Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

AusPAR Attachment 2

Extract from the Clinical Evaluation Report for Apixaban

Proprietary Product Name: Eliquis

Sponsor: Bristol-Myers Squibb Pty Ltd

Date of first round CER: 6 July 2012

Date of second round CER: 7 November 2012

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and Ageing, and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <http://www.tga.gov.au>.

About the Extract from the Clinical Evaluation Report

- This document provides a more detailed evaluation of the clinical findings, extracted from the Clinical Evaluation Report (CER) prepared by the TGA. This extract does not include sections from the CER regarding product documentation or post market activities.
- The words [Information redacted], where they appear in this document, indicate that confidential information has been deleted.
- For the most recent Product Information (PI), please refer to the TGA website <http://www.tga.gov.au/hp/information-medicines-pi.htm>.

Contents

List of abbreviations

Abbreviation	Meaning
AE	adverse event
ACC	American College of Cardiology
ACCP	American College of Chest Physicians
ACS	acute coronary syndrome
AF	atrial fibrillation
AHA	American Heart Association
ALT	alanine aminotransferase
ASA	acetyl salicylic acid
AST	aspartate aminotransferase
AXA	anti-factor Xa activity
AT	anti-thrombin
AUC	area under curve
BID	twice daily
BMI	body mass index
BMS	Bristol-Myers Squibb
BP	blood pressure
CABG	coronary artery bypass graft
CEC	clinical events committee
CHADS2	cardiac failure, hypertension, age, diabetes and stroke score
CHF	congestive heart failure
CI	confidence interval
CK	creatine kinase
CRNM	clinically relevant non-major bleeding
CT	computed tomography

Abbreviation	Meaning
DBP	diastolic blood pressure
DILI	drug induced liver injury
DMC	Data Monitoring Committee
DVT	deep venous thrombosis
ECG	electrocardiogram
ESC	European Society of Cardiology
ESI	events of special interest
ER	Exposure response
FCT	film coated tablet
FXa	Factor Xa
GCP	Good Clinical Practice
GGT	gamma glutamyltransferase
GP	glycoprotein
GUSTO	Global Use of Strategies to Open Occluded Coronary Arteries
HepBsAg	hepatitis B surface antigen
Hct	haematocrit
Hgb	haemoglobin
HR	hazard ratio
ICH	International Conference on Harmonisation
IIV	inter-individual variance
INR	international normalised ratio
IRB	institutional review board
ITT	intention to treat
ISTH	International Society on Thrombosis and Hemostasis
IVRS	Interactive Voice Response System

Abbreviation	Meaning
ka	absorption rate constant
LDH	lactate dehydrogenase
LFT	liver function tests
LLQ	lower limit of quantitation
LMWH	low molecular weight heparin
LVEF	left ventricular ejection fraction
MA	marked abnormality
MB	major bleeds
MedDRA	Medical Dictionary for Regulatory Activities
MI	myocardial infarction
MRI	magnetic resonance imaging
MