MI or vascular death; all-cause death. Objectives and Testing: Superiority for stroke/SE, followed by superiority for major vascular events, followed by superiority for all-cause death

2.5.1. Dose response study

No new dose response studies were provided by the MAH to support this appllication. In the phase 3 studies, 5 mg BID was the selected dose. For certain patients deemed to be at higher risk of bleeding with study drug (e.g., the elderly, small stature, renal impairment), a lower dose of apixaban (2.5 mg BID) was used.

Selection of the 5 mg BID dose of apixaban was based primarily on the Phase 2 dose-ranging study in VTEp (CV185010), the Phase 2 study in deep vein thrombosis (DVT) treatment (CV185017; 3 months treatment duration), and experiences from other anticoagulants studies in this patient population. In the Scientific Advice provided by the EMEA in 2005, it was agreed that dose selection for apixaban in AF studies could be derived from Phase II studies in prophylaxis and treatment of VTE and that there was no need in repeating dose-finding in patients with AF.

Study CV185010 (assessed within the original MAA) showed that all selected doses had favourable efficacy, but the rate of bleeding with the higher doses (10 and 20 mg/day) was similar or higher than with enoxaparin/warfarin (Fig E1).

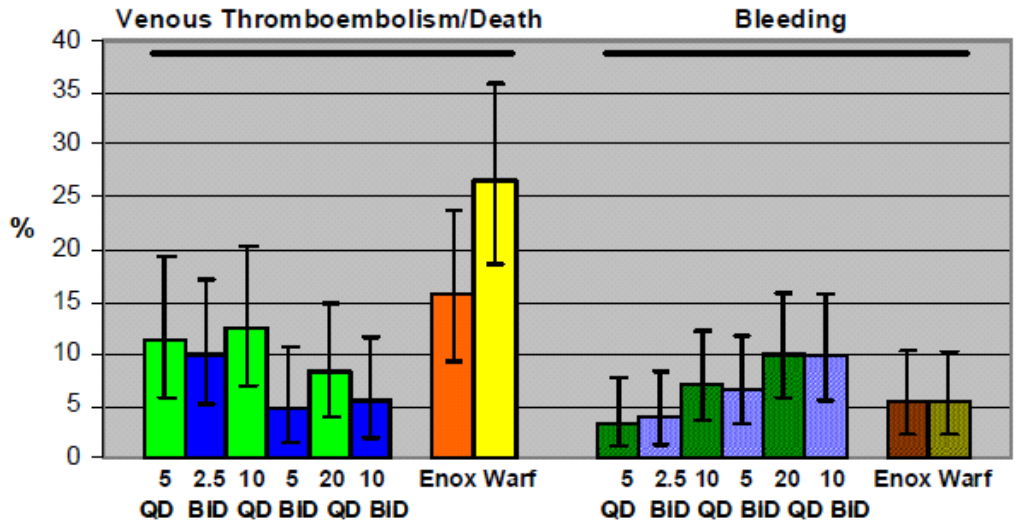


Figure E1: Apixaban Phase 2 VTEp after Knee Replacement (CV185010)

A dose of 2.5 mg BID was selected for the VTEp indication. In AF, where stroke is the primary endpoint, a failure of efficacy would result in substantial morbidity and mortality and is thus a much greater concern. This favoured the selection of 5 mg BID dose as it appeared to have increased efficacy compared to the 2.5 mg BID dose without a substantial increase in bleeding risk.

Modified dose: Results of PK/PD studies indicate that factors such as renal function, age, and body weight individually have limited effect on apixaban's exposure, however, combinations of these factors could result in clinically significant higher exposures. Accordingly, the Phase 3 program implemented a dose modification strategy (2.5 mg BID) in patients who fulfilled any 2 of the following criteria at baseline: Age ≥80 years; body weight ≤60 kg and serum creatinine ≥1.5 mg/dL (133 µmol/L).

2.5.2. Main studies

The two Phase 3 studies were both active-controlled, randomized, multi-national, multi-centre, double-blind, parallel-group studies with independent, blinded adjudication of efficacy and safety endpoints by an external Events Adjudication Committee. The treatment period of each study was to be completed after a pre-specified number of subjects (448 subjects in CV185030 and 226 subjects in CV185048) had a primary efficacy endpoint. Study CV185048 also included an optional Long-Term Open-label Treatment Extension (LTOLE).

Study CV185030 (ARISTOTLE)

Methods

This is a Phase 3 study designed to evaluate the efficacy and safety of apixaban versus warfarin (INR target range 2.0 - 3.0) in subjects with non-valvular AF and at least one additional risk factor for stroke. The comparator warfarin was well chosen since the European Society of Cardiology (ESC) clinical practice guidelines for the management of AF recommend VKA in AF patients with ≥1 stroke risk factor(s) provided there are no contraindications. For a valid comparison between a new anti-coagulant versus VKA, it is important to ensure that patients on VKA spend a relevant time (more than 60% of the time) in therapeutic range of INR 2-3. Challenges in maintaining an adequate INR level in a global trial are acknowledged. Control of INR for warfarin subjects was determined by using central monitoring of INR measurements. Methods described by the MAH appear adequate to maintain

therapeutic VKA levels, though only the results can confirm their adequacy. Rosendaal's method[3] to measure individual TTR (time in therapeutic range) was also employed in the RELY study and is acceptable.

Study Participants

The ARISTOTLE study included subjects with AF who were eligible for warfarin treatment (VKA naïve or experienced subjects). Main inclusion criteria were subjects ≥18 years of age with documented AF or atrial flutter, and presenting with at least 1 additional risk factor for stroke. Risk factors included the following: age ≥ 75 years; prior stroke, transient ischemic attack (TIA) or SE; either symptomatic congestive heart failure within 3 months or left ventricular (LV) dysfunction with an LV ejection fraction (LVEF) ≤40%; diabetes mellitus; hypertension requiring pharmacological treatment. Main exclusion criteria included: clinically significant (moderate or severe) mitral stenosis and increased bleeding risk that was believed to be a contraindication to oral anticoagulation. The inclusion and exclusion criteria used in the study are deemed adequate for AF patients who might benefit from this treatment.

Treatments

The dose of apixaban assigned at randomization (5 mg BID or 2.5 mg BID in special populations) was to be maintained throughout the study, even in case criteria changed during the study. Study dosage of warfarin treatment was based on INR measurements (INR target range 2.0 to 3.0). According to the MAH, a major effort to train, track and assure the quality of the INR control in the study was undertaken. INRs were measured and collected into a central database in a blinded fashion with point–of-care (POC) devices. The protocol specified the collection of INRs on all treated subjects by Day 4 after initiation of study drug, with increased frequency during titration of warfarin (or warfarin/placebo), and monthly after that. The POC devices would deliver true INR readings for VKA patients, but would sham the INR results for those on apixaban. INR control was assessed by the method of Rosendaal and divided into terciles (TTR <2.0, 2.0 - 3.0 and >3.0) and was carried out on the country level. Rosendaal's method provides each subject with an INR measurement every day, either actual or by estimation through linear interpolation.

The study included 3 periods: (1) the screening period of up to 14 days, (2) the treatment period lasted until the earlier of a subject's treatment discontinuation or the attainment of approximately 448 primary efficacy events and (3) the follow-up period lasted until the latter of 30 days after treatment discontinuation or the attainment of 448 primary efficacy events.

Objectives

The primary objective was to determine if apixaban was non-inferior (NI) to warfarin for the combined endpoint of stroke (haemorrhagic, ischemic or of unspecified type) or SE, in subjects with AF and at least one additional risk factor for stroke. The key secondary objectives were to determine if apixaban was superior to warfarin for: the combined endpoint of stroke or SE; major bleeding (International Society on Thrombosis and Hemostasis [ISTH] criteria); and all-cause death.

[3] Rosendaal FR, Cannegieter SC, van der Meer FJ, Briet E A method to determine the optimal intensity of oral anticoagulant therapy. Thromb Haemost. 1993;69:236-9

Outcomes/endpoints

The primary efficacy endpoint was the time from randomisation to first occurrence of confirmed stroke or SE, regardless of whether the subject was receiving treatment at the time of the event during the Intended Treatment Period.

Diagnosis of stroke required non-traumatic, focal neurological deficit lasting at least 24 hours. A retinal ischemic event (embolism, infarction) was considered as a stroke and transient ischemic attack (TIA) was defined as a non-traumatic abrupt onset of focal neurological symptoms lasting less than 24 hours. The study protocol recommended that a cerebral imaging study such as a computed tomography (CT) scan or magnetic resonance imaging (MRI) would be performed for all suspected strokes. Systemic embolism was judged to occur where there was a clinical history consistent with an acute loss of blood flow to a peripheral artery (or arteries), which was supported by evidence of embolism from surgical specimens, autopsy, angiography, or other objective testing.

All suspected efficacy events were adjudicated by an independent, expert panel of physicians experienced in adjudication of these types of clinical study endpoints.

The endpoints/outcome of the study was adequately chosen, discussed and agreed on during the scientific advise given by the CHMP. The chosen primary endpoint of stroke/SE is also in line with recently assessed clinical trials. Since imaging studies were not consistently performed to verify stroke or sub-classify ischemic stroke, the results might be influenced by the judgment of the study investigator. However, considering the double-blind design, the influence on study outcome would be limited.

Randomisation and blinding (masking)

Eligible subjects were randomized in a 1:1 ratio to either apixaban or warfarin. All subjects received matching placebo (double-dummy design).

Statistical methods and sample size

Populations for Statistical Analyses.

Randomized Population: includes all subjects who signed informed consent and were randomized. In this population, subjects are categorized to the group to which they were assigned by the automated voice response system (As Randomized).

Evaluable Population: subset of Randomized Population, excluding full (if deviation occurred prior to randomization) or partial data (if deviation occurred after randomization) from subjects with protocol deviations expected to affect the primary efficacy endpoint. If a deviation occurred after randomization, then the data up to the time of the deviation was included in the Evaluable data set. In this population subjects are categorized according to the As Randomized group. This population is used for sensitivity analyses associated with NI assessments in the CV185030 study.

Choice of NI margin. The following two analyses were performed; NI of apixaban relative to warfarin was demonstrated:

1. If the upper bound of the two-sided 95% confidence interval (CI) for risk reduction (RR) was less than 1.38.
2. If the upper bound of the two-sided 99% CI for RR was less than 1.44.

The 4 key objectives of the study were tested following a pre-specified hierarchical testing strategy at a significance level adjusted for the formal interim test for superiority. The adjustment was small and

did not impact the results. Overall type I error was preserved at ≤5%. NI for the primary efficacy endpoint was assessed first (at NI margin=1.38 and one-sided α= 0.025; and at NI margin=1.44 and one-sided α= 0.005).

The following tests in the sequence were performed at the one-sided α= 0.025:
• If NI for the primary efficacy endpoint (using a NI margin of 1.38) was demonstrated, then superiority for the primary efficacy endpoint was tested.
• If superiority for the primary efficacy endpoint was demonstrated, then superiority for ISTH major bleeding was tested.
• If superiority for major bleeding was demonstrated, then superiority for all-cause death was tested.

The study size was calculated to meet the NI margin of 1.44. With 448 subjects with confirmed strokes or SE, the study would have at least 90% power. Based on a sample size of 18,000 subjects allocated in a 1:1 ratio to the apixaban or warfarin group, assuming a primary efficacy endpoint rate of 1.20 per hundred subject-years, an average follow-up of ~2.1 years was estimated to be required to accrue the target number of primary efficacy events. These calculations assumed an incidence of 1% loss to follow-up.

Primary efficacy analysis: An intention-to-treat analysis was performed on the Randomized Population based on adjudicated primary efficacy endpoint events occurring during the Intended Treatment Period (starts on day of randomisation and ends at the efficacy cut-off date: 448 had a primary efficacy endpoint.).

Per-protocol analyses were sensitivity analyses used for NI assessments and included events occurring from first dose through x days after last dose of blinded study drug for the Evaluable Population (x=2, 7, or 30 days in each of the sensitivity assessments).

In the scientific advise (EMEA/CHMP/SAWP/411449/2005) the non-inferiority margin of 1.44 based on the relative risk of apixaban compared to warfarin was discussed and considered appropriately justified.

The rationale of the sample size calculations is plausible. The statistical methods used are acceptable. Superiority of apixaban was tested following a pre-specified hierarchical testing strategy, after NI for apixaban (primary outcome) was shown. The sequence of the tests used in the study is acceptable.

In general the design of ARISTOTLE study was considered by the CHMP as adequate and in line with recently conducted studies with dabigatran and rivaroxaban supporting the same indication, i.e. RELY and ROCKET-AF studies, respectively.

Results

Participant flow

A total of 20,998 subjects were enrolled in study CV185030. Of these subjects, 18,201 were randomised to receive study treatment. Around 25% of the patients discontinued the study, which is in line with the experience in similar studies. Main reasons for discontinuation were subject request to discontinue treatment (around 10 % in each treatment group), adverse events (7.4% and 8.1%, respectively) and deaths (3.6% and 3.8%, respectively). Stroke and SE are both listed as reasons for discontinuation which can lead to misinterpretation of the results, as they are primary endpoints. The incidence of SE (0.2% and < 0.1%, respectively) and MI (0.3% and 0.2%, respectively) leading to study discontinuation in the apixaban group are slightly higher than the VKA group, which is not in line with the efficacy results shown below. This discrepancy occurred as one calculation was based on the investigator's assessment, the other was based on the blinded adjudication by an independent

committee. When the same events were assessed by the latter committee, the results of both apixaban and warfarin were comparable.

Recruitment

The study was conducted globally across 40 countries and 1053 sites and included subjects from EU, NA, Asia/Pacific and Latin America (table E2). Subject's disposition was comparable between the treatment groups. About 40% of the patients were classified as in Europe. It is noted that Russia (~10%), Israel (2%) and South Africa (0.5%) were also included under Europe. Actual representation from the EU region was 2032 and 2026 patients randomized to apixaban and VKA groups, respectively (~22%). This latter population allows a better comparison considering the expected difference in INR control per region.

Table E2 Summary of Enrolment by Region - Randomized Subjects- CV185030

	CV185030		
	Apixaban (N = 9120)	Warfarin (N = 9081)	Total (N = 18201)
Europe	3672 (40.3)	3671 (40.4)	7343 (40.3)
North America	2249 (24.7)	2225 (24.5)	4474 (24.6)
Latin America	1743 (19.1)	1725 (19.0)	3468 (19.1)
Asia/Pacific	1456 (16.0)	1460 (16.1)	2916 (16.0)

"Europe" included: Russia, Israel and South Africa

Baseline data

The treatment groups were well balanced for the baseline disease characteristics, including risk factors, with no clinically relevant differences noted between the apixaban and warfarin groups (Table E3). The study population adequately reflects the target population for the intended indication. The mean age was 69.1 years, with adequate representation of patients ≥ 75 years. Mean $CHADS_2$ risk score was 2.1 in each treatment group; the majority of subjects (66.9%) in both treatment groups had ≥2 risk factors at baseline. Treated hypertension was the most common risk factor (87.4%) followed by CHF (35.4%), and age ≥75 years (31.2%). Overall, 19.4% of subjects had a prior stroke, TIA, or SE. Although the studies included subjects with AF and at least one additional risk factor for stroke, a small percentage (n=12) of subjects in both treatment groups had a $CHADS_2$ score of 0. The MAH explained that the CHADS2 score criteria are more restrictive than the study inclusion criteria based on risk factors, which explains inclusion patients with CHADS2 score=0. These patients were considered protocol deviations. Comparing participants in ARISTOTLE to those of recently published studies in the same indication shows that ARTISTOLE and RELY (dabigatran) recruited patients with comparable $CHADS_2$ scores (around 2). In ROCKET-AF (rivaroxaban) the mean $CHADS_2$ score was higher (3.47), making further comparisons among these agents difficult. Co-administered medications reflect the associated co-morbidities (anti-arrhythmics, anti-hypertensions and anti-platelets). ASA was co-administered in around 30% of the patients allowing adequate conclusions on the safety of this combination. Both VKA naïve and experienced patients are properly presented in the study (~42% and ~57%, respectively).

Table E3 Baseline characteristic of the randomized subjects in CV185030

	Apixaban N = 9120	Warfarin N = 9081	Total N = 18201
AGE (YRS)			
N	9120	9081	18201
MEAN	69.1	69.0	69.1
MEDIAN	70.0	70.0	70.0
MIN , MAX	21 , 95	19 , 97	19 , 97
Q1 , Q3	63.0 , 76.0	63.0 , 76.0	63.0 , 76.0
STANDARD DEVIATION	9.61	9.74	9.68
AGE CATEGORY (%)			
<65	2731 (29.9)	2740 (30.2)	5471 (30.1)
65-<75	3539 (38.8)	3513 (38.7)	7052 (38.7)
>=75	2850 (31.3)	2828 (31.1)	5678 (31.2)
NOT REPORTED	0	0	0
GENDER (%)			
MALE	5886 (64.5)	5899 (65.0)	11785 (64.7)
FEMALE	3234 (35.5)	3182 (35.0)	6416 (35.3)
NOT REPORTED	0	0	0
FEMALE AGE CATEGORY (%)			
<=50	81 (0.9)	88 (1.0)	169 (0.9)
>50	3153 (34.6)	3094 (34.1)	6247 (34.3)
NOT APPLICABLE(MALE)	5886 (64.5)	5899 (65.0)	11785 (64.7)
NOT REPORTED	0	0	0

	Apixaban N=9120	Warfarin N=9081	Total N=18201
Level of Renal Impairment (CrCL)			
SEVERE (<=30 ML/MIN) (%)	137 (1.5)	133 (1.5)	270 (1.5)
MODERATE (>30 - <=50 ML/MIN) (%)	1365 (15.0)	1382 (15.2)	2747 (15.1)
MILD (>50 - <=80 ML/MIN) (%)	3817 (41.9)	3770 (41.5)	7587 (41.7)
NORMAL (> 80 ML/MIN) (%)	3761 (41.2)	3757 (41.4)	7518 (41.3)
NOT REPORTED (%)	40 (0.4)	39 (0.4)	79 (0.4)
APIXABAN OR MATCHING PLACEBO DOSE AT RANDOMIZATION (%)			
2.5 MG BID	428 (4.7)	403 (4.4)	831 (4.6)
5.0 MG BID	8692 (95.3)	8678 (95.6)	17370 (95.4)
TYPE OF RISK FACTOR AT ENROLLMENT (%)			
AGE >= 75 YEARS	2850 (31.3)	2828 (31.1)	5678 (31.2)
PRIOR STROKE, TIA, OR SYSTEMIC EMBOLISM	1748 (19.2)	1790 (19.7)	3538 (19.4)
PRIOR STROKE	1045 (11.5)	1082 (11.9)	2127 (11.7)
PRIOR TIA	603 (6.6)	654 (7.2)	1257 (6.9)
PRIOR SYSTEMIC EMBOLISM	142 (1.6)	129 (1.4)	271 (1.5)
SYMPTOMATIC CHF WITHIN 3 MONTHS OR LVEF <= 40%	3235 (35.5)	3216 (35.4)	6451 (35.4)
SYMPTOMATIC CHF	2784 (30.5)	2757 (30.4)	5541 (30.4)
LVEF <=40%	1324 (14.5)	1301 (14.3)	2625 (14.4)
DIABETES MELLITUS	2284 (25.0)	2263 (24.9)	4547 (25.0)
HYPERTENSION WITH PHARMACOLOGICAL TREATMENT	7962 (87.3)	7954 (87.6)	15916 (87.4)
NUMBER OF RISK FACTORS AT ENROLLMENT (%)			
NOT REPORTED	0	0	0
<= 1	3025 (33.2)	3000 (33.0)	6025 (33.1)
>= 2	6095 (66.8)	6081 (67.0)	12176 (66.9)
CHADS-2 SCORE AT ENROLLMENT (%)			
NOT REPORTED	0	0	0
<= 1	3100 (34.0)	3083 (34.0)	6183 (34.0)
2	3262 (35.8)	3254 (35.8)	6516 (35.8)
>= 3	2758 (30.2)	2744 (30.2)	5502 (30.2)
MEAN (SD)	2.1 (1.10)	2.1 (1.11)	2.1 (1.10)
MIN, MAX	(0.0, 6.0)	(0.0, 6.0)	(0.0, 6.0)

Source: Source: Tables S.3.2C1 and S.3.3A1 of CV185030 CSR

Conduct of the study

Importantly, the level of INR control is highlighted, with several analyses submitted showing that generally the INR was controlled within the therapeutic range (2-3) for a median of 60%; and 66% after exclusion of the first 7 days and periods of VKA interruptions, in line with results of other recent studies (table E4).

Table E4 Median TTR for Recent Stroke Prevention in AF Studies

Study	TTR (median)
ACTIVE-W	65%
RE-LY	67.3%
ROCKET-AF	57.8%
CV185030	66.0%

This TTR allows a fair comparison versus apixaban. As expected VKA naïve patients had slightly lower levels of TTR (52.15%) vs 60.7% in the VKA experienced.

Numbers analysed

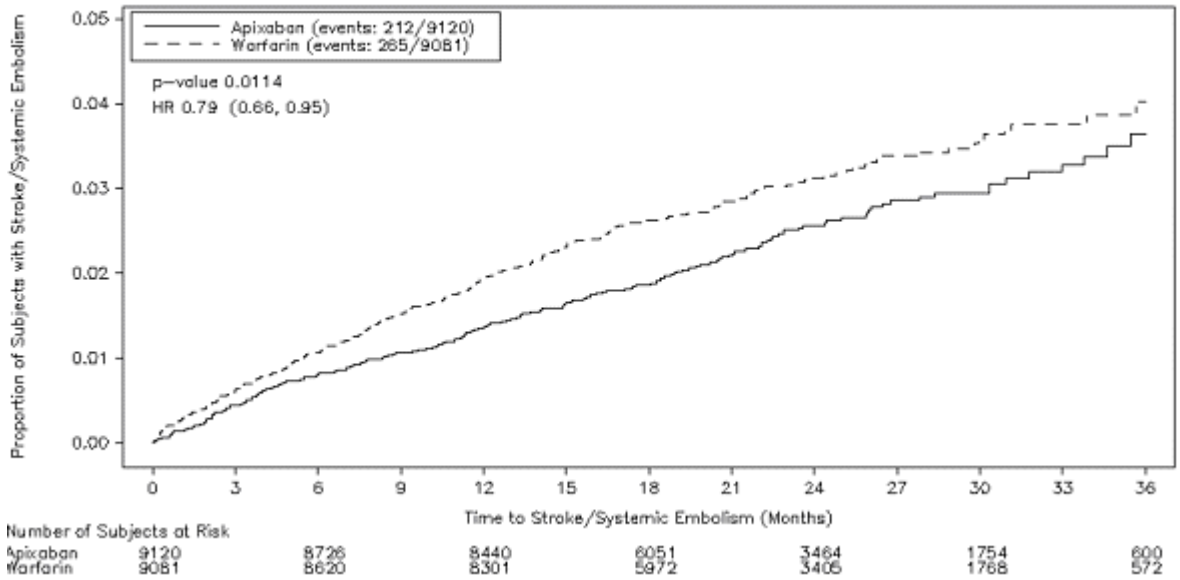
Table E5 Analysis Population Summary

	Apixaban	Warfarin	Total
RANDOMIZED SUBJECTS, N	9120	9081	18201
TREATED SUBJECTS, N	9088	9052	18140
EVALUABLE SUBJECTS (%)	8518 (93.4)	8475 (93.3)	16993 (93.4)

Outcomes and estimation

The non-inferiority NI of apixaban versus warfarin for the primary efficacy endpoint was demonstrated, followed by demonstration of superiority. The Kaplan-Meier Plot for stroke/SE during the Intended Treatment Period is presented in Figure E2. The NI assessment was also performed based on PP analyses. Three separate sets of PP analyses were performed including events from first dose through 2, 7, and 30 days after the last dose. The observed HR and p-values for NI and superiority tests were lower than those for intent-to-treat (ITT) analyses supporting the conclusion of superiority of apixaban relative to warfarin for the primary efficacy endpoint.

Figure E2 Kaplan-Meier Plot for Stroke/SE during the intended treatment period – randomised subjects CV185030



This superiority is mainly driven by the lower incidence of hemorrhagic stroke in the apixaban group (0.42%) compared to 0.84% in the VKA group and to a lesser extent ischemic stroke (1.74% vs 1.91% respectively), with comparable effect on SE (0.16% vs 0.18% respectively). The results point that apixaban is probably a safer alternative in terms of bleeding rather than a more effective one (See: Summary of efficacy tables, Table E24 and E25).

Apixaban showed a reduction in all-cause death, a secondary endpoint in the hierarchical testing strategy, results are on the border of statistical significance [HR=0.89; 95%CI= 0.80; 1.00, two-sided p-value=0.0465]. Both cardiovascular deaths [HR=0.89; 95%CI =0.76-1.04] and non-cardiovascular deaths [HR=0.93; 95%CI=0.77-1.13] were just numerically lower in the apixaban group, without showing robust superiority in either subgroup.

Of note, apixaban treatment was associated with a lower incidence of MI (0.53%/yr) compared to VKA (0.61%), HR =0.88 (95% CI:0.66-1.17). These results compare favourably with dabigatran which was associated with a slightly higher incidence of MI compared to VKA (overall rate in RELY: 0.82, 0.81, and 0.64 % / year for dabigatran 110 mg BID and 150 mg BID and VKA respectively).

Since warfarin effectiveness depends heavily on the degree of INR control, TTR of INR therapeutic levels (2-3) was taken into account. Most of presented analyses show a favourable effect of apixaban over VKA using different methods of calculating TTR, however superiority was not consistently shown except with study sites with INR below the median quartile of INR control (TTR individual 65.99%)(HR=0.78; 95% CI: 0.62-0.98) but lost in sites with INR ≥ median INR (HR=0.81; 95% CI: 0.61-1.08). Using TTR, presented by centres[4] TTRc, apixaban shows favourable results, with HR consistently below 1 (0.77-0.81) but no superiority compared to VKA; 95% CI varying from 0.57-1.07 to 0.52-1.26 (table E6). Conclusions are also applicable to all cause death, but importantly, in the highest TTRc quartile (> 72.2%), HR was 1.04 (95%CI: 0.82-1.33). Thus, although the overall results support the superiority of apixaban over VKA, this superiority was not shown in patients well controlled on VKA.

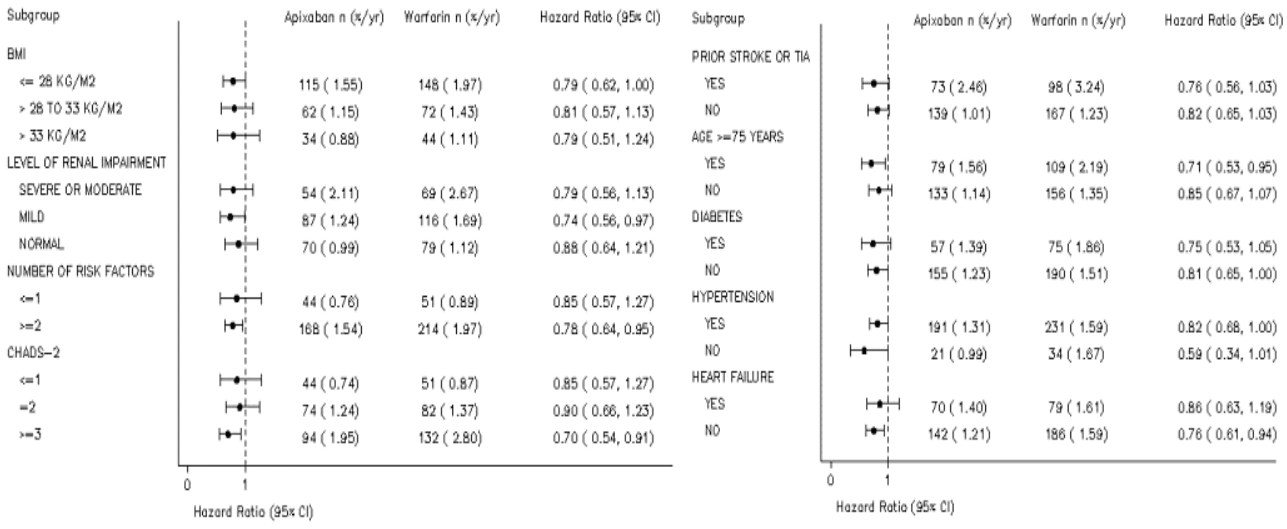
[4] Wallentin L, Yusuf S, Ezekowitz MD, et al. Efficacy and safety of dabigatran compared with warfarin at different levels of international normalised ratio control for stroke prevention in atrial fibrillation: an analysis of the RE-LY trial. Lancet. 2010; 376(9745): 975-83.

Table E6: Comparison of Apixaban and VKA Efficacy Outcome Events (Stroke/SE, All Cause Mortality) by TTRc Quartile

	N		Events		Rate/100 person yrs		HR	95% CI	Adjusted Interaction P-value
Center TTRc	Apixaban	Warfarin	Apixaban	Warfarin	Apixaban	Warfarin			
Stroke/SE									0.2842
< 58.1	2280	2263	71	88	1.78	2.28	0.78	0.57, 1.07	
58.1 -<65.7	2253	2277	53	68	1.28	1.61	0.79	0.55, 1.13	
65.7 -<72.2	2260	2273	51	65	1.21	1.55	0.79	0.54, 1.13	
≥ 72.2	2277	2261	36	44	0.83	1.02	0.81	0.52, 1.26	
All cause death									0.4093
< 58.1	2280	2263	162	195	3.93	4.85	0.81	0.66, 1.00	
58.1 -<65.7	2253	2277	139	173	3.74	4.00	0.93	0.73, 1.16	
65.7 -<72.2	2260	2273	147	174	3.44	4.07	0.84	0.68, 1.05	
≥ 72.2	2277	2261	133	127	3.03	2.91	1.04	0.82, 1.33	

Efficacy results presented in different subgroups were generally consistent with the primary efficacy results for the study (Figure E3). Importantly, for the subgroup of patients receiving the reduced dose of apixaban (2.5 mg BID), event rates favoured apixaban over warfarin (1.43%/yr vs 7.23%/yr, HR=0.19, 95% CI: 0.04, 0.91), suggesting effective exposure in this reduced dose group (Figure E3). In *patients < 65 years*, incidence of stroke/SE was slightly higher in the apixaban group than VKA group resulting in a HR=1.16 (95% CI: 0.77- 1.73), although results of patients above 75 years were in line with the general favourable results. The MAH explored three parameters which could have led to worse results in patients <65 years, mainly: patient's characteristics, VKA control and apixaban exposure in the ARISTOTLE study. Submitted analyses show that none of these parameters could have significantly affected the results. This is further supported by data from the AVERROES study presented below. It can be concluded that the trend for worse efficacy results in patients <65 years is probably a chance finding.

Figure E3 Forest Plot for Stroke/SE during the Intended Treatment Period – Randomised Subjects (CV185030)



Reduced efficacy is shown in patients randomized in the EU: HR for stroke/SE= 0.92; (95% CI = 0.56; 1.52), HR for all cause death= 0.89 (95% CI = 0.68; 1.18). This could probably be attributed to a better INR control (median 68.93%). Patients with severe renal impairment were poorly represented in ARISTOTLE (n=270, apixaban group = 137). Generally lower events rates were reported in the apixaban group compared to the warfarin group; with more favourable results in patients administered the lower dose (n=89) (1.43%/yr vs 7.23%/yr, HR=0.19, 95% CI: 0.04-0.91), than patients administered the full dose (n=48) (HR and upper bound of the associated 95% CI were ≥1; 95% CI was wide (0.43-34.72). Further analysis of the data showed that patients with exclusive severe renal impairment have a more favourable benefit risk profile when administered the reduced dose (see: Clinical Safety section of the CHMP AR).

During the period from the end of Intended Treatment Period up to 30 days after the last dose of study medication, a total of 27 stroke/SE events in the apixaban group versus only 10 events occurred in the warfarin group. A similar observation was seen in the ROCKET-AF (31 cases of stroke/SE in the rivaroxaban group compared to 12 cases warfarin group between day 2 and day 7 after discontinuation of randomized treatment). According to the MAH, this excess number of events in the apixaban group is unlikely to represent a lack of efficacy nor is it a "rebound" phenomenon as most of the events occurred more than 2 weeks after discontinuation of study drug. The MAH believed that the "rebound" phenomenon is more observed in inhibitors of thrombin. Direct FXa inhibitor, such as apixaban or rivaroxaban or an indirect FXa inhibitor, such as fondaparinux, are not expected to impact thrombin or activated protein C levels. Cessation of rivaroxaban following orthopedic surgery was not followed by rebound[5]. It can be agreed that since subjects were still on apixaban treatment in only four cases versus three cases still on warfarin therapy, a direct relation with apixaban was not shown. Of note, the PP sensitivity analysis still showed superiority of apixaban over warfarin in an analysis inclusive of events till 30 days from last study drug intake. Further analyses shows that the highest risk of stroke/SE is seen in patients not used to VKA (either VKA naïve, or on apixaban) switching to VKA. Most of the events in these switchers occurred 2 weeks after the switch. These findings support that this higher incidence events is probably due to the difficulties associated with establishing an adequate INR in VKA naïve patients. The late onset of events precludes a rebound hypercoagulability problem. These conclusions can also explain the slight imbalance of mortality (apixaban=53; VKA=48) following discontinuation of these anticoagulants.

To minimise the risk of stroke/SE when switching from apixaban to VKA, the MAH proposed some SmPC changes in section 4.2. These recommendations were generally acceptable by the CHMP.

Study CV185048 (AVERROES)

To support the indication of administration of apixaban in patients unsuitable for VKA, the MAH submitted the AVERROES study.

[5] Lassen MR, Ageno W, Borris LC, et al. Rivaroxaban vs enoxaparin for thromboprophylaxis after total knee arthroplasty. N Engl J Med. 2008;358:2776-2786.

Methods

Recruitment to AVERROES study was limited to subjects with AF and at least one additional risk factor for stroke, who were not receiving VKA therapy at study entry and included both those subjects who had previously used but discontinued VKA (Demonstrated VKA Unsuitable) and those subjects who had not previously used VKA but were considered unsuitable candidates by the investigator (Expected VKA Unsuitable). This study was initiated after ARISTOTLE, but was terminated earlier due to the shown efficacy (an interim analysis showed clinically relevant efficacy of apixaban over ASA). Subjects who discontinued VKA therapy (demonstrated unsuitable) were patients in whom laboratory monitoring was unsuccessful (e.g., unable to obtain or maintain INR measurements at requested intervals, unable or refused to adhere to dose or INR monitoring instructions); patients who experienced adverse events; and patients who refused further treatment with VKA. Expected VKA unsuitable group included patients who were considered unlikely to comply with dosing or monitoring requirements; patients considered unlikely to adhere to restrictions on alcohol, diet or non-prescription medications, or were unwilling to take VKA and patients in whom the risk of VKA therapy was considered to outweigh the potential benefits for preventing stroke or SE.

The chosen criteria to indicate patient's unsuitability to VKA is quite subjective. It depends on the perception of both the investigator and the patient, and also based on medical as well as social preferences. It can be agreed that in real life such decisions are also not entirely objective. However, in a clinical study and in order to allow proper extrapolation of the results, more objective measures should have been chosen for recruitment, in particular previous discontinuation of VKA due to bleeding. As shown below, this subgroup is very limitedly represented.

Study Participants

The main inclusion criteria were subjects ≥50 years of age, with documented permanent, paroxysmal or persistent AF, presenting with at least one risk factor for stroke, and not currently receiving VKA therapy. Main study exclusion criteria included: AF due to reversible causes, valvular disease requiring surgery and planned AF ablation procedure to be performed within 3 months. The study population adequately reflected the target population for the intended indication.

Treatments

Subjects were randomised in a 1:1 ratio to either apixaban or ASA. Apixaban posology followed the same algorithm used in ARISTOTLE Study. The ASA dose (81, 162, 243, or 324 mg QD) was at the discretion of the investigator. The ASA dose initially assigned to the subject was to be maintained throughout the study unless a change in dose within the range was clinically indicated. Additional open-label ASA was permitted for subjects who had a clear clinical indication for anti-platelet therapy, but was not to exceed 100 mg QD.

The study consisted of a Screening period of 0 to 28 days; followed by the Double-blind Treatment Period lasting until the earlier of a subject's discontinuation of double-blind study drug or the attainment of approximately 226 primary efficacy events. The 30-day Follow-up Period started after the last dose of double-blind study drug for subjects who did not enter the Optional Open-label Treatment Period (LTOLE). Subjects who discontinued study treatment were followed for outcome events until the double-blind phase of the study end date.

The choice of ASA as the active comparator deserves some discussion as it impacts on the interpretation of the results. According to the *ESC clinical practice guideline for the management of AF (2010)*, the combination of ASA and clopidogrel could be used in patients intolerant to VKA, for reasons

other than an increased risk of bleeding. This could apply in particular to patients with a relatively high risk of thrombosis. However, this combination was not approved at the time AVERROES was started. The efficacy of ASA in the updated focused *ESC guideline (2012)* is considered weak, with a potential for harm, since the risk of major bleeding (and ICH) with aspirin is not significantly different to that of OAC, especially in the elderly. However, based on the available guidance at the time of conducting the trials, ASA appeared to be the only available choice for patients intolerant to VKA due to an increased risk of bleeding. The suitability of using ASA as the active comparator could only be determined by the actual representation of each of the different sub-groups, in particular patients who discontinued VKA due to bleeding. This subgroup is also important as it is expected to be the main group to support the claim that patients who had a higher bleeding risk with VKA are being better managed with apixaban. Most of the patients in the ASA group were administered doses of 81 or 162 mg, which is a bit higher than currently advised by the ESC clinical practice guideline (75-100 mg), but no strict recommendations are given.

Objectives

Primary objective was to determine if apixaban is superior to ASA for preventing the composite outcome of stroke or SE in subjects with AF and at least one additional risk factor for stroke who have failed or are unsuitable for VKA therapy. Secondary objectives were to determine, in the same subjects, if apixaban is superior to ASA for prevention of the composite outcome of stroke, SE, MI, or vascular death (major vascular events).

Outcomes/endpoints

The primary efficacy endpoint was the time from randomisation to first occurrence of un-refuted stroke (any type including ischemic, hemorrhagic or of uncertain type) or SE during the Intended Treatment Period.

Statistical methods and sample size

The testing strategy was as follows:

• Superiority of apixaban relative to ASA for stroke/SE (primary efficacy endpoint) was tested first.
• If superiority for stroke/SE was demonstrated, then superiority was tested for major vascular events (stroke/SE/MI/vascular death) at the one-sided α= 0.00003. (The small significance level resulted from meeting the early stopping criterion for the primary endpoint).
• If superiority for major vascular events was demonstrated, then superiority was tested for all-cause death at the one-sided α= 0.00003.

Sample size: Assuming an average 1.6 years follow-up and a stroke rate of 3.3 per hundred subject years in ASA-treated subjects, the study would have at least 90% power to detect a 35% relative risk reduction (RRR) of apixaban versus ASA at the one-sided α = 0.025 if there were 226 subjects with un-refuted strokes or systemic emboli. It was calculated that 5600 subjects need to be randomised and allocated in a 1:1 ratio to the apixaban or ASA group to achieve the desired power. These calculations assumed an incidence of 1% loss to follow up. Event rates and between group assumptions for this study were based on intent-to-treat analyses of previous outcome studies.

The study included 2 planned interim analyses for efficacy:

1. The first analysis was targeted to occur when approximately 50% of the total 226 subjects with primary events un-refuted by adjudication had accrued. In this interim look, the primary endpoint

would be monitored using a modified Haybittle- Peto boundary of 4 standard deviations (two-sided p-value <0.00006). The boundary refers to a treatment difference that is greater than the prescribed number of standard errors and that favours apixaban.
2. The second analysis was targeted to occur when approximately 75% of the total 226 subjects with primary events un-refuted by adjudication had accrued. In this interim look, the primary endpoint would be monitored using a modified Haybittle- Peto of 3 standard deviations (two-sided p-value <0.0026).

Results

Participant flow

A total of 6,421 subjects were enrolled in study CV185048; of these subjects, 5,598 were randomised to receive study treatment. Discontinuation rates were 558 (19.9%) subjects in the apixaban treatment group, versus 649 (23.3%) patients in the ASA treatment group. Importantly, discontinuations due to bleeding are more frequently reported in the apixaban group (n=35, 1.2%) compared to ASA (n=20, 0.7%).

Recruitment

The trial was conducted across 36 countries and 526 sites (Table E15). The countries with the greater proportion of randomized subjects (≥5% of the total) were Russia (12.5%), USA (9.5%), Brazil (7.4%), Mexico (6.2%), and Germany (5.8%).

Table E15 Summary of Enrolment by Region and Country - Randomized Subjects

Region (%)	Apixaban N=2807	ASA N=2791	Total N=5598
NORTH AMERICA	408 (14.5)	396 (14.2)	804 (14.4)
LATIN AMERICA	589 (21.0)	596 (21.4)	1185 (21.2)
EUROPE	1263 (45.0)	1244 (44.6)	2507 (44.8)
ASIA/PACIFIC	547 (19.5)	555 (19.9)	1102 (19.7)

Europe included Turkey, Russia, South Africa and Israel.

The treatment groups were balanced at End of Treatment subject disposition with no clinically relevant differences in these data, except for events related to the primary efficacy endpoint (Table E16).

Table E16 End of Treatment Period Subject Status Summary – Randomised Subjects (CV185048)

	Apixaban	ASA
NUMBER OF RANDOMIZED SUBJECTS, n	2807	2791
NUMBER OF SUBJECTS DISCONTINUED, n (%)	558 (19.9)	649 (23.3)
REASON FOR DISCONTINUATION, n (%)		
DEATH	31 (1.1)	56 (2.0)
ADVERSE EVENT	174 (6.2)	260 (9.3)
STROKE	18 (0.6)	73 (2.6)
SYSTEMIC EMBOLISM	0	12 (0.4)
MYOCARDIAL INFARCTION	10 (0.4)	6 (0.2)
BLEEDING	35 (1.2)	20 (0.7)
OTHER	112 (4.0)	149 (5.3)
SUBJECT REQUEST TO DISCONTINUE STUDY TREATMENT	156 (5.6)	171 (6.1)
SUBJECT WITHDREW CONSENT	92 (3.3)	98 (3.5)
LOST TO FOLLOW-UP	26 (0.9)	29 (1.0)
POOR/NON-COMPLIANCE	17 (0.6)	22 (0.8)
PREGNANCY	0	0
SUBJECT NO LONGER MEETS STUDY CRITERIA	18 (0.6)	18 (0.6)
ADMINISTRATIVE REASON BY SPONSOR	1 (<0.1)	0
OTHER	131 (4.7)	102 (3.7)

Approximately one-third of the subjects in CV185048 (31.6% in the apixaban group and 33.4% in the ASA group) did not enter the optional Open-label Extension (LTOLE) and completed the planned 30-day Follow-up Period. At the time of database lock for the double-blind phase of the study, 40.4% of subjects in the apixaban group and 38.2% in the ASA group had entered the LTOLE (i.e., had received at least one dose of open-label apixaban).

Baseline data

Treatment groups were well balanced for baseline demographic characteristics and physical measurements with no clinically relevant differences noted in these characteristics for randomised subjects (Table E17). The mean age of randomised subjects was 69.9 years; 33.8% of subjects were ≥75 years of age and 35.5% of subjects were ≥65 but <75 years of age. Most subjects were white (78.6%) and male (58.5%). Approximately 84% were >60 kg in weight and approximately 47% had a BMI of >28 kg/m^2.

Table E17 Baseline Characteristics of Randomised Subject (CV185048)

	Apixaban N=2807	ASA N=2791	Total N=5598
AGE (yrs)			
N	2807	2791	5598
MEAN	69.7	70.0	69.9
AGE CATEGORY (%)			
< 65	855 (30.5)	865 (31.0)	1720 (30.7)
>= 65 BUT < 75	1049 (37.4)	938 (33.6)	1987 (35.5)
>= 75	903 (32.2)	988 (35.4)	1891 (33.8)
NOT REPORTED	0	0	0
GENDER (%)			
MALE	1660 (59.1)	1617 (57.9)	3277 (58.5)
FEMALE	1147 (40.9)	1174 (42.1)	2321 (41.5)
NOT REPORTED	0	0	0
ETHNICITY (%)			
HISPANIC / LATINO	557 (19.8)	559 (20.0)	1116 (19.9)
NOT HISPANIC / LATINO	2224 (79.2)	2196 (78.7)	4420 (79.0)
NOT REPORTED	26 (0.9)	36 (1.3)	62 (1.1)

The mean $CHADS_2$ score was 2.0 in each treatment group. Overall, 38.3% of randomised subjects had a $CHADS_2$ score of 1, 35.2% had a score of 2 and 26.5% had a score ≥3. The most common risk factors were hypertension with pharmacological treatment (86.4%).

Conduct of the study

Study CV185048 was stopped early because a planned interim analysis by an independent DMC demonstrated evidence of a clinically important reduction in stroke and SE in subjects in this AF population who had received apixaban in comparison with ASA; in addition to reduction of major vascular events and all cause deaths. These impressive results should be treated with caution considering the above concerns about the choice of ASA as a comparator in the first place.

Numbers analysed

Table E21 Analysis Population Summary

	Apixaban	ASA	Total
RANDOMIZED SUBJECTS, n	2807	2791	5598
TREATED SUBJECTS, n	2798	2780	5578
EVALUABLE SUBJECTS (%)	2714 (96.7)	2695 (96.6)	5409 (96.6)

Outcomes and estimation

Due to the premature termination of the study, the original target number of efficacy events was not achieved prior to ending the Double-blind Treatment Period of Study CV185048.

Primary Efficacy Endpoint. Apixaban was superior to ASA [HR=0.45; (95%CI; 0.32; 0.62); two-sided p-value <0.00001] for the prevention of stroke/SE (see table E22). The majority of the primary outcome events were ischemic or unspecified strokes with 43 (1.53%) events in the apixaban group, versus 95 (3.4%) events in the ASA group [HR = 0.44 (95% CI =0.31, 0.63)]. Apixaban [n=2 (0.07%)] was also associated with lower numbers in SE relative to ASA [n=11 (0.39%)].

Overall, 2237 of 5598 (40%) randomized subjects had previously used VKA (demonstrated VKA unsuitable) and 60% were expected VKA unsuitable. Among prior VKA users, 48.4% had difficulty with INR control and 23.9% experienced bleeding on VKA (4.3% major bleeds) (Table E22). The actual representation of patients who had discontinued VKA due to bleeding was very small (11.9%); the most common reasons provided for discontinuations were physician's decision (20.4%), patient's decision (19.7%), and difficulty to control INR (19.1%).

Table E22 Summary of Prior VKA Experience - Randomized Subjects Who Previously Used VKA

	Apixaban N = 1121	ASA N = 1116	Total N = 2237
DIFFICULTY WITH INR CONTROL (%)			
NO	280 (25.0)	308 (27.6)	588 (26.3)
YES	539 (48.1)	544 (48.7)	1083 (48.4)
UNKNOWN	289 (25.8)	257 (23.0)	546 (24.4)
ESTIMATED % OF INR VALUES OUTSIDE RANGE OF 2.0-3.0 (%)			
<= 25% OF TIME	256 (22.8)	284 (25.4)	540 (24.1)
> 25% - 40% OF TIME	134 (12.0)	127 (11.4)	261 (11.7)
> 40% - 50% OF TIME	102 (9.1)	94 (8.4)	196 (8.8)
> 50% OF TIME	255 (22.7)	270 (24.2)	525 (23.5)
NOT REPORTED	374 (33.4)	341 (30.6)	715 (32.0)
BLEEDING WHILE ON VKA (%)			
NO	839 (74.8)	845 (75.7)	1684 (75.3)
YES	269 (24.0)	265 (23.7)	534 (23.9)
MAJOR BLEED	48 (4.3)	48 (4.3)	96 (4.3)
MINOR BLEED	221 (19.7)	217 (19.4)	438 (19.6)
NOT REPORTED	13 (1.2)	6 (0.5)	19 (0.8)
REASONS FOR DISCONTINUING VKA BEFORE SCREENING (%)			
BLEEDING	127 (11.3)	139 (12.5)	266 (11.9)
DIFFICULT TO CONTROL INR	212 (18.9)	216 (19.4)	428 (19.1)
INDICATION RESOLVED OR TREATED ADEQUATELY	56 (5.0)	48 (4.3)	104 (4.6)
OTHER COMPLICATIONS	30 (2.7)	48 (4.3)	78 (3.5)
PARTICIPANT DECISION	231 (20.6)	209 (18.7)	440 (19.7)
PHYSICIAN DECISION	210 (18.7)	247 (22.1)	457 (20.4)
UNKNOWN	10 (0.9)	13 (1.2)	23 (1.0)

Based on the investigator's judgement, more than half of the randomised patients were considered unsuitable for VKA due to reasons related to bleeding (Table E23). Still this population is not considered to reflect VKA unsuitable patients compared to patients who actually had bleeding or discontinued VKA due to bleeding. Also, the majority of patients who had a history of bleeding on VKA, reported mainly minor bleeds on VKA with only few major bleedings. This specifically questions the ability of AVERROES to address VKA unsuitable patients, and whether apixaban offers to these patients a safer and equally effective alternative to VKA. The question of the comparability of apixaban to VKA in general is addressed in ARISTOTLE.

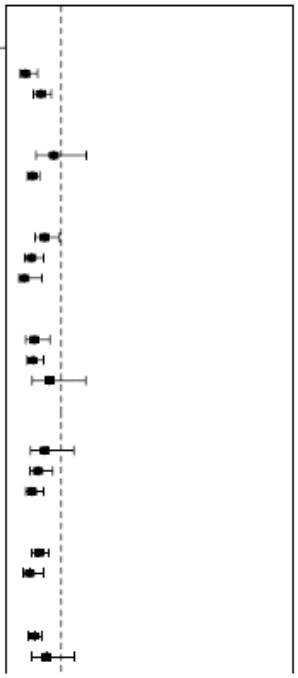
Table E23 Summary of Reasons that Vitamin K Antagonist (VKA) Therapy is Unsuitable - Randomized Subjects

	Apixaban N=2807	ASA N=2791	Total N=5598
NOT CURRENTLY RECEIVING VKA THERAPY AT SCREENING	2807 (100.0)	2791 (100.0)	5598 (100.0)
VKA DEMONSTRATED TO BE UNSUITABLE	1108 (39.5)	1107 (39.7)	2215 (39.6)
VKA EXPECTED TO BE UNSUITABLE	1699 (60.5)	1684 (60.3)	3383 (60.4)
NOT REPORTED	0	0	0
REASONS VKA IS UNSUITABLE (PRIOR OR NO PRIOR USE)			
UNABLE/UNLIKELY TO OBTAIN INRS AT REQUESTED INTERVALS	1196 (42.6)	1191 (42.7)	2387 (42.6)
DIFFICULTY/EXPECTED DIFFICULTY IN CONTACTING PARTICIPANT IN CASE OF URGENT DOSE CHANGE	322 (11.5)	331 (11.9)	653 (11.7)
PARTICIPANT CANNOT BE RELIED ON TO ADHERE TO VKA MEDICATION INSTRUCTIONS	437 (15.6)	405 (14.5)	842 (15.0)
NEED FOR MEDICATIONS WHICH MAY ALTER THE ANTICOAGULANT ACTIVITY OF VKA	50 (1.8)	53 (1.9)	103 (1.8)
NEED FOR MEDICATIONS WHOSE METABOLISM MAY BE AFFECTED BY VKA	35 (1.2)	46 (1.6)	81 (1.4)
UNABLE/UNLIKELY TO ADHERE TO VKA-RELATED RESTRICTIONS	134 (4.8)	141 (5.1)	275 (4.9)
HEPATIC DISEASE	13 (0.5)	9 (0.3)	22 (0.4)
MILD COGNITIVE IMPAIRMENT	85 (3.0)	86 (3.1)	171 (3.1)
HEART FAILURE/CARDIOMYOPATHY	179 (6.4)	188 (6.7)	367 (6.6)
OTHER FACTORS WHICH MAY BE ASSOCIATED WITH INCREASED RISK OF VKA USE	96 (3.4)	123 (4.4)	219 (3.9)
CHADS-2 SCORE = 1 AND PHYSICIAN DOES NOT RECOMMEND VKA	590 (21.0)	605 (21.7)	1195 (21.3)
OTHER CHARACTERISTICS WHICH INDICATE THAT STROKE RISK IS TOO LOW TO WARRANT TREATMENT WITH VKA	55 (2.0)	40 (1.4)	95 (1.7)
PARTICIPANT REFUSES TREATMENT WITH VKA	1053 (37.5)	1039 (37.2)	2092 (37.4)
OTHER	184 (6.6)	189 (6.8)	373 (6.7)
REASONS VKA IS UNSUITABLE (PRIOR USE)			
UNABLE TO MAINTAIN INR IN THERAPEUTIC RANGE	465 (16.6)	468 (16.8)	933 (16.7)
AES RELATED TO VKA THERAPY	86 (3.1)	94 (3.4)	180 (3.2)
SIGNFICIANT BLEEDING WHILE ON COUMADIN	92 (3.3)	82 (2.9)	174 (3.1)
INR < 3.0	41 (1.5)	45 (1.6)	86 (1.5)
INR >= 3.0	40 (1.4)	34 (1.2)	74 (1.3)
VKA THERAPY UNSUITABLE STATUS			
SUBJECT REFUSED TREATMENT WITH VKA (ONLY REASON)	421 (15.0)	394 (14.1)	815 (14.6)
CHADS-2 SCORE = 1 AND PHYSICIAN DOES NOT RECOMMEND VKA (ONLY REASON)	294 (10.5)	318 (11.4)	612 (10.9)
ALL OTHER REASONS	2091 (74.5)	2079 (74.5)	4170 (74.5)
NOT REPORTED	1 (<0.1)	0	1 (<0.1)

Overall results within each subgroup were consistent with the primary efficacy endpoint. Importantly, results of patients with demonstrated VKA intolerance (apixaban: 1.73% vs. ASA: 4.2%; HR=0.33; 95% CI: 0.19-0.56) were comparable to those expected to be intolerant (apixaban: 1.79% vs. ASA: 3.25%; HR=0.55; 95% CI: 0.36-0.84) (Figure E4). The subgroup of patients with CHADS2 =1 and physician did not recommend VKA was the only subgroup with conflicting results (HR= 2.18; 95% CI; 0.040- 11.91).

Figure E4 Forest Plot for Stroke or SE during the Intended Treatment Period – Randomised Subjects (Study CV185048)

Subgroup	Apixaban n (%/yr)	ASA n (%/yr)	Hazard Ratio (95% CI)
Ethnicity			
Hispanic/latino	6 (1.02)	30 (5.21)	0.20(0.08,0.47)
Not hispanic/latino	45 (1.78)	82 (3.29)	0.54(0.38,0.78)
Weight			
Weight <= 60 kg	18 (3.88)	20 (4.61)	0.84(0.44,1.58)
Weight > 60 kg	33 (1.23)	93 (3.48)	0.36(0.24,0.53)
BMI			
BMI <= 28 kg/m2	34 (2.20)	56 (3.49)	0.63(0.41,0.97)
BMI > 28 to 33 kg/m2	14 (1.42)	40 (4.30)	0.33(0.18,0.61)
BMI > 33 kg/m2	3 (0.50)	17 (2.99)	0.17(0.05,0.57)
Level of Renal Impairment			
Severe/Moderate	13 (2.25)	32 (5.61)	0.40(0.21,0.76)
Mild	22 (1.83)	58 (4.95)	0.37(0.23,0.61)
Normal	12 (1.09)	16 (1.48)	0.74(0.35,1.57)
CHADS2 Score			
<=1	12 (1.00)	19 (1.58)	0.63(0.31,1.30)
2	23 (1.95)	43 (4.04)	0.49(0.29,0.81)
>=3	16 (2.09)	51 (6.04)	0.35(0.20,0.61)
Prior Stroke or TIA			
No	41 (1.50)	80 (2.95)	0.51(0.35,0.74)
Yes	10 (2.45)	33 (8.29)	0.29(0.14,0.60)
Diabetes Mellitus			
No	37 (1.44)	91 (3.66)	0.40(0.27,0.58)
Yes	14 (2.40)	22 (3.54)	0.67(0.34,1.31)



Summary of main studies

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

Table E24 Summary of Efficacy for trial ARISTOTLE (CV185030)

Title: A Phase 3, Active (Warfarin)-Controlled, Randomized, Double-blind, Parallel Arm Study to Evaluate Efficacy and Safety of Apixaban in Preventing Stroke and Systemic Embolism (SE) in Subjects with Nonvavular Atrial Fibrillation (AF)			
Study identifier	Study code: CV185030		
Design	Design: randomized, double-blind, multi-national, double-dummy, parallel-arm study		
	Duration of main phase:		Double-blind Treatment Period lasting until the earlier of a subject's discontinuation of double-blind study drug or the attainment of the target number of primary efficacy events
	Follow-up phase:		30-day Follow-up Period starting after the latter of 30 days after treatment discontinuation or the attainment of 448 primary efficacy events.
Hypothesis	Apixaban is non-inferior to warfarin for the primary efficacy endpoint.		
Treatments groups	Apixaban		Apixaban (or matching apixaban-placebo) 5.0 mg BID or 2.5 mg BID for subjects deemed to be at increased risk of bleeding. Subjects randomized to the 2.5 mg BID dose of apixaban (or matching placebo) continued on this dose throughout the study. Scheduled study visits occurred quarterly during the treatment period (Months 3, 6, 9, 15, 18, 21, 27, 30, 33, 39, 42, 45, 51, 54, 57) until completion of the double-blind phase of the study.
	Warfarin		Warfarin sodium 2 mg titrated to INR 2.0-3.0. INR testing frequency occurred at least every month during the treatment period, more frequently during titration and, if clinically indicated.
Endpoints and definitions	Primary endpoint	Primary endpoint	Time to first occurrence of confirmed stroke (ischemic, hemorrhagic, or of unspecified type) or SE, during the Intended Treatment Period
	Secondary endpoint	Key Secondary endpoint	Time to first occurrence of all-cause death during the Intended Treatment Period
	Secondary endpoint	Other Secondary endpoint	Time to first occurrence of the individual efficacy endpoints, including the components of the primary efficacy endpoint (ischemic stroke, stroke of unspecified type, hemorrhagic stroke, SE) and MI, during the Intended Treatment Period.
Database lock	10-Jun-2011		

Results and Analysis				
Analysis description	**Primary Analysis**			
Analysis population and time point description	This analysis was performed on the Randomized Population based on adjudicated primary efficacy endpoint events occurring during the Intended Treatment Period.			
Descriptive statistics	Treatment group	Apixaban	Warfarin	
	Number of subjects	9120	9081	
	Primary endpoint (rate)	1.27	1.60	
Effect estimate per comparison	Primary endpoint	Comparison groups	Apixaban vs. Warfarin	
		Hazard Ratio	0.79	
		95% CI	(0.66, 0.95)	
		P-value*	<0.0001	
		P-value**	<0.0001	
		P-value***	0.0114	
Notes	* denotes 1-sided p-value for NI test (NI margin = 1.38)			
	** denotes 1-sided p-value for NI test (NI margin = 1.44)			
	*** denotes 2-sided p-value for superiority test			
Analysis description	**Secondary analysis - All-cause Death**			
Analysis population and time point description	All analyses of secondary efficacy endpoints were performed on the Randomized Population.			
Descriptive statistics	Treatment group	Apixaban	Warfarin	
	Number of subjects	9120	9081	
	All-cause death (rate)	3.52	3.94	
Effect estimate per comparison	All-cause death	Comparison groups	Apixaban vs. Warfarin	
		Hazard Ratio	0.89	
		95% CI	(0.80, 1.0)	
		P-value	0.0465	
Analysis description	**Ischemic or Unspecified Stroke**			
Descriptive statistics	Treatment group	Apixaban	Warfarin	
	Number of subjects	9120	9081	
	Ischemic or Unspecified Stroke (rate)	0.97	1.05	

Effect estimate per comparison	Ischemic or Unspecified Stroke	Comparison groups	Apixaban vs. Warfarin
		Hazard Ratio	0.92
		95% CI	(0.74, 1.13)
		P-value	0.4220
Analysis description	**Hemorrhagic Stroke**		
Descriptive statistics	Treatment group	Apixaban	Warfarin
	Number of subjects	9120	9081
	Hemorrhagic Stroke (rate)	0.24	0.47
Effect estimate per comparison	Hemorrhagic Stroke	Comparison groups	Apixaban vs. Warfarin
		Hazard Ratio	0.51
		95% CI	(0.35, 0.75)
		P-value	0.0006
Analysis description	**Systemic Embolism**		
Descriptive statistics	Treatment group	Apixaban	Warfarin
	Number of subjects	9120	9081
	Systemic Embolism (rate)	0.09	0.10
Effect estimate per comparison	Systemic Embolism	Comparison groups	Apixaban vs. Warfarin
		Hazard Ratio	0.87
		95% CI	(0.44, 1.75)
		P-value	0.7020
Analysis description	**MI**		
Descriptive statistics	Treatment group	Apixaban	Warfarin
	Number of subjects	9120	9081
	MI (rate)	0.53	0.61
Effect estimate per comparison	MI	Comparison groups	Apixaban vs. Warfarin
		Hazard Ratio	0.88
		95% CI	(0.66, 1.17)
		P-value	0.3720

Table E25 Summary of Efficacy for trial AVERROES (CV185048)

Title: Apixaban Versus Acetylsalicylic Acid (ASA) to Prevent Stroke in Atrial Fibrillation Patients Who Have Failed or Are Unsuitable for Vitamin K Antagonist Treatment: A Randomized Double-Blind Trial			
Study identifier	Study code: CV185048		
Design	Design: randomized, multi-national, multi-center, double-blind, double-dummy, parallel-group		
	Duration of main phase: Follow-up phase: Duration of Extension phase:		Double-blind Treatment Period lasting until the earlier of a subject's discontinuation of double-blind study drug or the attainment of the target number of primary efficacy events 30-day Follow-up Period starting after the last dose of double-blind study drug for subjects who did not enter the Long-term open-label extension (LTOLE) Optional LTOLE (all eligible subjects receive open-label apixaban) intended to start if the study continued to its protocol-described, event-driven conclusion or if the study was stopped early due to the superior efficacy of apixaban.
Hypothesis	Apixaban is superior to ASA for the primary efficacy endpoint		
Treatments groups	Apixaban		Apixaban (or matching apixaban-placebo) 5.0 mg BID or 2.5 mg BID for subjects deemed to be at increased risk of bleeding. Subjects randomized to the 2.5 mg BID dose of apixaban (or matching placebo) continued on this dose throughout the study. Scheduled study visits occurred at Month 1, Month 3 and each 3 months thereafter until completion of the double-blind phase of the study.
	ASA		ASA (or matching ASA-placebo) was dosed QD (81, 162, 243, or 324 mg at the discretion of the investigator).
Endpoints and definitions	Primary endpoint	Primary endpoint	Time from randomization to first occurrence of unrefuted stroke (any type including ischemic, hemorrhagic, or of uncertain type) or SE during the Intended Treatment Period
	Secondary endpoint	Key Secondary endpoint	Time from randomization to first occurrence of unrefuted stroke (any type including ischemic, hemorrhagic, or of uncertain type), SE, MI, or vascular death during the Intended Treatment Period (Major vascular events)
	Other endpoints	Other Efficacy Endpoints	Time to first occurrence of the individual efficacy endpoints, including the components of the primary efficacy endpoint (ischemic stroke, stroke of unspecified type, hemorrhagic stroke, SE) and MI, during the Intended Treatment Period.
Database lock	08-Dec-2010		

Results and Analysis				
Analysis description	**Primary Analysis**			
Analysis population and time point description	Primary efficacy population consisted of all randomized subjects based on unrefuted primary efficacy endpoint events occurring during the Intended Treatment Period.			
Descriptive statistics	Treatment group	Apixaban	ASA	
	Number of subjects	2807	2791	
	Primary endpoint (rate)	1.62	3.63	
Effect estimate per comparison	Primary endpoint	Comparison groups	Apixaban vs. ASA	
		Hazard Ratio	0.45	
		95% CI	(0.32, 0.62)	
		P-value*	<0.00001	
Notes	* denotes two-sided p-value for superiority			
Analysis description	**Major Vascular Events**			
Analysis population and time point description	The key secondary efficacy population consisted of all randomized subjects based on unrefuted primary efficacy endpoint events occurring during the Intended Treatment Period.			
Descriptive statistics	Treatment group	Apixaban	ASA	
	Number of subjects	2807	2791	
	Major VTE (rate)	4.21	6.35	
Effect estimate per comparison	Major Vascular Events	Comparison groups	Apixaban vs. ASA	
		Hazard Ratio	0.66	
		95% CI	(0.53, 0.83)	
		P-value	0.00026	
Analysis description	**All-cause Death**			
Analysis population and time point description	The key secondary efficacy population consisted of all randomized subjects based on unrefuted primary efficacy endpoint events occurring during the Intended Treatment Period.			
Descriptive statistics	Treatment group	Apixaban	ASA	
	Number of subjects	2807	2791	
	All-cause death (rate)	3.51	4.42	

Effect estimate per comparison	All-cause death	Comparison groups	Apixaban vs. ASA
		Hazard Ratio	0.79
		95% CI	(0.62, 1.02)
		P-value	0.06782
Analysis description	**Ischemic or Unspecified Stroke**		
Analysis population and time point description	The other secondary efficacy population consisted of all randomized subjects based on unrefuted primary efficacy endpoint events occurring during the Intended Treatment Period.		
Descriptive statistics	Treatment group	Apixaban	ASA
	Number of subjects	2807	2791
	Ischemic or Unspecified Stroke (rate)	1.37	3.11
Effect estimate per comparison	Ischemic or Unspecified Stroke	Comparison groups	Apixaban vs. ASA
		Hazard Ratio	0.44
		95% CI	(0.31, 0.63)
		P-value	<0.00001
Analysis description	**Hemorrhagic Stroke**		
Analysis population and time point description	The other secondary efficacy population consisted of all randomized subjects based on unrefuted primary efficacy endpoint events occurring during the Intended Treatment Period.		
Descriptive statistics	Treatment group	Apixaban	ASA
	Number of subjects	2807	2791
	Ischemic or Hemorrhagic Stroke (rate)	0.19	0.28
Effect estimate per comparison	Ischemic or Hemorrhagic Stroke	Comparison groups	Apixaban vs. ASA
		Hazard Ratio	0.67
		95% CI	(0.24, 1.88)
		P-value	0.44707
Analysis description	**Systemic Embolism**		
Analysis population and time point description	The other secondary efficacy population consisted of all randomized subjects based on unrefuted primary efficacy endpoint events occurring during the Intended Treatment Period.		
Descriptive statistics	Treatment group	Apixaban	ASA
	Number of subjects	2807	2791
	Systemic Embolism (rate)	0.06	0.41
Effect estimate per comparison	Systemic Embolism	Comparison groups	Apixaban vs. ASA
		Hazard Ratio	0.15
		95% CI	(0.03, 0.68)
		P-value	0.01390

Analysis description	MI		
Analysis population and time point description	The other secondary efficacy population consisted of all randomized subjects based on unrefuted primary efficacy endpoint events occurring during the Intended Treatment Period.		
Descriptive statistics	Treatment group	Apixaban	ASA
	Number of subjects	2807	2791
	MI (rate)	0.76	0.89
Effect estimate per comparison	MI	Comparison groups	Apixaban vs. ASA
		Hazard Ratio	0.86
		95% CI	(0.50, 1.48)
		P-value	0.58618

Supportive study

Study CV185067 was presented in clinical safety section.

2.5.3. Discussion on clinical efficacy

In the ARISTOTLE study a total of 18,201 patients were randomized to double-blind treatment with apixaban 5 mg twice daily (or 2.5 mg twice daily in selected patients [4.7%]) or warfarin (target INR range 2.0-3.0), patients were exposed to study drug for a mean of 20 months. The mean age was 69.1 years, the mean $CHADS_2$ score was 2.1 and 18.9 % of patients had prior stroke or TIA. In the study, apixaban achieved statistically significant superiority in the primary endpoint of prevention of stroke (haemorrhagic or ischaemic) and systemic embolism compared with warfarin. For patients randomized to warfarin, the median percentage of time in therapeutic range (TTR) (INR 2-3) was 66%. Apixaban showed a reduction of stroke and systemic embolism compared to warfarin across the different levels of center TTR; within the highest quartile of TTR according to center, the hazard ratio for apixaban vs warfarin was 0.73 (95% CI, 0.38, 1.40). Key secondary endpoints of major bleeding and all cause death were tested in a pre-specified hierarchical testing strategy to control the overall type 1 error in the trial. Statistically significant superiority was also achieved in the key secondary endpoints of both major bleeding and all-cause death. With improving monitoring of INR the observed benefits of apixaban compared to warfarin regarding all cause death diminished. The efficacy results for prespecified subgroups, including $CHADS_2$ score, age, body weight, gender, status of renal function, prior stroke or TIA and diabetes were consistent with the primary efficacy results for the overall population studied in the trial.

In the AVERROES study a total of 5,598 patients considered to be unsuitable for VKA by the investigators were randomized to treatment with apixaban 5 mg twice daily (or 2.5 mg twice daily in selected patients [6.4%]) or ASA. ASA was given at a once daily dose of 81 mg (64%), 162 (26.9%), 243 (2.1%), or 324 mg (6.6%) at the discretion of the investigator. Patients were exposed to study drug for a mean of 14 months. The mean age was 69.9 years, the mean $CHADS_2$ score was 2.0 and 13.6% of patients had prior stroke or TIA. Common reasons for unsuitability for VKA therapy in the AVERROES study included unable/unlikely to obtain INRs at requested intervals (42.6%), patient refused treatment with VKA (37.4%), CHADS2 score = 1 and physician did not recommend VKA (21.3%), patient could not be relied on to adhere to VKA medication instruction (15.0%), and difficulty/expected difficulty in contacting patient in case of urgent dose change (11.7%). AVERROES was stopped early based on a recommendation by the independent Data Monitoring Committee due to

clear evidence of reduction of stroke and systemic embolism with an acceptable safety profile. In this study, apixaban achieved statistically significant superiority in the primary endpoint of prevention of stroke (haemorrhagic, ischaemic or unspecified) or systemic embolism compared to ASA.

Both phase 3 studies CV185030 and CV185048 show that apixaban 5 mg (2.5 mg for restricted patients) is associated with significantly lower incidence of stroke and SE than VKA or ASA, respectively. Also the secondary endpoint of all cause death is significantly less frequent in the apixaban arm compared to VKA arm. Benefits were weaker in subgroups with better INR control, but this was still an acceptable result considering that apixaban offers other advantages over VKA, like a more favourable interaction profile and no need for routine monitoring. The use of apixaban as an alternative to patients unsuitable to VKA was not supported by the CHMP, as the criteria defining this unsuitability were too subjective. Actual representation of patients who discontinued VKA due to bleeding was very limited. Superiority of apixaban over ASA was acknowledged with the caveat that ASA may not have been the most suitable active comparator for the whole cohort as clopidogrel is sometimes added according to the *ESC Clinical practice guideline for the management of atrial fibrillation 2010*. The main study results were included in section 5.1 of the SmPC.

2.5.4. Conclusions on the clinical efficacy

In conclusion, apixaban has shown to be a beneficial anti-thrombotic for the prevention of stroke/SE in AF patients, with no extra burden in the bleeding risk compared to VKA.

2.6. Clinical safety

This section presents safety information from the two completed Phase 3 studies (CV185030 and CV185048). Relevant data will be presented pooled or separately for each of the studies. Safety information is also presented for 218 treated subjects with AF from a completed Phase 2 study (CV185067) conducted in Japan. Reference will also be made in certain sections to the available safety data from apixaban investigated in other indications.

Patient exposure

The total number of subjects who received at least 1 dose of any double-blind study drug in the Phase 2/3 AF studies was 23,936, of which 23,718 were in the phase 3 studies. Of these, 11,886 subjects received apixaban 5 mg BID (or 2.5 mg BID for subjects meeting criteria for dose reduction at randomization in the Phase 3 studies), 9052 subjects received warfarin, and 2780 subjects received ASA (Figure S1).

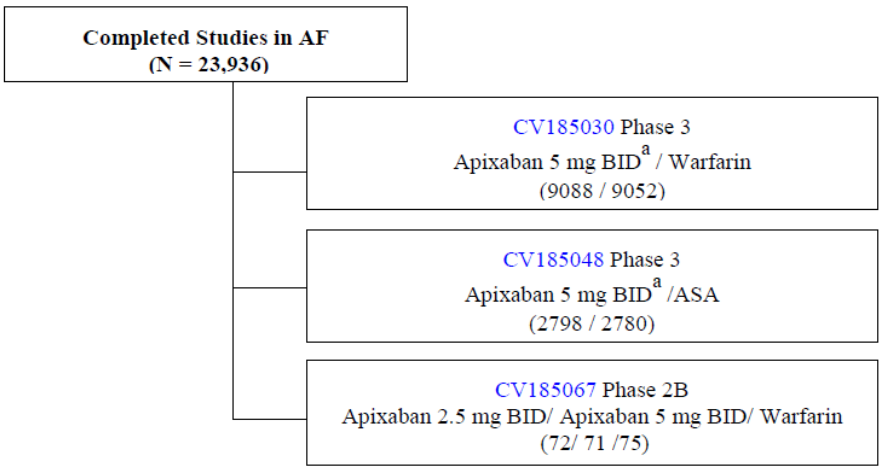


Figure S1 Completed Apixaban Studies in the Phase 2 / 3 Clinical Program - Treated Subjects

Adverse events

The overall AE profile of apixaban in the Phase 3 studies was similar to that of warfarin in CV185030, and was similar to that of ASA in CV185048 (Table S1).

Table S1 Summary of Safety During the Treatment Period – Treated Subjects, Study CV185030 and Study CV185048

CV185030	Apixaban N = 9088	Warfarin N = 9052
AE (%)	7406 (81.5)	7521 (83.1)
SAE (%)	3182 (35.0)	3302 (36.5)
BLEEDING AE (%)	2288 (25.2)	2961 (32.7)
DISCONTINUATIONS DUE TO AE (%)	688 (7.6)	758 (8.4)
DEATHS (%)	429 (4.7)	468 (5.2)
CV185048	**Apixaban N = 2798**	**ASA N = 2780**
AE (%)	1833 (65.5)	1925 (69.2)
SAE (%)	657 (23.5)	804 (28.9)
BLEEDING AE (%)	281 (10.0)	259 (9.3)
DISCONTINUATIONS DUE TO AE (%)	266 (9.5)	362 (13.0)
DEATHS (%)	91 (3.3)	115 (4.1)

In Study CV185030 the frequency of AEs was similar in the apixaban and warfarin groups for warfarin/VKA-naive and warfarin/VKA-experienced subjects. Drug-related AEs were reported for 27.8% of subjects in the apixaban group and 34.2% in the warfarin group. The most common drug-related AEs were related to bleeding. For the reported events, the frequency of bleeding with apixaban was generally less than that reported with VKA: epistaxis (apixaban 5.0%; warfarin 6.1%), haematuria (apixaban 2.6%; warfarin 3.2%), contusion (apixaban 1.7%; warfarin 3.2%), hematoma (apixaban 1.4%; warfarin 3.5%), gingival bleeding (apixaban 1.0%; warfarin 2.1%), and ecchymosis (apixaban 0.9%; warfarin 2.0%). In CV185048, the frequency of drug-related AEs was similar in the two treatment groups (apixaban 16.6%, ASA 16.7%). No drug-related AEs (preferred terms) were reported in ≥2% of subjects in either group. During the Follow-up Period, there were no clinically meaningful differences between the apixaban and comparator groups for the frequency for AEs in either study (3.3% in the apixaban group and 3.4% in the warfarin group in CV185030; apixaban 7.2%, ASA 7.8% in CV185048).

Serious adverse event / deaths / other significant events

In study CV185030, the incidence of death was shown to be lower in the apixaban group (4.7%) compared to VKA (5.2%) during the treatment period. Also, in study CV185048, serious AEs SAEs with outcome of death were reported slightly more frequently in the ASA group (4.1%) compared to apixaban (3.3%).

For SAEs, overall frequency was similar in the apixaban group compared with the warfarin group in CV185030. In CV185048, the overall frequency of SAEs with onset during the treatment period was 23.5% in the apixaban group vs. 28.9% in the ASA group (table S1). The most common SAEs were Cardiac Disorders in both studies. No new safety signals were detected in these studies.

Adverse events of Special Interest

1. Bleeding. Adjudicated **major bleeding** (adapted from ISTH guidelines) was the primary safety endpoint in both Phase 3 studies. According to the pre-specified sequential testing strategy in study CV185030, the superiority of apixaban compared to warfarin demonstrated for the primary efficacy endpoint signalled the sequential testing of ISTH major bleeding. Apixaban was superior to warfarin for ISTH major bleeding, major or CRNM bleeding (clinically relevant non-major) and all bleeding (table S2 and figure S2).

Table S2 Summary of Adjudicated Bleeding Endpoint (ISTH and All Bleeding) during treatment period – treated subjects (CV185030)

	Apixaban N = 9088	Warfarin N = 9052
ISTH CRITERIA		
MAJOR, n (%)	327 (3.60)	462 (5.10)
EVENT RATE (%/YR)	2.13	3.09
HAZARD RATIO (APIXABAN/WARFARIN)	0.69	
95% CI FOR HAZARD RATIO	(0.60, 0.80)	
P-VALUE	<.0001	
MAJOR OR CRNM, n (%)	613 (6.75)	877 (9.69)
EVENT RATE (%/YR)	4.07	6.01
HAZARD RATIO (APIXABAN/WARFARIN)	0.68	
95% CI FOR HAZARD RATIO	(0.61, 0.75)	
P-VALUE	<.0001	
ALL BLEEDING, n (%)	2356 (25.92)	3060 (33.80)
EVENT RATE (%/YR)	18.08	25.82
HAZARD RATIO (APIXABAN/WARFARIN)	0.71	
95% CI FOR HAZARD RATIO	(0.68, 0.75)	
P-VALUE	<.0001	

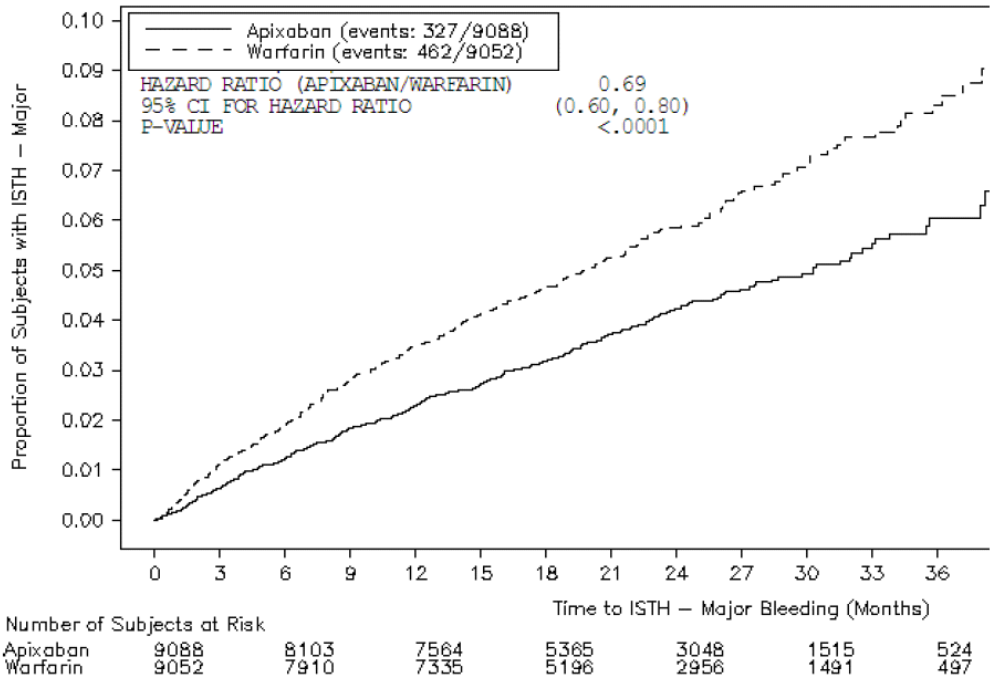


Figure S2 Kaplan-Meier Plot for ISTH Major Bleeding During the Treatment Period - Treated Subjects - CV185030

Bleeding classified by INR. Consistent with the primary safety results, apixaban demonstrated a reduction in ISTH major bleeding compared to warfarin for study sites with INR control below and above the median TTR as well as in each of the 4 quartile intervals (table S3). Similar results were observed when these analyses were performed by using the TTR value when warfarin interruptions were included in the calculation.

Table S3 Summary of ISTH Major Bleeding During the Treatment Period (Excluding First 7 Days of the Study and Warfarin Interruptions), by Level of INR control, in Quartiles– Treated Subjects (CV185030).

	Apixaban	Warfarin
Study Sites With INR Control < Q1*, n/N (%)	24/1187 (2.02)	50/1174 (4.26)
EVENT RATE (%/YR)	1.25	2.81
HAZARD RATIO (APIXABAN / WARFARIN)	0.44	
95% CI FOR HAZARD RATIO	(0.27, 0.72)	
Study Sites With INR Control >= Q1 - < Median*, n/N (%)	105/3446 (3.05)	174/3471 (5.01)
EVENT RATE (%/YR)	1.82	3.08
HAZARD RATIO (APIXABAN / WARFARIN)	0.60	
95% CI FOR HAZARD RATIO	(0.47, 0.76)	
Study Sites With INR Control >= Median - < Q3*, n/N (%)	150/3346 (4.48)	174/3395 (5.13)
EVENT RATE (%/YR)	2.61	3.03
HAZARD RATIO (APIXABAN / WARFARIN)	0.87	
95% CI FOR HAZARD RATIO	(0.70, 1.08)	
Study Sites With INR Control >= Q3*, n/N (%)	47/1060 (4.43)	64/1007 (6.36)
EVENT RATE (%/YR)	2.57	3.61
HAZARD RATIO (APIXABAN / WARFARIN)	0.70	
95% CI FOR HAZARD RATIO	(0.48, 1.03)	

* Quartiles of time in the therapeutic range of INR (2.0 - 3.0) are 52.35%, 65.99%, and 76.50% INR measurements on or after Day 8 of randomization until the earliest of (last dose of warfarin, last INR measurement), after excluding INR measurements during warfarin interruptions, are included in TTR computation
* Corrected table

The frequency of the individual components of major bleeding were generally lower or similar in the apixaban group compared with the warfarin group except for intraocular bleeding (Table S4).

Table S4 Summary of Components of ISTH Major Bleeding During Treatment Period (CV185030).

	Apixaban N = 9088	Warfarin N = 9052
MAJOR BLEEDING, n (%)	327 (3.60)	462 (5.10)
EVENT RATE (%/yr)	2.13	3.09
FATAL HEMORRHAGE, n (%)	10 (0.11)	37 (0.41)
EVENT RATE (%/yr)	0.06	0.24
FATAL BLEED, n (%)	8 (0.09)	11 (0.12)
EVENT RATE (%/yr)	0.05	0.07
FATAL HEMORRHAGIC STROKE, n (%)	2 (0.02)	26 (0.29)
EVENT RATE (%/yr)	0.01	0.17
BLEEDING INTO A CRITICAL SITE, n (%)	91 (1.00)	158 (1.75)
EVENT RATE (%/yr)	0.59	1.04
INTRACRANIAL, n (%)	52 (0.57)	122 (1.35)
EVENT RATE (%/yr)	0.33	0.80
INTRAARTICULAR, n (%)	6 (0.07)	10 (0.11)
EVENT RATE (%/yr)	0.04	0.07
INTRAOCULAR, n (%)	28 (0.31)	19 (0.21)
EVENT RATE (%/yr)	0.18	0.13
PERICARDIAL, n (%)	0	0
EVENT RATE (%/yr)	0	0
INTRASPINAL, n (%)	2 (0.02)	2 (0.02)
EVENT RATE (%/yr)	0.01	0.01
INTRAMUSCULAR WITH COMPARTMENT SYNDROME, n (%)	1 (0.01)	1 (0.01)
EVENT RATE (%/yr)	< 0.01	< 0.01
RETROPERITONEAL, n (%)	2 (0.02)	5 (0.06)
EVENT RATE (%/yr)	0.01	0.03
DECREASE IN HEMOGLOBIN>= 2G/DL OVER 24 HRS, n (%)	165(1.82)	222 (2.45)
EVENT RATE (%/yr)	1.07	1.47
TRANSFUSION OF >= 2 UNITS OF PRBCs, n (%)	70 (0.77)	101 (1.12)
EVENT RATE (%/yr)	0.45	0.67

Event rates for ***GI bleeding*** (including upper GI, lower GI, and rectal bleeding) reported by the investigator and adjudicated as major bleeding in CV185030 were 1.30%/year in the apixaban group and 1.44%/year in the warfarin group.

Study CV185048. The observed event rate for adjudicated adapted ISTH major bleeding was 45 subjects (1.41%/year) in the apixaban group and 29 subjects (0.92%/year) in the ASA group [HR=1.54 (95%CI: 0.96-2.45); p=0.07] (Table S5 and Figure S3).

Table S5 Summary of Adjudicated Bleeding Endpoints During the Double-blind Treatment Period – Treated Subjects (CV185048)

	Apixaban N = 2798	ASA N = 2780
MAJOR BLEEDING, n (%)	45 (1.61)	29 (1.04)
EVENT RATE (%/yr)	1.41	0.92
HAZARD RATIO (APIXABAN/ASA)	1.54	
95% CI FOR HAZARD RATIO	(0.96, 2.45)	
P-VALUE	0.0716	
MAJOR OR CRNM BLEEDING, n (%)	140 (5.00)	101 (3.63)
EVENT RATE (%/yr)	4.46	3.24
HAZARD RATIO (APIXABAN/ASA)	1.38	
95% CI FOR HAZARD RATIO	(1.07, 1.78)	
P-VALUE	0.0144	
ALL BLEEDING, n (%)	325 (11.62)	250 (8.99)
EVENT RATE (%/yr)	10.85	8.32
HAZARD RATIO (APIXABAN/ASA)	1.30	
95% CI FOR HAZARD RATIO	(1.10, 1.53)	
P-VALUE	0.0017	

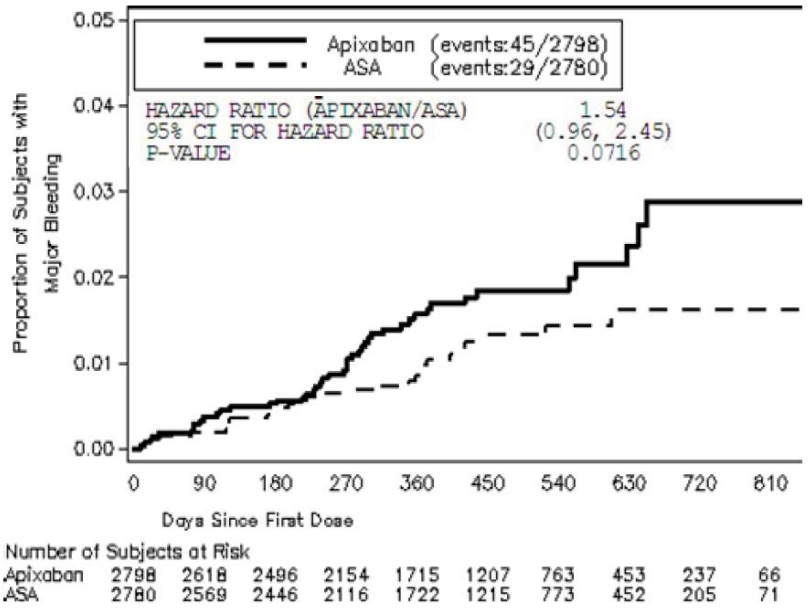


Figure S3 Kaplan-Meier Plot for Major Bleeding during the Double-blind Treatment Period - Treated Subjects

The frequencies of the components of ISTH major bleeding are displayed in Table S6.

Table S6 Summary of Components of ISTH Major Bleeding During Treatment Period – Treated Subjects (CV185048)

	Apixaban N = 2798	ASA N = 2780
MAJOR BLEEDING, n (%)	45 (1.61)	29 (1.04)
EVENT RATE (%/yr)	1.41	0.92
FATAL BLEED, n (%)	5 (0.18)	5 (0.18)
EVENT RATE (%/yr)	0.16	0.16
BLEEDING INTO A CRITICAL SITE, n (%)	22 (0.79)	12 (0.43)
EVENT RATE (%/yr)	0.69	0.38
INTRACRANIAL BLEED, n (%)	11 (0.39)	11 (0.40)
EVENT RATE (%/yr)	0.34	0.35
INTRAARTICULAR BLEED, n (%)	2 (0.07)	1 (0.04)
EVENT RATE (%/yr)	0.06	0.03
INTRAOCULAR BLEED, n (%)	6 (0.21)	0
EVENT RATE (%/yr)	0.19	0
PERICARDIAL BLEED, n (%)	1 (0.04)	0
EVENT RATE (%/yr)	0.03	0
INTRAMUSCULAR WITH COMPARTMENT SYNDROME BLEED, n (%)	1 (0.04)	0
EVENT RATE (%/yr)	0.03	0
RETROPERITONEAL BLEED, n (%)	1 (0.04)	0
EVENT RATE (%/yr)	0.03	0
DECREASE IN HEMOGLOBIN >= 2G/DL OVER 24 HOURS, n (%)	14 (0.50)	12 (0.43)
EVENT RATE (%/yr)	0.44	0.38
TRANSFUSION OF >= 2 UNITS OF PRBCs, n (%)	16 (0.57)	13 (0.47)
EVENT RATE (%/yr)	0.50	0.41

Six of 2798 subjects (0.21%, 0.19%/year) in the apixaban group (0 in the ASA group) had ISTH major bleeding for which the investigator-assigned location was intraocular. Further analysis revealed an extra case of vitreous haemorrhage, originally classified “Other”. Of these 7 ISTH major bleeding events, 3 were vitreous haemorrhage (resolving in 10, 12, and 19 days, respectively); 2 events of eye haemorrhage (ocular haemorrhage resolving in 21 days, and intraocular bleeding, resolving in 129 days) and one event of loss of vision (occurred approximately 3 months after eye surgery of a macular hole). Two of the 7 apixaban-treated subjects with intraocular ISTH major bleeding had diabetes. The frequency of diabetes in the overall population was 19.1% in the apixaban group and 20.0% in the ASA group.

2. Liver-related safety results. The frequency of elevations of LFTs with onset during the Treatment Period was low and similar in the apixaban and comparator groups (table S7).

Table S7 Summary of LFT Elevations during the Treatment Period - Treated Subjects with Available Measurements (Pooled CV185030 and CV185048)

	Apixaban	Comparator
AST ELEVATION, n/N(%)		
>3xULN	134/ 11569 (1.2)	132/ 11514 (1.1)
>5xULN	52/ 11569 (0.4)	55/ 11514 (0.5)
>10xULN	23/ 11569 (0.2)	20/ 11514 (0.2)
>20xULN	10/ 11569 (<0.1)	14/ 11514 (0.1)
ALT ELEVATION, n/N(%)		
>3xULN	123/ 11569 (1.1)	120/ 11512 (1.0)
>5xULN	54/ 11569 (0.5)	60/ 11512 (0.5)
>10xULN	18/ 11569 (0.2)	24/ 11512 (0.2)
>20xULN	8/ 11569 (<0.1)	14/ 11512 (0.1)
TBILI ELEVATION, n/N(%)		
>1.5xULN	383/ 11575 (3.3)	331/ 11519 (2.9)
>2xULN	118/ 11575 (1.0)	129/ 11519 (1.1)
BOTH AST AND ALT ELEVATION ON THE SAME DATE, n/N(%)		
>3xULN	88/ 11569 (0.8)	83/ 11512 (0.7)
>5xULN	36/ 11569 (0.3)	38/ 11512 (0.3)
>10xULN	13/ 11569 (0.1)	18/ 11512 (0.2)
>20xULN	7/ 11569 (<0.1)	12/ 11512 (0.1)
AT AND TBILI ELEVATION ON THE SAME DATE, n/N(%)		
(ALT>3xULN OR AST>3xULN) AND TBILI>2xULN	35/ 11567 (0.3)	40/ 11509 (0.3)
(ALT>3xULN OR AST>3xULN) AND TBILI>1.5xULN	45/ 11567 (0.4)	49/ 11509 (0.4)
(ALT>3xULN OR AST>3xULN) AND TBILI>2xULN AND ALP<2xULN	20/ 11565 (0.2)	23/ 11508 (0.2)
ALT AND TBILI ELEVATION ON THE SAME DATE, n/N(%)		
ALT>3xULN AND TBILI>2xULN	26/ 11567 (0.2)	31/ 11508 (0.3)
ALT>3xULN AND TBILI>1.5xULN	32/ 11567 (0.3)	41/ 11508 (0.4)
ALT>3xULN AND TBILI>2xULN AND ALP<2xULN	15/ 11565 (0.1)	20/ 11507 (0.2)
ALP ELEVATION, n/N(%)		
>1.5xULN	282/ 11576 (2.4)	283/ 11520 (2.5)

Liver-related SAEs occurred with low and similar frequency in the apixaban and comparator groups (59 [0.5% and 55 [0.5%] subjects, respectively). Liver-related SAEs with outcome of death were reported for a total of 13 subjects (7 subjects in the apixaban group and 6 subjects in the comparator group). Of 13 deaths, 4 (2 in each treatment group) occurred during the Follow-up Period. Most subjects with SAEs related to elevations in LFT with outcome of death had underlying disease conditions, such as hepatic malignancy. Liver-related AEs leading to treatment discontinuation occurred in 35 (0.3%) subjects in the apixaban group and 42 (0.4%) in the comparator group. All liver-related AEs leading to discontinuation were reported for ≤0.1% of subjects in either treatment group. Comparable results were also reported during the follow-period.

Three independent hepatologists provided blinded assessments of subjects with concurrent elevations of ALT >3x ULN and total bilirubin >2 x ULN and/or pre-selected SAEs (jaundice, hepatitis, and hepatic failure) related to elevated LFTs across the entire Phase 2/3 clinical program for apixaban (N=57,706 treated subjects). The number of cases assessed as possible or probable relationship to the study drug by the independent, blinded, hepatologists' panel was low and balanced between the 2 groups. Six apixaban-treated subjects had on-study concurrent LFT elevations of ALT>3xULN and TBili>2xULN assessed by as possibly or probably related to study drug. All 6 apixaban-treated subjects had AEs or SAEs of hepatitis, and 2 of these 6 subjects had SAEs of hepatitis with outcome of death assessed as possibly related to study drug. Another of these 6 subjects had a nonfatal SAE of acute hepatitis assessed as probably related to study drug.

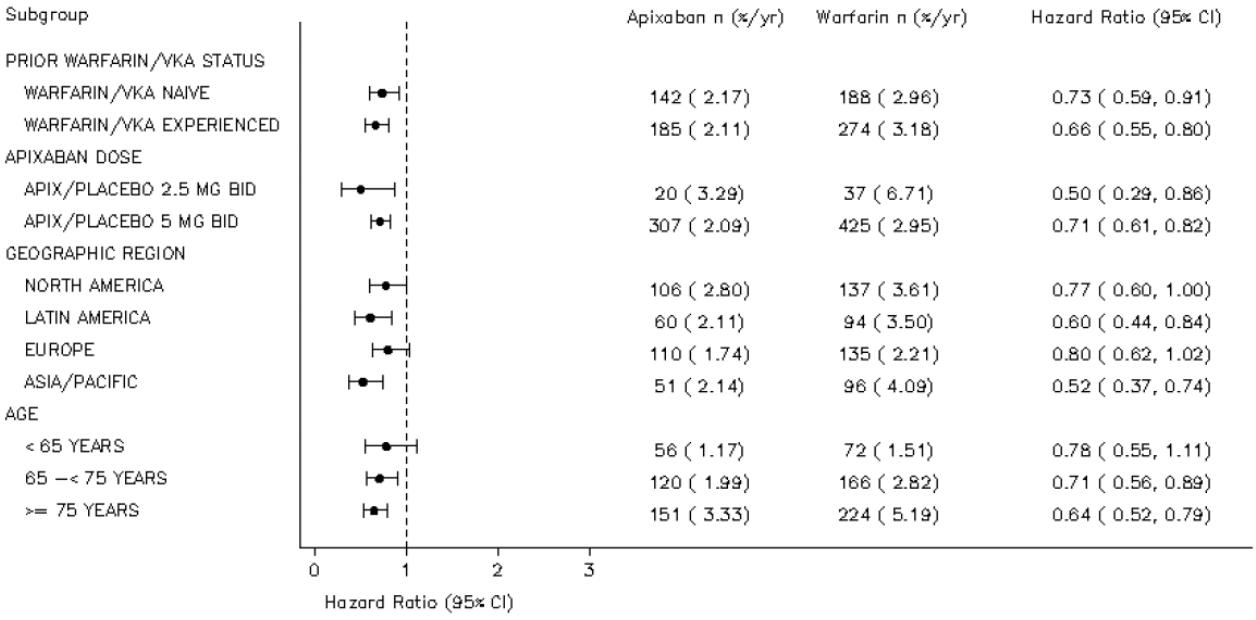
For the non-AF studies (22,386 subjects apixaban or reference treatments (placebo, enoxaparin, or warfarin) in eight completed studies in non-AF indications), a total of 11 cases were assessed as possibly related to study drug (apixaban 7, comparator 5). Of the 7 cases in apixaban-treated subjects, one subject had a liver-related SAE with fatal outcome.

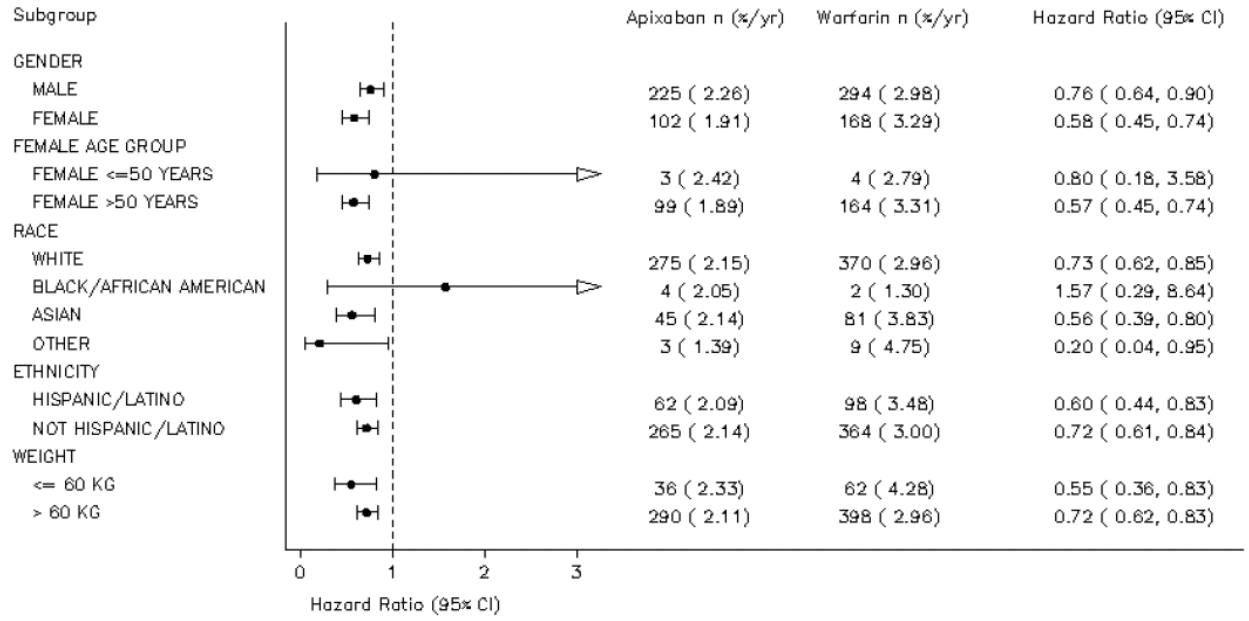
Laboratory findings

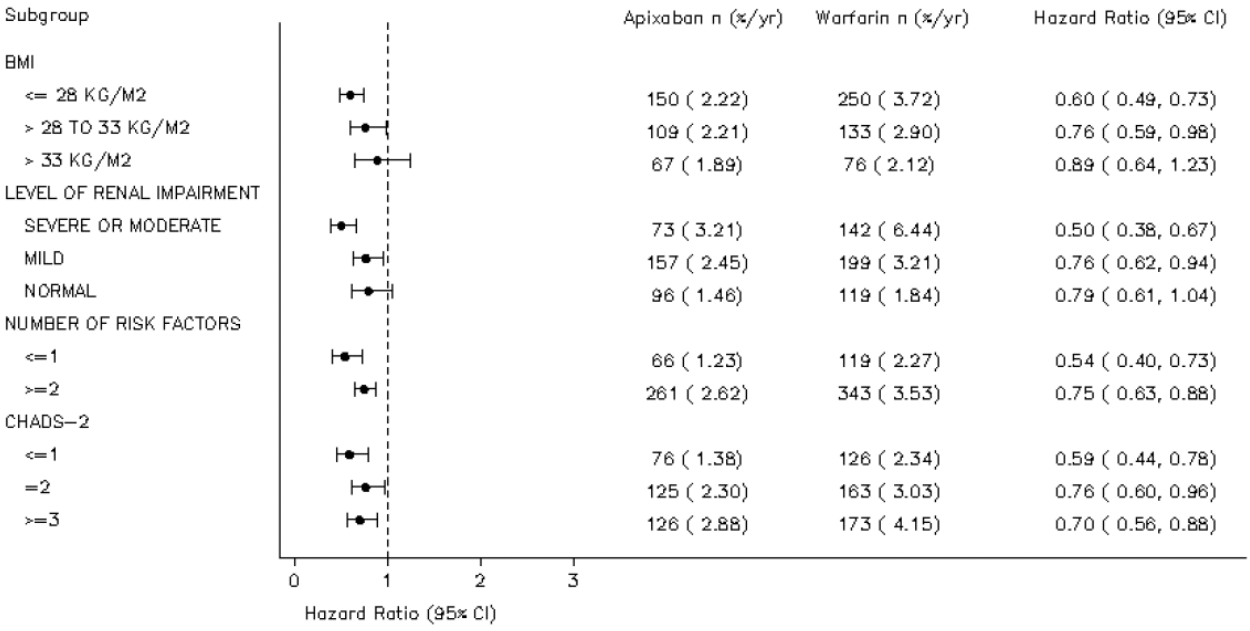
The incidence of laboratory values that met the criteria for marked abnormalities was similar in both treatment groups. Few subjects had platelet counts decreased from baseline to <50,000/mm3 (4 [<0.1%] subjects in each treatment group. A total of 111 (1.3%) subjects in the apixaban group and 101 (1.2%) subjects in the warfarin group had platelet counts decreased from baseline to <100,000/mm3 during the Treatment Period. Five (<0.1%) subjects in the apixaban group and 7 (<0.1%) subjects in the warfarin group had an SAE of thrombocytopenia during the Treatment Period.

Safety in special populations

Bleeding. In study CV185030, the results within each subgroup were consistent with the results for the study for ISTH major, composite of ISTH major or CRNM and all bleeding (data shown in figure S4 are only for ISTH major bleeding).




Subgroup
Apixaban n (%/yr)
Warfarin n (%/yr)
Hazard Ratio (95% CI)
GENDER
MALE 225 (2.26) 294 (2.98) 0.76 (0.64, 0.90)
FEMALE 102 (1.91) 168 (3.29) 0.58 (0.45, 0.74)
FEMALE AGE GROUP
FEMALE <=50 YEARS 3 (2.42) 4 (2.79) 0.80 (0.18, 3.58)
FEMALE >50 YEARS 99 (1.89) 164 (3.31) 0.57 (0.45, 0.74)
RACE
WHITE 275 (2.15) 370 (2.96) 0.73 (0.62, 0.85)
BLACK/AFRICAN AMERICAN 4 (2.05) 2 (1.30) 1.57 (0.29, 8.64)
ASIAN 45 (2.14) 81 (3.83) 0.56 (0.39, 0.80)
OTHER 3 (1.39) 9 (4.75) 0.20 (0.04, 0.95)
ETHNICITY
HISPANIC/LATINO 62 (2.09) 98 (3.48) 0.60 (0.44, 0.83)
NOT HISPANIC/LATINO 265 (2.14) 364 (3.00) 0.72 (0.61, 0.84)
WEIGHT
<= 60 KG 36 (2.33) 62 (4.28) 0.55 (0.36, 0.83)
> 60 KG 290 (2.11) 398 (2.96) 0.72 (0.62, 0.83)
0
1
2
3
Hazard Ratio (95% CI)


Subgroup
Apixaban n (%/yr)
Warfarin n (%/yr)
Hazard Ratio (95% CI)
BMI
<= 28 KG/M2 150 (2.22) 250 (3.72) 0.60 (0.49, 0.73)
> 28 TO 33 KG/M2 109 (2.21) 133 (2.90) 0.76 (0.59, 0.98)
> 33 KG/M2 67 (1.89) 76 (2.12) 0.89 (0.64, 1.23)
LEVEL OF RENAL IMPAIRMENT
SEVERE OR MODERATE 73 (3.21) 142 (6.44) 0.50 (0.38, 0.67)
MILD 157 (2.45) 199 (3.21) 0.76 (0.62, 0.94)
NORMAL 96 (1.46) 119 (1.84) 0.79 (0.61, 1.04)
NUMBER OF RISK FACTORS
<=1 66 (1.23) 119 (2.27) 0.54 (0.40, 0.73)
>=2 261 (2.62) 343 (3.53) 0.75 (0.63, 0.88)
CHADS-2
<=1 76 (1.38) 126 (2.34) 0.59 (0.44, 0.78)
=2 125 (2.30) 163 (3.03) 0.76 (0.60, 0.96)
>=3 126 (2.88) 173 (4.15) 0.70 (0.56, 0.88)
0
1
2
3
Hazard Ratio (95% CI)

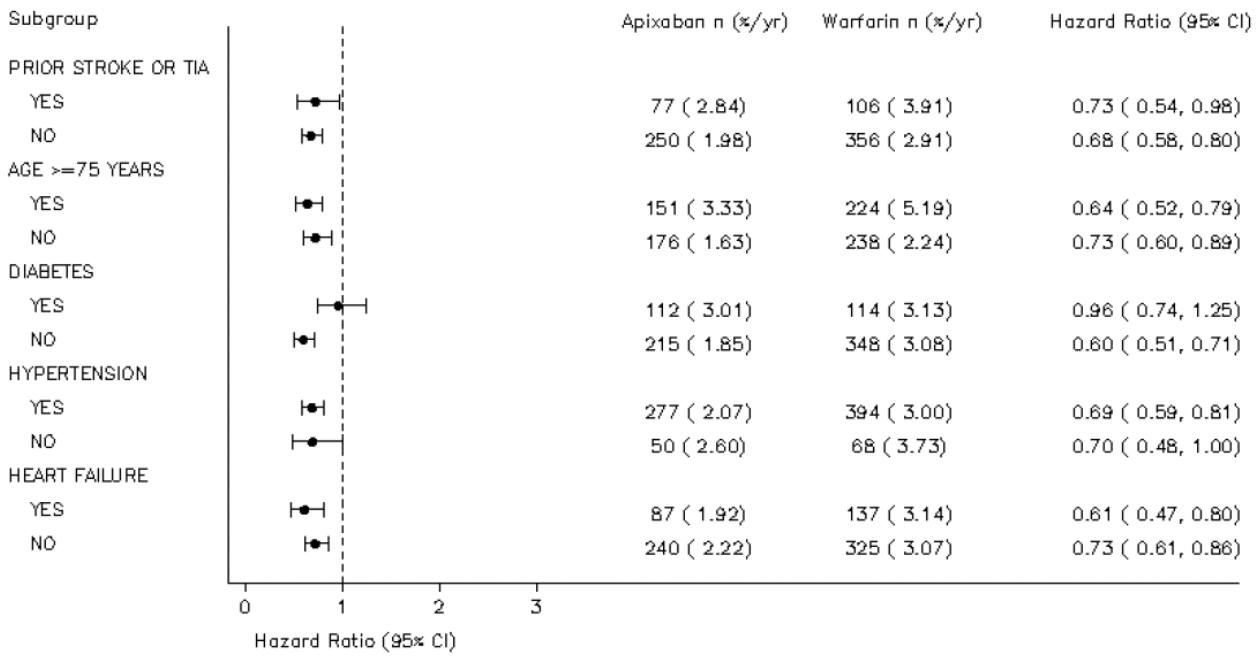
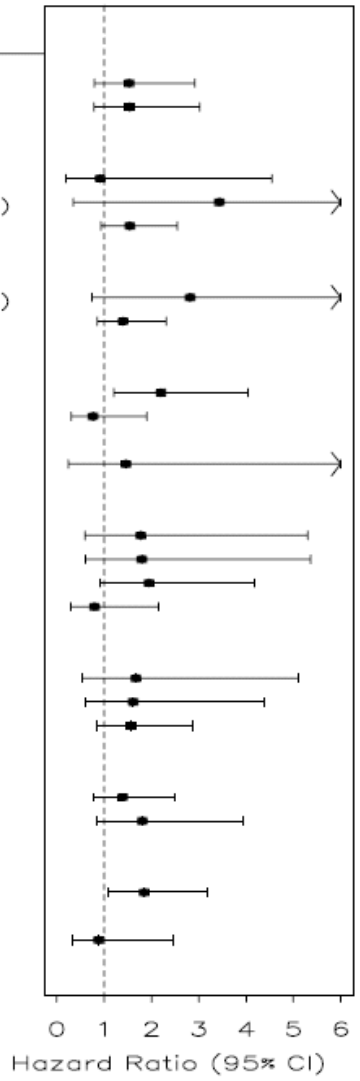


Figure S4 Analyses for ISTH major Bleeding – Treated Subjects (CV185030)

Results of a post hoc analysis of major bleeding in the small subset of subjects with severe renal impairment (136 and 132 subjects in the apixaban and warfarin groups, respectively) were consistent (event rate of 3.8%/year vs. 11.9%/year, respectively). Another post-hoc sub-group analysis was performed in subjects from countries of the EU (apixaban 2,032, warfarin 2,026). Event rates for major bleeding were slightly higher in the apixaban and warfarin groups (2.29%/yr and 2.56%yr, respectively; HR 0.90 [95% CI: 0.66, 1.22]) than were major bleeding event rates in the larger pre-specified EU subgroup depicted in figure S4 (1.74%/yr and 2.21%/yr for apixaban and warfarin, respectively; HR 0.80 [95% CI: 0.62, 1.02]). Hazard ratios were favourable for apixaban in each of these subgroup analyses, albeit of lesser magnitude in the smaller EU member state analysis.

Study CV185048. Overall, the results within each subgroup were consistent with the results for the study for ISTH major, composite of ISTH major or CRNM and all bleeding identified by the investigator, as shown in figure S5.

Subgroup	Apixaban n (%/yr)	ASA n (%/yr)	Hazard Ratio (95% CI)
VKA Unsuitable			
Demonstrated	23 (1.84)	15 (1.21)	1.52(0.80,2.92)
Expected	22 (1.13)	14 (0.73)	1.55(0.79,3.02)
Reason VKA unsuitable			
Subj. refused trt w/VKA	3 (0.61)	3 (0.67)	0.92(0.19,4.55)
CHADS2 Scr=1/Phy not rec	3 (0.93)	1 (0.28)	3.44(0.36,33.06)
All other reasons	39 (1.64)	25 (1.07)	1.54(0.93,2.55)
Apixaban Dose			
Apix/Pla 2.5 mg BID	8 (4.48)	3 (1.59)	2.82(0.75,10.62)
Apix/Pla 5 mg BID	37 (1.23)	26 (0.88)	1.40(0.85,2.32)
ASA Dose			
ASA/Pla 81 mg QD	34 (1.65)	15 (0.75)	2.20(1.20,4.04)
ASA/Pla 162 mg QD	8 (0.98)	11 (1.29)	0.77(0.31,1.90)
ASA/Pla 243 mg QD	0	1 (1.44)	<0.01(NE)
ASA/Pla 324 mg QD	3 (1.31)	2 (0.92)	1.46(0.24,8.74)
Geographic Region			
North America	9 (1.77)	5 (1.02)	1.78(0.60,5.30)
Latin America	9 (1.38)	5 (0.77)	1.80(0.60,5.37)
Europe	20 (1.35)	10 (0.69)	1.95(0.91,4.17)
Asia/Pacific	7 (1.28)	9 (1.61)	0.80(0.30,2.15)
Age			
<65 yrs	8 (0.81)	5 (0.49)	1.67(0.55,5.11)
>=65 and <75 yrs	11 (0.90)	6 (0.56)	1.61(0.60,4.36)
>=75 yrs	26 (2.65)	18 (1.70)	1.57(0.86,2.86)
Gender			
Male	27 (1.43)	19 (1.03)	1.39(0.77,2.50)
Female	18 (1.38)	10 (0.76)	1.81(0.84,3.92)
Race			
White	38 (1.46)	20 (0.79)	1.85(1.07,3.17)
Black/African American	0	0	NE
Asian	7 (1.31)	8 (1.47)	0.89(0.32,2.45)
Other	0	1 (2.09)	<0.01(NE)



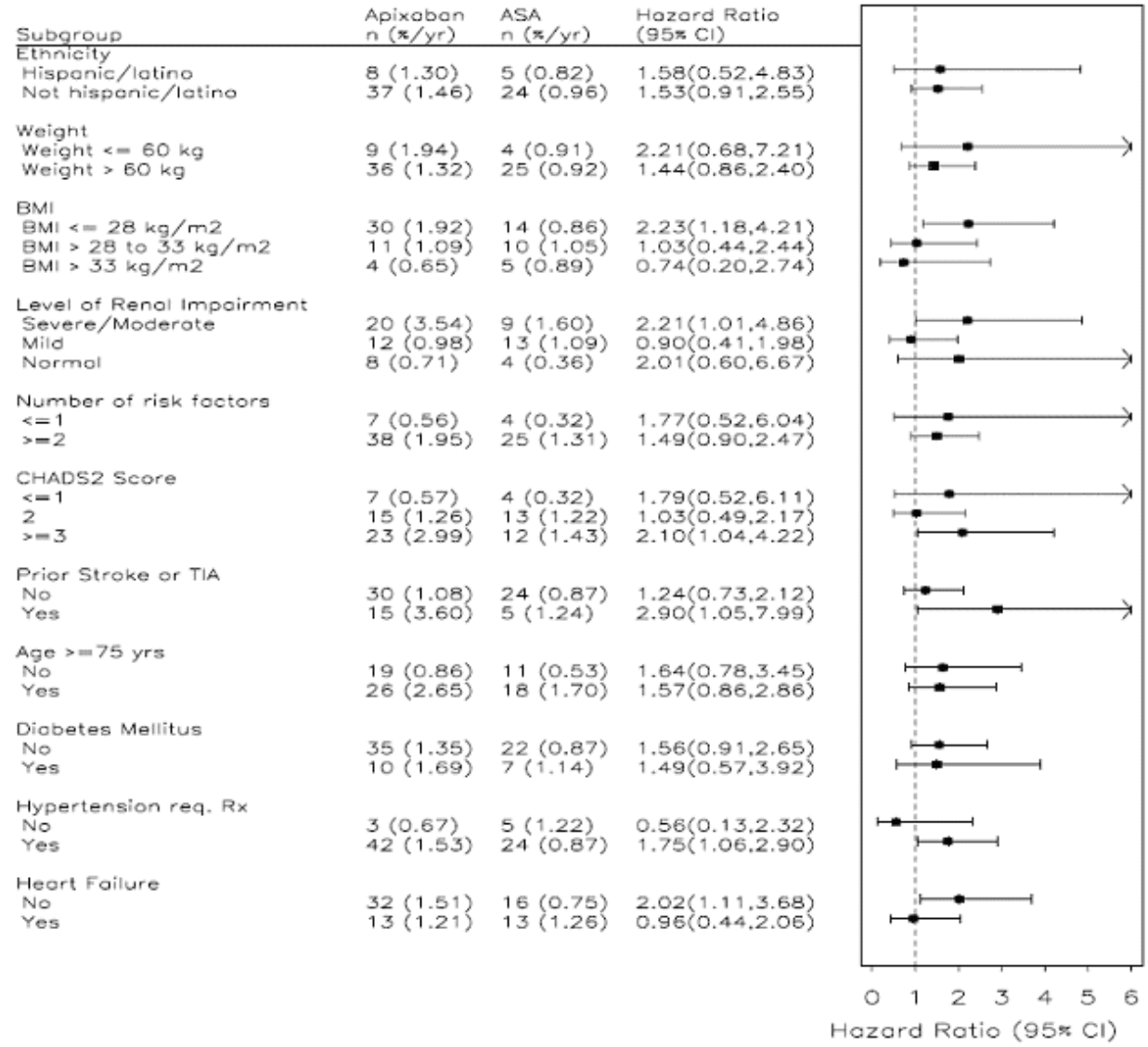


Figure S5 Subgroup Analyses for Major Bleeding – Treated Subjects (CV185048)

Safety related to drug-drug interactions and other interactions

Bleeding Risk with Concomitant Use of ASA or ASA+Thienopyridine. The number of subjects receiving ASA+study drug was 3529/9088 in the apixaban group and 3431/9052 in the warfarin group The addition of ASA to study drug increased the risk of ISTH major bleeding in each treatment group (apixaban 3.42%/year vs.1.78%/year for subjects receiving vs. not receiving ASA; warfarin 4.59%/year vs. 2.70%/year for subjects receiving vs. not receiving ASA). The bleeding risk associated with concomitant use of ASA+study drug was lower for apixaban compared with warfarin for ISTH major bleeding and all other bleeding endpoints, including intracranial bleeding. Fatal haemorrhages were observed for 3 subjects on apixaban and 9 subjects on warfarin while receiving ASA+study drug.

The number of subjects receiving ***ASA+thienopyridine+study drug*** was 211/9088 (2.3%) in the apixaban group and 170/9052 (1.9%) in the warfarin group. The addition of ASA+thienopyridine to study drug increased the risk of bleeding in each treatment group (apixaban 7.53%/year vs. 2.11%/year for subjects receiving vs. not receiving ASA+thienopyridine; warfarin 20.80%/year vs. 3.04%/year for subjects receiving vs. not receiving ASA+thienopyridine). The bleeding risk associated with concomitant use of ASA+thienopyridine+study drug was lower for apixaban than warfarin for all

bleeding endpoints and intracranial bleeds (observed rate difference < 0). Given the infrequent use of the triple combination in the study, the number of events observed for subjects while on triple therapy was small, and all 95% CI for rate difference included 0. There were no fatal haemorrhages observed for subjects in either treatment group while on triple therapy.

Discontinuation due to adverse events

No marked differences between the treatment groups were observed in the frequencies of AEs leading to discontinuation in either of the Phase 3 studies. In CV185030, the frequency of AEs leading to study treatment discontinuation was similar in the apixaban and warfarin groups in the overall population (apixaban 7.6%, warfarin 8.4%) and in warfarin/VKA-naïve subjects (apixaban 7.8%, warfarin 8.8%) and warfarin/VKA-experienced subjects (apixaban 7.4%. warfarin 8.1%).

In CV185048, the frequency of AEs leading to study treatment discontinuation was 9.5% vs. 13.0% in the apixaban vs. ASA groups, respectively. Most AEs leading to discontinuation were reported for <1% of subjects in either treatment group.

Supportive Studies

Study CV185067

Table S8 Overview of study CV185067

Title: A Phase 2b, Randomized, Partially Blind (Open Label Warfarin), Active-Controlled (Warfarin), Multicenter Study to Evaluate the Safety and Efficacy in 2 Doses of Apixaban in Comparison to Warfarin, Administered for 12 Weeks in Subjects with NVAF					
Study identifier	Study code: CV185067				
Design	Design: randomized, partially blind (double-blind apixaban, open-label warfarin), active-controlled (warfarin sodium), multicenter study				
	Duration of main phase:		12 weeks: Week -1 (starting day of the observation period/enrollment), Week 0 (day of transition to the treatment period/baseline), Week 1, Week 2, Week 4 and Week 8 (visits during the treatment period), and Week 12/discontinuation (last visit).		
	Follow-up phase:		starting after the end of the treatment period through 30 days after the discontinuation of the study drug (for treated subjects).		
Hypothesis	No formal statistical hypothesis testing was planned in this study				
Treatments groups	Apixaban		Apixaban (or matching apixaban-placebo) 5.0 mg BID or 2.5 mg BID		
	Warfarin		Warfarin sodium 2 mg tablets QD to achieve a target prothrombin time-international normalized ratio [PT-INR] range of 2.0-3.0.		
Endpoints and definitions Primary objective of the study was safety; all efficacy endpoints were secondary endpoints.	Efficacy Endpoint	Efficacy Endpoint	Composite of stroke or systemic embolism during the Intended Treatment Period.		
	Efficacy Endpoint	Efficacy Endpoint	Composite of stroke, systemic embolism, or all-cause death during the Intended Treatment Period.		
	Efficacy Endpoint	Efficacy Endpoint	Composite of MI or all-cause death during the Intended Treatment Period		
	Safety endpoints	Bleeding	The proportion of subjects with major or CRNM bleeding during the treatment period		
Last Subject Last Visit	28-Sep-2009				
Results and Analysis - The primary objective of the study was related to safety.					
Analysis description	Composite of stroke or systemic embolism during the Intended Treatment Period.				
Analysis population and time point description	The key secondary efficacy population consisted of all randomized subjects during the Intended Treatment Period.				
Descriptive statistics	Treatment group		Warfarin	Apix 2.5 mg	Apix 5.0 mg
	Number of subjects		74	74	74
	Stroke/systemic embolism (rate)		4.1	0	0
	95% CI		(1.1, 10.7)	(0.0, 4.8)	(0.0, 4.8)
Effect estimate per comparison	Stroke/systemic embolism		Comparison groups	Apix 2.5 mg vs Warfarin	Apix 5.0 mg vs Warfarin
			Proportion Difference	-4.1	-4.1
			95% CI	(-11.4, 1.1)	(-11.4, 1.1)

Analysis description	Composite of stroke, systemic embolism, or all-cause death during the Intended Treatment Period.			
Analysis population and time point description	The key secondary efficacy population consisted of all randomized subjects during the Intended Treatment Period.			
Descriptive statistics	Treatment group	Warfarin	Apix 2.5 mg	Apix 5.0 mg
	Number of subjects	74	74	74
	Stroke/systemic embolism/all-cause death (rate)	4.1	0	0
	95% CI	(1.1, 10.7)	(0.0, 4.8)	(0.0, 4.8)
Effect estimate per comparison	Stroke/systemic embolism/all-cause death	Comparison groups	Apix 2.5 mg vs Warfarin	Apix 5.0 mg vs Warfarin
		Proportion Difference	-4.1	-4.1
		95% CI	(-11.4, 1.1)	(-11.4, 1.1)
Analysis description	Composite of MI or all-cause death during the Intended Treatment Period			
Analysis population and time point description	The key secondary efficacy population consisted of all randomized subjects during the Intended Treatment Period.			
Descriptive statistics	Treatment group	Warfarin	Apix 2.5 mg	Apix 5.0 mg
	Number of subjects	74	74	74
	MI/all-cause death (rate)	0	0	0
	95% CI	(0.0, 4.8)	(0.0, 4.8)	(0.0, 4.8)
Effect estimate per comparison	MI/all-cause death	Comparison groups	Apix 2.5 mg vs Warfarin	Apix 5.0 mg vs Warfarin
		Proportion Difference	0	0
		95% CI	(-4.9, 4.9)	(-4.9, 4.9)

Safety in the Ongoing, Long-term, Open-label Extension of CV185048. This phase is till ongoing, data presented has a cut-off date of 01-Apr-2011. A total of 2570 subjects received open-label apixaban in the LTOLE. The mean extent of exposure was 25.8 weeks (range 0.1 to 62.6 weeks). Approximately 60% of subjects had completed at least 26 weeks of open-label apixaban at the data cutoff date. The frequencies of deaths (24 [0.9%] subjects), SAEs (7.4%), and AEs leading to open-label treatment discontinuation (1.9%) were well within the ranges for the same AE categories reported for apixaban-treated subjects during the Treatment Periods of these studies.

2.6.1. Discussion on clinical safety

The safety database of the two phase 3 studies and the duration of exposure were considered adequate to investigate the safety of long term administration of apixaban in AF patients. In study CV195030 VKA was used as comparator. As shown in the efficacy section, the maintenance of an INR in the therapeutic range between 2-3 is challenging and can confound any claims of superiority of efficacy or safety. The overall AE profile of apixaban in the Phase 3 studies was similar to that of warfarin in CV185030, and was similar to that of ASA in CV185048. As could be expected, the most common drug-related AEs were related to bleeding. In line with the general results, the frequency of bleeding with apixaban was generally less than that reported with VKA, and comparable to or slightly higher than that reported with ASA.

Reported serious events with outcome **death** were reported less frequently in the apixaban arm compared to VKA or ASA, further supporting the efficacy data. No new safety signals were detected in these studies.

Adjudicated **major bleeding** (adapted from ISTH guidelines) was the primary safety endpoint in both Phase 3 studies. The use of ISTH definitions of bleeding was considered acceptable by the CHMP.

In study CV185030, apixaban was associated with significantly less risk of ISTH major bleeding composite of ISTH major or CRNM bleeding, and for all bleeds indentified by the investigator than VKA. Intracranial bleeding, including all adjudicated hemorrhagic strokes and intracranial bleeds reported by the investigator that were adjudicated as major bleeds, occurred with lower frequency in the apixaban group. These results were in line with the efficacy data showing a benefit for apixaban in reduction of haemorrhagic stroke compared to VKA. Individual components of major bleeding were also reported in lower frequencies in the apixaban group compared to the VKA group, except for intraocular bleedings.

Additional analyses of major bleeding were performed taking INR levels into consideration. Study sites with better INR control still showed numerically better safety results in the apixaban group; although as expected the efficacy is less than sites with worse INR control. Also in study sites divided by quartiles, sites with INR control ≥ Median- Q3 and study sites ≥ Q3, apixaban shows numerically better results and acceptable HR [HR=0.87 (95% CI: 0.70-1.08) and HR=0.7 (95% CI: 0.48-1.03), respectively, but no superiority over VKA. Surprisingly, this difference is driven by difference in bleeding rates reported in the apixaban in addition to the VKA group. The MAH clarified that comparisons across the different TTR quartiles in the apixaban group are invalid as these are grouped by centre control of INR, and not based on patient's characteristics.

The frequency of bleeding events using GUSTO and TIMI criteria were in line with the other bleeding data, providing further reassurance of the safer profile of apixaban compared to VKA.

In Study CV185048 apixaban showed numerically higher bleeding rates than ASA. Analyses of major bleeding showed that the results were driven by the incidence of intraocular bleeding, in addition to a slightly higher incidence of the components of decrease in haemoglobin ≥ 2 gm/dl and transfusion ≥ 2 units. A higher bleeding risk associated with apixaban compared to ASA was not surprising, considering the known pharmacodynamic properties of both agents.

The MAH addressed the results of the subgroup of patients with Demonstrated VKA unsuitable. Data of this subgroup are considered more relevant as it represents patients with prior VKA experience. The other 60% of AVERROES are Expected VKA unsuitable comprising patients who were considered by their physician be unsuitable for VKA for different reasons, without actual prior experience with VKA. However, these 2 subgroups are shown to share the same baseline characteristics and CHADS2 score. The investigator-identified reasons for unsuitability were similar for both treatment groups. These issues support that patients considered to be Expected VKA unsuitable reflect the experiences of physicians with reasonable judgement of the suitability of these patients to VKA treatment, and that they are not actually different from patients with actual prior experience.

The Demonstrated VKA unsuitable comprises three subgroups mainly: patients with a history of bleeding on VKA, discontinued VKA due to bleeding, and combination of bleeding risks. Although not the bigger subgroup (40% of AVERROES), they actually count 2237/5598, which was considered as adequate representation. Results of both efficacy and safety of this subgroup are in line with the general results (Table S9). There is consistent superiority regarding efficacy (stroke and SE); HR of different bleeding endpoints is also in line with the main results. Submitted data support that the general favourable results of apixaban is consistent in VKA naïve and experienced patients.

Table S9 AVERROES outcomes overall, in expected and demonstrated VKA unsuitable subgroups and in patients with bleeding on VKA or at increased bleeding risk

	Total Patients		Stroke/Systemic Embolism		Major Bleeding		All Bleeding		DC Due to Bleeding	
AVERROES	Apix	ASA	n Apix/n ASA with Event	HR (95% CI)	n Apix/n ASA with Event	HR (95% CI)	n Apix/n ASA with Event	HR (95% CI)	n Apix / ASA with Event	HR (95% CI)
Overall	2807	2791	51/113	0.45 (0.32, 0.62)	45/29	1.54 (0.96, 2.45)	325/250	1.30 (1.10, 1.53)	35/20	1.72 (1.00, 2.99)
Expected VKA Unsuitable	1699	1684	34/61	0.55 (0.36, 0.84)	22/14	1.55 (0.79,3.02)	171/124	1.38 (1.09, 1.74)	17/10	1.68 (0.77, 3.67)
Demonstrated VKA Unsuitable	1108	1107	17/52	0.33 (0.19, 0.56)	23/15	1.52 (0.80, 2.92)	154/126	1.22 (0.97, 1.55)	18/10	1.77 (0.82, 3.84)
Bleeding on VKA	269	265	6/18	0.32 (0.13, 0.81)	7/7	0.93 (0.32, 2.64)	59/48	1.18 (0.81, 1.73)	8/3	2.44 (0.65, 9.20)
DC VKA due to bleeding	127	139	2/10	0.21 (0.05, 0.95)	4/4	1.03 (0.26, 4.11)	23/26	0.92 (0.53, 1.62)	3/2	1.51 (0.25, 9.06)
Combination of bleeding risk	502	503	10/30	0.32 (0.16, 0.66)	10/9	1.06 (0.43, 2.62)	59/47	1.23 (0.84, 1.80)	10/8	1.19 (0.47, 3.03)

Further analysis of subgroup of patients CHADS2=1 and physician not recommending VKA showing a HR=3.44 (95%CI: 0.36-33.06) is submitted (Table S10).

Table S10 Bleeding and Stroke / Systemic Embolism in CHADS2 ≤ 1 Patients (CV185048)

	Apixaban n/N (%/year)	ASA n/N (%/year)	HR (95% CI)
All $CHADS_2 \leq 1$ (N=2142)			
Bleeding			
Major	7/1061 (0.57)	4/1072 (0.32)	1.79 (0.52, 6.11)
Major or CRNM	38/1061 (3.13)	37/1072 (3.01)	1.04 (0.66, 1.64)
All bleeding	103/1061 (8.86)	102/1072 (8.64)	1.03 (0.78, 1.35)
Stroke/Systemic embolism	12/1066 (1.00)	19/1076 (1.58)	0.63 (0.31, 1.30)
$CHADS_2$ = 1 and physician does not recommend VKA (only reason) (N = 612)			
Bleeding			
Major	3/294 (0.93)	1/316 (0.28)	3.44 (0.36, 33.06)
Major or CRNM	9/294 (2.83)	14/316 (3.98)	0.70 (0.30, 1.62)
All bleeding	25/294 (8.14)	27/316 (7.88)	1.02 (0.59, 1.76)
Stroke/Systemic embolism	4/294 (1.25)	2/318 (0.57)	2.18 (0.40, 11.91)
$CHADS_2$ = 1 and physician does not recommend VKA (all) (N = 1195)			
Bleeding			
Major	7/589 (1.03)	5/603 (0.72)	1.44 (0.46, 4.54)
Major or CRNM	20/589 (2.98)	27/603 (3.94)	0.76 (0.42, 1.35)
All bleeding	59/589 (9.16)	63/603 (9.55)	0.96 (0.67, 1.37)
Stroke/Systemic embolism	9/590 (1.37)	12/605 (1.76)	0.77 (0.32, 1.83)

Intraocular bleeding. Data from both studies show that apixaban was associated with a higher frequency of intraocular bleeding compared to either VKA or ASA. The frequency of different categories of intraocular bleeding was comparable between treatment groups and does not show a special prevalence in the apixaban group. There is also a slight imbalance in the prevalence of diabetes in study CV185030 which could explain the results at least in this study (among subjects with ISTH major intraocular bleeding 14/32 (43.8%) subjects in the apixaban group and 9/22 (40.9%) subjects in the warfarin group). Further analysis showed no clear relationship between apixaban and specific intraocular pathology. The fact that the overall intraocular bleeding is lower for apixaban is reassuring. The small imbalance found in major intraocular bleeding can be a chance finding. The warning already included in section 4.4 of the SmPC about higher haemorrhage risk is considered adequate to alert about possible bleeding events, including intraocular bleeding events.

The cases of intramuscular bleeding with compartment syndrome, retroperitoneal and pericardial ISTH major bleeding during the Treatment Period in ARISTOTLE and AVERROES are summarised in Table S11 and indicate no concern for the profile of apixaban.

Table S11 Summary of Pericardial, Intramuscular and Retroperitoneal ISTH Major Bleeding During the Treatment Period – Treated Subjects (CV185030 and CV185048)

ARISTOTLE	Apixaban N=9088	Warfarin N=9052
PERICARDIAL BLEED, n (%/yr)	0	0
INTRAMUSCULAR WITH COMPARTMENT SYNDROME BLEED, n (%/yr)	1 (<0.01)	1 (<0.01)
RETROPERITONEAL BLEED, n (%/yr)	2 (0.01)	5 (0.03)
AVERROES	**Apixaban N=2798**	**Aspirin N=2780**
PERICARDIAL BLEED, n (%/yr)	1 (0.03)	0
INTRAMUSCULAR WITH COMPARTMENT SYNDROME BLEED, n (%/yr)	1 (0.03)	0
RETROPERITONEAL BLEED, n (%/yr)	1 (0.03)	0

The comparable event rates for **GI bleeding** reported in study CV185030 between apixaban and VKA is reassuring considering recent concerns with other anti-thrombotics. However, results compared to ASA are less positive with a GI bleeding risk of GI bleedings reported as AEs in 2.7% (apixaban) and 1.8% (ASA), mostly gingival and rectal.

The results generally support that apixaban is associated with a lesser bleeding risk than VKA, however, one major advantage of VKA is the presence of an antidote in case of overdose. In light of the recent concerns with other anti-thrombotics and the management of bleeding in clinical practice, the development of an antidote to apixaban was considered important and the timeline regarding the developments of antidote were agreed with the CHMP and included into the RMP of this product. The MAH submitted data on the value of activated charcoal to decrease absorption. The SmPC sections 4.9 and 4.5 were updated accordingly. The MAH explained that based on available clinical data, the most promising agents appear to be prothrombin complex concentrate (PCC) and factor VII. Two recently published studies already indicate these non-specific prohaemostatic agents are capable of reversing the anticoagulant effect of another anti factor X anticoagulant (rivaroxaban) in healthy volunteers.

The proposal of the MAH to conduct a targeted bleeding questionnaire that will collect information on serious bleeding events and interventions attempted to control the bleeding was considered appropriate. The protocol of the questionnaire was agreed to be assessed by the CHMP before implementing and included with timelines in the RMP as an “additional pharmacovigilance activity”.

The kit for monitoring anti-Xa activity (Rotachrom assay) was not used in clinical decisions during the ARISTOTLE trial, limiting its applicability in the clinical settings. The MAH is not the owner of the Rotachrom assay, and can not guarantee its commercial availability. However, the company discussed alternative assays like that by STAGO. Both assays are currently marketed in all of the EU member states, according to the MAH. The development of assay to measure an anticoagulant activity of apixaban was included together with timelines in the RMP. Importantly, there is the Rotachrom assay, with a LMWH standard, that could be used to assess apixaban exposure (expressed in LMWH units).

Liver-related safety results. The MAH presented an adequate assessment of the liver-related safety aspects associated with apixaban use. This topic was also thoroughly discussed during the initial MAA assessment and apixaban liver profile was considered to be adequately reflected in the SmPC and RMP. The currently presented database is much wider with the addition of the whole phase 3 database in AF, which specifically addresses the AF population. Presented data do not indicate a safety concern for apixaban compared to VKA or ASA. The small imbalance of total bilirubin >1.5xULN in the apixaban group vs. the pooled comparator group (3.3% vs. 2.9% respectively) was in the opinion of the CHMP driven by the presence of a slightly larger percentage of subjects with peak total bilirubin >1.5xULN but ≤2xULN in the apixaban group than in the comparator group. The 8 cases of cholestasis and jaundice of hepatic origin reported in apixaban group did not have a common cause (underlying cancer, cardiac failure, cholecystitis and cholelithiasis). No evidence of clinically significant bilirubin elevation in the apixaban group has been detected and no subgroup seems to be at an increased risk. The assessment of the reported cases of fatal outcome associated with hepatic toxicity was endorsed by the CHMP. One case reported as possibly related to apixaban was previously assessed in a FUM (CV185030-836-9443) and did not lead to any changes in the conclusions. Causality of apixaban in the case CV185048-627-23 reported as possibly related is confounded by the co-administration of other hepatotoxic co-medications and co-morbidities. The one case of fatal outcome reported in non-AF studies was also assessed in the original MAA (CV185047-201-936). In the opinion of the CHMP current data do not point to the need of any further action, other than vigilant monitoring for any liver-safety events in post marketing data assessments. The MAH proposed and the CHMP agreed to add liver injury as a potential risk in the RMP.

The MAH proposed to delete the recommendation to measure LFT before therapy. This was not endorsed. LFTs should be assessed before apixaban administration as the safety profile of apixaban is based on specific exclusion criteria in clinical trials. This is mentioned in the SmPC (*Patients with elevated liver enzymes (ALT/AST >2 x ULN) or total bilirubin ≥1.5 x ULN were excluded in clinical trials*) and should be implemented in clinical practice to ensure a favourable safety profile. In addition, considering that AF is associated with multiple co-morbidities, in particular heart failure and co-administration of multiple medicinal products is expected (some of them are hepatotoxic, e.g., amiodarone, dronedarone) as currently reported in case CV185048-627-23 the measurement of LFT at the beginning of therapy should be advised and this is included in section 4.2 of the SmPC. This would constitute a value for further reference in case LFT elevations are noted during therapy. No regular LFT are considered necessary during long term treatment.

Neurological Adverse events: In the AF Studies 2 cases of Guillain Barre syndrome (GBS) both in the warfarin arm and 1 case of amyotrophic lateral sclerosis ALS in the warfarin arm were observed. There was no evidence of an increased risk for GBS or ALS in the AF population, the ongoing surveillance is considered acceptable. No new cases of GBS or ALS were reported.

Subgroup analysis showed that generally the results of investigated subgroups were in line with the main results. This confirms the favourable profile of apixaban over VKA even in vulnerable subgroups like patients above 75 years, prior stroke, different CHADS2 scores and renal impairment. However patients with diabetes had a HR=0.96 (95% CI: 0.74-1.25), slightly worse results than the general

cohort. The MAH addressed this issue but no obvious differences in patients characteristics were identified which could explain the slightly higher risk of ISTH major bleeding, except may be the lower frequency of patients with BMI ≤ 28 kg/m2 in the diabetic group (33.9% vs 45.9%). For "all bleeding" the results were comparable. Also the results of AVERROES are supportive that no relevant difference is found in the risk of bleeding between diabetic and non-diabetic patients.

No conclusions can be made on females ≤50 years and blacks as the numbers of events were too few. Presented data in severe renal impairment do not strongly indicate a trend of higher risk of bleeding in patients who were administered 5 mg compared to the 2.5 mg, except when counting the ISH major bleedings/CRNM bleedings (7.45% vs.4.22%). The lower dose is currently recommended for this subgroup. Analysis of bleeding in patients with different degrees of hepatic impairment was not submitted as recruited patients were mostly with normal liver functions.

Interactions. In study CV185030, there was an adequate representation of patients co-administered the study drug with ASA (around 38% in each group). The combined use of apixaban and ASA was generally accompanied with a lower bleeding risk than the co-administration of VKA+ASA. There were limited representation of patients co-administered the study drug + ASA + a thienopyridine (around 2% in each group). No conclusions can be made on this triple combination. Current SmPC recommendations are considered adequate to reflect the risk associated with such combinations.

Discontinuations due to AEs. In both studies discontinuation due to AES were numerically lower in the apixaban group compared to the VKA or ASA groups. In study CV185048, more patients discontinued in the apixaban group (n=35; 1.2%) due to bleeding compared to ASA (n=20; 0.7%). In the subgroup Demonstrated VKA unsuitable, the numbers discontinued for bleeding for apixaban versus ASA were 8 versus 3 for subjects with bleeding on previous VKA, 3 versus 2 for subjects who had previously discontinued VKA due to bleeding, and 10 versus 8 for subjects who had previously received VKA and were unsuitable for VKA due to bleeding-related reasons. Not all of the bleeding events resulting in study drug discontinuation were considered clinically important enough to be adjudicated as major bleeding. Whereas there were numerically more apixaban discontinuations for bleeding in patients with bleeding on previous VKA (8 vs. 3), there were a similar number of major bleeding events (7 vs. 7) compared with ASA. The higher discontinuation rate in the ASA group seems to be driven by a higher number of ischemic events related to lower efficacy showed in the ASA group as compared to apixaban.

Long term data. The presented data from the LTOLE does not indicate any new safety issues. The CHMP recommend to submit the final results of this extension phase of the AVERROES to the CHMP when available.

Study CV185067 is a supportive safety study conducted in Japan. It is of little additive value due to the limited database (n=222). Generally results are in line with what is already presented in studies CV185030/048.

2.6.2. Conclusions on the clinical safety

Results of study CV185030 support that apixaban is associated with a significantly better bleeding profile than VKA, but results are less robust when taking different levels of INR control into consideration. The bleeding risk on apixaban is numerically higher than ASA, which is expected. Presented data from study CV185048 is insufficient to assess if apixaban is indeed an eligible alternative to patients unsuitable to VKA, in particular those with a higher bleeding risk. The lack of an antidote to apixaban is still a concern, but the MAH proposed adequate measures to address this issue. Incidence of liver injury was comparable in the studies, which was reassuring considering the available

database. However as this is based on patients with normal liver functions, LFT should be performed prior to treatment to exclude unsuitable patients.

2.7. Pharmacovigilance

Detailed description of the pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the MAH fulfils the legislative requirements.

Risk Management Plan

The MAH submitted an updated risk management plan, which included a risk minimisation plan.

Based on individual case review, the MAH has identified liver injury as an important potential risk with routine PV and risk minimization activities proposed for the AF indication. At the time of the approval of the VTE prevention indication hepatic safety has been thoroughly discussed and was adequately reflected in the SmPC and RMP. The MAH now included liver injury as a potential risk from a precautionary point of view, which will allow to fit in ongoing pharmacovigilance activities in the overall risk management strategy. Furthermore, information on the important identified risks of bleeding and the potential risk of transient elevation of liver tests for the VTE prevention indication already existed in the RMP and are now presented for both indications in the updated RMP.

For the newly introduced potential risk of liver injury, the MAH proposes and the CHMP agreed to the following pharmacovigilance activities:

- Routine PV activities
- Continue blinded external liver expert review of prespecified liver cases
- Comprehensive pivotal study clinical safety program for liver related events (including supplemental case report forms)
- Targeted questions for spontaneous reports of liver events
- Ad hoc follow-up contact with the CHMP for specific severe liver events as needed
- Applicant commits to keep “hepatotoxicity” under close monitoring in the PSUR

Also for the newly introduced potential risk of liver injury with the AF indication, the MAH considered and the CHMP agreed that the routine risk minimization activities are sufficient. Consistent with the recommendation for the indication of VTEp, LFTs will be assessed before apixaban administration.

For the important identified risk of “bleeding,” the MAH will utilize a targeted bleeding questionnaire that will collect information on serious bleeding events and interventions attempted to control the bleeding. The contents of the questionnaire will be submitted for the CHMP assessment before implementing.

The applicant amended the summary of the RMP as follows:

Table 1. Summary of the risk management plan

Table Summary of the Risk Management Plan		
Safety concern	**Proposed pharmacovigilance activities**	**Proposed risk minimisation activities**
Identified Risks		
Bleeding	Routine PV including blinded adjudication of bleeding events in pivotal clinical trials DMC oversight of all ongoing Phase 3 studies The MAH commits to use the haemorrhage SMQ for case identification to describe bleeding in the apixaban PSURs. The MAH commits to provide the final results of the open label extension phase of the AVERROES study (CV185048) to the Health Authorities when it becomes available. Additional Pharmacovigilance with implementation of a Targeted Bleeding Questionnaire for reports of excessive bleeding events received during the post marketing period.	The risk of bleeding will be communicated in the following sections of the product information (SmPC) 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 • Dose reduction in 2 of the 3: elderly, severe renal impairment, low body weight • 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 **Additional Risk Minimisation measures** • Educational materials for Healthcare Professionals • Patient alert cards • Development plan for a reversal agent for apixaban • Development plan for an assay for apixaban
Transient elevation of liver test	Routine PV including: DMC oversight of all ongoing Phase 3 studies Supplemental case report forms for liver events of interest as needed Enhanced monitoring and signal detection in clinical trials External blinded hepatologist panel assessment for targeted hepatic events in clinical studies Ad hoc follow up for specific cases of severe liver events	Communication of elevated liver tests in appropriate product literature (SmPC) • Information regarding patients with elevated liver enzymes in section 4.2 • Warning in section 4.4 • SmPC Section 4.4 Special warnings and precautions for use: Hepatic impairment: Prior to initiating ELIQUIS, liver function testing should be performed. • Listed in section 4.8 • Further information in section 5.2

Table Summary of the Risk Management Plan		
Potential Risk:		
Liver Injury	Routine PV including: DMC oversight of all ongoing Phase 3 studies Supplemental case report forms for liver events of interest as needed Enhanced monitoring and signal detection in clinical trials External blinded hepatologist panel assessment for targeted hepatic events in clinical studies Ad hoc follow up for specific cases of severe liver events	Communication of hepatic impairment in appropriate product literature (SmPC) • Contraindications in section 4.3 • Warning in section 4.4 • SmPC Section 4.4 Special warnings and precautions for use: Hepatic impairment: Prior to initiating ELIQUIS, liver function testing should be performed. • Further information in section 4.2 and 4.2 **Additional Risk Minimisation measures** • Educational materials for Healthcare Professionals • Patient alert cards
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.
Paediatric population	Routine PV Additional information from PIP	Communication of indication in product information (SmPC) • 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 (SmPC) • 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 **Additional Risk Minimisation measures** • Educational materials for Healthcare Professionals • Patient alert cards

Table Summary of the Risk Management Plan		
Hip Fracture Surgery	Routine PV	Section 4.1 of SmPC for the VTEp indication states *"Prevention of venous thromboembolic events (VTE) in adult patients who have undergone elective hip or knee replacement surgery."*
Black / African Americans	Routine PV	There is limited clinical experience of Black/African American subjects in the AF studies with apixaban. All the routine risk minimization measures described for the Important Identified and Potential risks described above apply.
Patients with valvular disease or prosthetic heart valve	Routine PV	Section 4.1 of the SmPC for the AF indication states *"Prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation (NVAF) with one or more risk factors"*
Potential for off-label use	Routine PV Drug utilization study program	Communication of target indication in product information (SmPC) • Clarifying the target patient population in section 4.1 • Warning in section 4.4
Long-term therapy > 3 years	Routine PV	There is limited clinical experience for long-term therapy > 3 years at present. No risk minimization activity is currently required.

The CHMP, having considered the data submitted, was of the opinion that the below additional pharmacovigilance activity in addition to the use of routine pharmacovigilance and the previously agreed additional pharmacovigilance activities detailed in the pharmacovigilance plan of the RMP are needed to investigate further some of the safety concerns:

Description	Due date
A targeted bleeding questionnaire that will collect information on serious bleeding events and interventions attempted to control the bleeding. (MEA)	The protocol to be submitted to the CHMP prior to the implementation on 1Q2013
Submission of the final results of the open label extension phase of the AVERROES study (CV185048) when it becomes available. (MEA)	To be submitted 1Q2018

The following additional risk minimisation activities were required:

The MAH shall provide an educational pack, targeting all physicians who are expected to prescribe/use Eliquis, prior to the launch of the new indication for the prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation with one or more risk factors.

The educational pack is aimed at increasing awareness about the potential risk of bleeding during treatment with Eliquis and providing guidance on how to manage that risk.

The MAH must agree the content and format of the educational material, together with a communication plan, with the national competent authority in each Member State prior to distribution of the educational pack in their territory.

The physician educational pack should contain:

- The Summary of Product Characteristics
- Prescriber Guide
- Patient Alert Cards

The Prescriber Guide should contain the following key safety messages:

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

The Patient alert card should contain the following key safety messages:

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

- Development plan for a reversal agent for apixaban
- Development plan for an assay for apixaban

2.8. User consultation

A full user test was performed on the Package Leaflet (PL) for Eliquis 2.5mg in March and April 2010 during initial marketing authorisation application. A bridging study for PL of Eliquis 2.5mg and 5 mg was performed in October and November 2011 to test the new information regarding the additional indication. The original and newly proposed PLs have a common design and layout. The bridging study successfully tested the key messages relating to the new indication. Key similarities in PL layout and house style have been described. It is therefore agreed that the results of the user consultation with target patient groups on the package leaflet submitted by the MAH 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.*

3. Benefit-Risk Balance

Apixaban is a direct reversible inhibitor of the coagulation factor Xa. Apixaban (2.5 mg film-coated tablets) has been approved for the venous thromboembolic events prophylaxis in patients undergoing total hip or knee replacement surgeries in May 2011. Current application contains grouped variation and a line extension and was submitted for the addition of apixaban 5 mg film-coated tablets to support a new proposed indication of prevention of stroke and systemic embolism in adult patients with AF including those unsuitable for VKA with a recommended dose of 5 mg twice daily. The grouped variation contained a type II variation to add the newly proposed indication and a type IB variation to add a pack size of 168 tablets for Eliquis 2.5 mg film-coated tablets. The initial MAA for the 2.5 tablets already included sufficient pharmacokinetic data to support the marketing authorisation of the 5 mg tablet, as the pharmacokinetics of both tablets were sufficiently investigated in the submitted phase I-III studies for Eliquis 2.5 mg. All studies in this application were relevant for both strengths, and the 2.5 and 5 mg tablets showed linear dose proportionality in pharmacokinetics. To support the new indication the MAH submitted two new phase 3 studies.

Benefits

Beneficial effects

Both clinical studies (CV185030 and CV185048) investigate the primary endpoints of stroke and systemic thromboembolism which are relevant endpoints in the proposed indication and have been accepted in similar studies.

In study CV185030 (ARISTOTLE), non-inferiority of apixaban 5 mg BID versus warfarin (INR target range 2.0-3.0) for the primary efficacy endpoint, was demonstrated for AF patients and at least one additional risk factor for stroke. Superiority of apixaban was then assessed and demonstrated: annual event rates 1.27% versus 1.60%; HR=0.79 [95% CI=0.66; 0.95; two-sided p-value= 0.0114]. Sensitivity analysis confirmed the results. Analysis of stroke showed a lower incidence of hemorrhagic stroke in the apixaban group (0.42%) compared to VKA group (0.84%) and a lesser effect on ischemic stroke (1.74% vs 1.91% respectively), with comparable effect on SE (0.16% vs 0.18% respectively). Apixaban also showed a reduction in all-cause death, a secondary endpoint in the hierarchical testing strategy, HR=0.89 [95%CI= 0.80; 1.00, two-sided p-value=0.0465]. Both cardiovascular deaths [HR=0.89; 95%CI =0.76- 1.04] and non-cardiovascular deaths [HR=0.93; 95%CI=0.77- 1.13] were numerically lower in the apixaban group.

Efficacy results presented in different subgroups were generally consistent with the primary efficacy results for the study. In the subgroup of patients receiving the reduced dose of apixaban (2.5 mg BID), event rates favoured apixaban over VKA (1.43%/yr vs 7.23%/yr respectively, HR=0.19, 95% CI: 0.04, 0.91).

In study CV185048 (AVERROES) apixaban (1.62%/yr) was superior to ASA (3.63 %/yr) [HR=0.45; 95%CI= 0.32- 0.62; two-sided p-value <0.00001] for the prevention of stroke or SE in subjects with AF and at least one additional risk factor for stroke and who were considered not suitable for VKA by the investigators. The majority of the primary outcome events were ischemic or unspecified strokes with 43 (1.53%) events in the apixaban group, versus 95 (3.4%) events in the ASA group [HR = 0.44; 95% CI =0.31, 0.63]. Apixaban [n=2 (0.07%)] was also associated with lower numbers in SE relative to ASA [n=11 (0.39%)].

Results within most subgroups were consistent with the primary efficacy endpoint. Results of patients with demonstrated VKA intolerance (apixaban: 1.73% vs ASA: 4.2%; HR=0.33; 95% CI: 0.19-0.56)

were comparable to those expected to be intolerant (apixaban: 1.79% vs ASA: 3.25%; HR=0.55; 95% CI: 0.36-0.84).

Uncertainty in the knowledge about the beneficial effects

In Study CV185030 (ARISTOTLE) the all cause death was investigated as a secondary endpoint with borderline significance [HR=0.89; 95%CI= 0.80; 1.00, two-sided p-value=0.0465]. Superiority of apixaban was less convincing in situations where INR control was well controlled. In the highest TTRc quartile (> 72.2%) benefit was shown for VKA over apixaban; HR =1.04 (95%CI: 0.82-1.33). Also no superiority was shown for apixaban over VKA in either components of all cause death (cardiovascular and non-cardiovascular deaths).

The general benefit of apixaban in reduction of risk of stroke/SE over VKA varied according to the control of INR: benefit was observed in study sites with INR below the median quartile of INR control (HR=0.78; 95% CI: 0.62-0.98) but lost with INR ≥ median INR (HR=0.81; 95% CI: 0.61-1.08). Using TTRc, apixaban showed favourable results, with HR consistently below 1 (0.77-0.81) but no superiority compared to VKA; 95% CI varying from 0.57-1.07 to 0.52-1.26.

Subgroups. In patients < 65 years, the primary efficacy endpoint was slightly higher in the apixaban group than VKA group (HR=1.16; 95% CI: 0.77- 1.73). The MAH explored three parameters which could have led to worse results in patients <65 years, mainly: patients characteristics, VKA control and apixaban exposure in the ARISTOTLE study. Submitted analyses showed that none of these parameters could have significantly affected the results. This is further supported by data from the AVERROES study. It can be concluded that the trend for worse efficacy results in patients <65 years is probably a chance finding. Reduced efficacy was showed in patients randomized in the EU: HR for stroke/SE= 0.92; (95% CI = 0.56; 1.52) and HR for all cause death= 0.89 (95% CI = 0.68; 1.18). In patients with severe renal impairment generally lower events rates were reported in the apixaban group compared to the warfarin group, with more favourable results in patients administered 2.5 mg BID (n=89) (1.43%/yr vs 7.23%/yr, HR=0.19, 95% CI: 0.04-0.91), than patients administered 5 mg BID (n=48) (HR and upper bound of the associated 95% CI were ≥ 1; 95% CI was wide (0.43-34.72).

The incidence of SE (0.2% and < 0.1%, respectively) and MI (0.3% and 0.2%, respectively) leading to study discontinuation in the apixaban group are slightly higher than the VKA group, and not in line with the efficacy data. This discrepancy occurs as one calculation is based on the investigator's assessment, the other is based on the blinded adjudication by an independent committee. When the same events are assessed by the latter committee, the results of both apixaban and warfarin were comparable. During the period from the end of Intended Treatment Period up to 30 days after the last dose of study medication, a total of 27 stroke/SE events in the apixaban group versus only 10 events occurred in the warfarin group. Further analyses showed that the highest risk of stroke/SE was seen in patients not used to VKA (either VKA naïve, or on apixaban) switching to VKA. Most of the events in these switchers occurred 2 weeks after the switch. These findings support the view that this higher incidence of events is probably due to the difficulties associated with establishing an adequate INR in VKA naïve patients. The late onset of events precludes a rebound hypercoagulability problem. These conclusions can also explain the slight imbalance of mortality (apixaban=53; VKA=48) following discontinuation of these anticoagulants.

In study CV185048 (AVERROES) the definitions used to define VKA unsuitability were quite subjective, and depend on the perception of both the investigator and the patient, making it difficult to ascertain their true unsuitability for VKA treatment. Only 40% of the patients had prior VKA experience. In this subgroup, the actual representation of patients who discontinued VKA due to bleeding was very small (11.9%) and even the majority of these patients reported mainly minor bleedings. The most common

reasons provided for discontinuation of VKA were physician's decision (20.4%), patient's decision (19.7%), and difficulty to control INR (19.1%). Further exploration of the recruited subgroups showed that the investigator gave "$CHADS_2$ score = 1 and physician does not recommend VKA" as a reason for VKA unsuitability for 1195 subjects. Of this group, 612 patients included "physician does not recommend" as the only reason given for VKA unsuitability. In AVERROES, the decision that VKA therapy was unsuitable was made for all 2142 patients with a $CHADS_2$ score of ≤1, whether or not the investigator indicated that a low $CHADS_2$ score was the reason for VKA unsuitability, either as one of multiple reasons or as the sole reason.

The choice of ASA as a valid comparator for all VKA unsuitable patients was not fully supported by the CHMP. According to the Clinical Practice Guidelines of the European Society of Cardiology for the management of patients with AF, ASA could be chosen as an alternative to VKA in patients with a higher risk of bleeding. For the rest of the patients, a combination of ASA and clopidogrel could now be considered, however this combination was not approved at the time the study was initiated.

Discontinuation of double-blind study drug due to bleeding was infrequent for both apixaban (1.2%) and for ASA (0.7%) treatment arms and similar for Expected VKA unsuitable and Demonstrated VKA unsuitable cohorts. The subgroup of patients with CHADS2 =1 and investigator did not recommend VKA was the only subgroup with conflicting results (HR= 2.18; 95% CI; 0.040- 11.91).

Risks

Unfavourable effects

The safety database of the two phase 3 studies consisted of 11,886 patients administered apixaban (5 mg BID or 2.5 mg BID) with a mean double-blind exposure of 1.7 years (ARISTOTLE) and 1.1 years (AVERROES). The overall AE profile of apixaban in the Phase 3 studies was similar to that of warfarin in CV185030 (ARISTOTLE), and to that of ASA in CV185048 (AVERROES). The event rates for bleeding-related AEs were lower for apixaban vs. warfarin (25.2% and 32.7%, respectively). The frequency of bleeding-related AEs for apixaban vs. ASA was similar (10.0% and 9.3%), respectively. The overall frequency of drug-related AEs with onset during the Treatment Period was similar in the apixaban and comparator groups. In CV185030, drug-related AEs were reported for 27.8% of subjects in the apixaban group and 34.2% in the warfarin group. Drug-related AEs reported for ≥2% of subjects in either group included epistaxis (apixaban 5.0%; warfarin 6.1%), haematoma (apixaban 1.4%; warfarin 3.5%), contusion (apixaban 1.7%; warfarin 3.2%), haematuria (apixaban 2.6%; warfarin 3.2%), gingival bleeding (apixaban 1.0%; warfarin 2.1%), and ecchymosis (apixaban 0.9%; warfarin 2.0%). In CV185048, the frequency of drug-related AEs was similar in the two treatment groups (apixaban 16.6%, ASA 16.7%). No drug-related AEs were reported in ≥2% of subjects in either group. During the Follow-up Period, there were no clinically meaningful differences between the apixaban and comparator groups for the frequency of AEs in either study (3.3% in the apixaban group and 3.4% in the warfarin group in CV185030; apixaban 7.2%, ASA 7.8% in CV185048).

In study CV185030 (ARISTOTLE), SAEs with outcome of death were reported in 4.7% and 5.2% in the apixaban and VKA groups respectively. The lower incidence of death in the apixaban was also shown compared to either VKA naïve/experienced patients (apixaban 5.7% vs VKA naïve 6%; and apixaban 4% vs VKA experienced 4.5%). During the treatment period in this study the frequency of SAEs was similar in the overall apixaban (35.0%) and warfarin (36.5%) groups, in warfarin/VKA-naïve subjects (34.5% and 36.0% respectively) and warfarin/VKA-experienced subjects (35.4% and 36.9% respectively). In study CV185048 (AVERROES) SAEs with outcome of death were reported slightly more frequently in the ASA group (4.1%) compared to apixaban (3.3%). The overall frequency of SAEs

with onset during the treatment period was 23.5% in the apixaban group vs. 28.9% in the ASA group. The most common SAEs were cardiac disorders in both studies.

Adjudicated major bleeding (adapted from ISTH guidelines) was the primary safety endpoint in both Phase 3 studies. In study CV18030 (ARISTOTLE), apixaban was superior to warfarin for ISTH major bleeding [HR=0.69; (95% CI= 0.60; 0.80); two-sided p<0.0001 (pre-specified sequential testing strategy). A similar effect was observed for the composite of ISTH major or CRNM bleeding, and for all bleeds indentified by the Investigator [HR=0.68; 95% CI=0.61; 0.75); two-sided p<0.0001, for major/CRNM; HR=0.71; [(95% CI= 0.68; 0.75); two-sided p<0.0001 for all bleeds)]. The frequency of the individual components of major bleeding was generally lower or similar in the apixaban group compared with the warfarin group except intraocular bleeding. In study CV185048 (AVERROES), the observed event rate for adjudicated adapted ISTH major bleeding was 45 subjects (1.41%/year) in the apixaban group and 29 subjects (0.92%/year) in the ASA group [HR=1.54 (95%CI: 0.96-2.45); p=0.07]. Analyses of major bleeding showed that the results are driven by the incidence of introcular bleeding in addition to a slightly higher incidence of the components of decrease in haemoglobin ≥ 2 gm/dl (0.44%/yr and 0.38%/yr respectively) and transfusion ≥ 2 units (0.5%/yr and 0.41%/yr respectively).

Event rates for GI bleeding (including upper GI, lower GI, and rectal bleeding) reported by the investigator and adjudicated as major bleeding in CV185030 (ARISTOTLE) were 1.30%/year in the apixaban group and 1.44%/year in the warfarin group. In study CV185048 (AVERROES), GI bleedings were reported as AEs in 2.7% (apixaban) and 1.8% (ASA), mostly gingival and rectal.

Subgroup analysis did not show relevant differences for the investigated subgroups from the main cohort of either study in the bleeding risk.

Current safety database does not indicate an increased risk for hepatotoxicity associated with apixaban use however LFTs should be assessed before apixaban administration as the safety profile of apixaban is based on specific exclusion criteria in clinical trials.

Uncertainty in the knowledge about the unfavourable effects

In study CV185030 (ARISTOTLE), bleeding was investigated as a secondary endpoint. A better bleeding profile is not consistently shown when INR control is taken into account: in study sites divided by quartiles, sites with INR control ≥ Median, Q3 and study sites ≥ Q3, apixaban showed numerically better results but not consistently superior to VKA [HR=0.87 (95% CI: 0.70-1.08) and HR=0.7 (95% CI: 0.48-1.03), respectively.

Both strengths (2.5 mg BID or 5 mg BID) were administered to patients with severe renal impairment. There was no indication of a higher risk of bleeding in patients administered 5 mg compared to the 2.5 mg, except when counting the ISH major bleedings/CRNM bleedings (7.45% vs. 4.22% respectively). Apixaban was associated with better results in patients randomised in Europe: HR 0.80 [95% CI: 0.62, 1.02] but of a lesser magnitude in the EU member states analysis HR 0.90 (95% CI: 0.66, 1.22), in line with the efficacy data. Patients with diabetes had a HR=0.96 (95% CI: 0.74-1.25), slightly worse than the general cohort. No obvious differences in patients characteristics could explain this results except may be the lower frequency of patients with BMI ≤28 kg/m2 in the diabetic group (33.9% vs. 45.9%). For "all bleeding" the results were comparable. Also, in the results of AVERROES no relevant difference was found in the risk of bleeding between diabetic and non-diabetic patients.

In study CV185048 (AVERROES), the "demonstrated VKA unsuitable" included three specific subgroups (bleeding on VKA, discontinued VKA due to bleeding, and combination of bleeding risks). In each of these 3 subgroups, apixaban demonstrates a favourable benefit-risk profile compared to ASA. Also

results of the subgroup of patients with CHADS2=1 and physician not recommending VKA showed the highest HR =3.4 (95%CI: 0.36-33.06). However, the number of endpoints was too few to allow any conclusions. Further analysis shows that the risk in the subgroup of CHADS≤1 [Major bleeding HR 1.79 (0.52, 6.11)] is in line with the general results of the study.

Data from both studies show that apixaban was associated with a higher frequency of intraocular bleeding compared to either VKA or ASA. In study CV185030 (ARISTOTLE), intraocular bleeding adjudicated as major bleeding were reported in 32 cases with apixaban vs 22 cases reported with VKA; in study CV185048: 6 cases (0.21%) in the apixaban group vs 0 cases in the ASA group. The frequency of different categories of intraocular bleeding was comparable between treatment groups and does not show a special prevalence in the apixaban group.

Benefit-risk balance

Importance of favourable and unfavourable effects

Apixaban was associated with significant reduction in the risk of stroke and SE compared to VKA. The results are clinically relevant considering that VKA is the standard of therapy in this population. Apixaban also compares favourably with available published data of other new anti-thrombotics, like dabigatran and rivaroxaban, but direct comparison is lacking. A reduction in the incidence of haemorrhagic stroke appears to be the main driving endpoint for the benefit, highlighting that apixaban is probably a safer alternative to VKA, rather than a more effective one. Apixaban was associated with a significant reduction in all cause death, but superiority is lost in subgroups with better INR control. A significantly lower incidence of major bleeding is observed with apixaban compared to VKA, which further supports the favourable profile of apixaban. Again results are of lower significance when INR is well controlled. This questions an extra benefit of apixaban in patients who have well controlled INR, though still in these patients apixaban can offer other advantages like the absence of monitoring. It is reassuring that most of the investigated subgroups showed a consistent benefit over VKA regarding the bleeding profile, in particular elderly patients or patients with renal impairment. Importantly also there was no increased risk of GI bleeding compared to VKA, as was reported with dabigatran.

Considering the results of study CV185030 (ARISTOTLE) the superiority of apixaban over ASA in reducing the risk of stroke/SE shown in AVERROES was not surprising. Most of the recruited patients were not shown to have a high bleeding risk on VKA. In addition, 60% of the recruited patients did not even have prior VKA experience questioning the external validity of the study results. A non-significant higher rate of bleeding was reported in the apixaban group compared to ASA, which is generally reassuring. Further analysis of the results showed that both these subgroups (VKA experienced or naïve) share common characteristics, stroke risk and more importantly the benefit risk balance, supporting that the results of VKA experienced can be extrapolated to VKA naïve patients. However, the decision that these patients are not eligible for VKA in the first place is a subjective decision that is not clearly defined. The main reasons why these patients were considered to be intolerant to VKA was inability/unlikely to obtain regular INR (42%) or patient refusal to be administered VKA (37%). In a strictly medical sense, a label including "patients unsuitable for VKA" as proposed by the MAH would not specifically include the above groups, but more importantly would be referring to patients who have discontinued VKA due to bleeding. These patients constitute only 266 patients in AVERROES. Patients who are unsuitable to VKA due to increased bleeding risk have not been specifically studied. Thus, the data in itself are not robust enough to support the inclusion of patients who are unsuitable to VKA in the indication.

There is a slightly higher rate of stroke/SE and death recorded in the apixaban group compared to the VKA in the 30 days period following study drug discontinuation. Analysis showed that the highest risk of stroke/SEE is seen in patients not using VKA (either VKA naïve, or on apixaban) switching to VKA. Most of the events in these switchers occurred 2 weeks after the switch, supporting that this is probably due to the difficulties associated with establishing an adequate INR in VKA naïve patients. The late onset of events precludes a rebound hypercoagulability problem. These conclusions can also explain the slight imbalance of mortality (apixaban=53; VKA=48) following discontinuation of these anticoagulants. The proposals in section 4.2 of the SmPC addressing the switch were considered by the CHMP acceptable.

Benefit-risk balance

In general, the benefit risk of apixaban in patients with AF is favourable. Apixaban was associated with a significantly lesser risk of stroke/SE, all cause death and bleedings compared to VKA. The inclusion of patients defined as VKA unsuitable was however, not supported.

Discussion on the benefit-risk balance

Apixaban has shown to be a beneficial anti-thrombotic for the prevention of stroke/SE in AF patients, with no extra burden in the bleeding risk compared to VKA. Benefits were smaller in subgroups with better INR control, but this is still an acceptable effect considering that apixaban offers other advantages over VKA, like a more favourable interaction profile and no need for routine monitoring. The main disadvantage of apixaban compared to VKA is still the lack of a specific antidote or a method to monitor anticoagulant activity (which can be necessary in emergency situations), disadvantages also shared with dabigatran and rivaroxaban. This can clearly constitute a major concern in clinical practice, especially with chronic use as in AF patients. The MAH has presented some data to show that apixaban absorption can be decreased by charcoal and elimination could be improved by dialysis. In addition, the MAH submitted adequate plans for the development of a specific antidote and they were included in the RMP for apixaban. In addition, the MAH agreed to use of a questionnaire to document the management of bleeding in clinical practice. The protocol for the questionnaire will be submitted for the assessment of the CHMP and was included as additional pharmacovigilance activity in the RMP. Regarding the monitoring of the anticoagulant activity, the MAH was requested to develop an assay, and the details of the development plans were also included in the RMP for apixaban. Importantly, the Rotachrom assay with a LMWH standard is available in the EU and that could be used to assess apixaban exposure (expressed in LMWH units).

Results pertaining to comparisons of apixaban and VKA in all cause death and bleeding were presented in the SmPC.

The use of apixaban as an alternative to patients unsuitable to VKA was not supported, as the criteria defining this unsuitability was considered by the CHMP as too subjective. Actual representation of patients who discontinued VKA due to bleeding was very limited. The main study results were included in the labelling.

The transition of patients on apixaban to other anti-coagulants was adequately addressed in the SmPC.

Further analysis of benefits and bleeding risks in certain subgroups which were originally shown to be of concern is currently seen to be in line with the general results. This concerns patients below 65 years old and diabetic patients. Analysis of data showed that patients with severe renal impairment should be administered the lower dose and this was included in the SmPC.

Assessment of liver safety data did not indicate the need of further action. The vigilant monitoring as a potential risk was endorsed. A detailed report was submitted analyzing all available safety data with reassuring conclusions. However, this wide database excluded patients with any form of hepatic impairment. This information was included in the SmPC along the recommendation to perform the liver function tests before administration to ensure safe use.

During the assessment of this application some important GCP issues were raised in ARISTOTLE study regarding possible errors in medication dispensing, integrity of the interactive voice responses system and the discrepancies between the trial database and the data collected on the eCRF. All the concerns were convincingly explained by the MAH and the CHMP agreed with the conclusions of the GCP inspection to consider ARISTOTLE study to be GCP compliant.

4. Recommendations

The CHMP, having considered the application, recommended by consensus the granting of an extension of the Marketing Authorisation for Eliquis concerning a new 5 mg strength.

In addition, based on the CHMP review of data on quality, safety and efficacy, the CHMP recommends by consensus the variations to the terms of the Marketing Authorisation, concerning the following changes:

1

Variation(s) requested		**Type**
B.II.e.5	Change in pack size of the finished product	IB

Addition of a new pack size for Eliquis 2.5mg film-coated tablets of 168 film coated tablets (12 blisters of 14 film-coated tablets each).

2

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

Update of the SmPC to include a new indication for the new strength (5 mg) and for 2.5 mg strength: Prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation (NVAF), with one or more risk factors, such as prior stroke or transient ischaemic attack (TIA); age ≥ 75 years; hypertension; diabetes mellitus; symptomatic heart failure (NYHA Class ≥ II). Furthermore, the MAH took this opportunity to update information of the local representatives in the Package Leaflet.

The above CHMP recommendation is subject to the following new conditions:

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

The MAH shall provide an educational pack, targeting all physicians who are expected to prescribe/use Eliquis, prior to the launch of the new indication for the prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation with one or more risk factors.

The educational pack is aimed at increasing awareness about the potential risk of bleeding during treatment with Eliquis and providing guidance on how to manage that risk.

The MAH must agree the content and format of the educational material, together with a communication plan, with the national competent authority in each Member State prior to distribution of the educational pack in their territory.

The physician educational pack should contain:

- The Summary of Product Characteristics
- Prescriber Guide
- Patient Alert Cards

The Prescriber Guide should contain the following key safety messages:

- Details of populations potentially at higher risk of bleeding
- Recommendations for dose adjustment in at risk populations, including renal or hepatic impairment patients
- Guidance regarding switching from or to Eliquis treatment
- Guidance regarding surgery or invasive procedure, and temporary discontinuation
- Management of overdose situations and haemorrhage
- The use of coagulation tests and their interpretation
- That all patients should be provided with a Patient alert card and be counseled about:

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

The Patient alert card should contain the following key safety messages:

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

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

Not applicable.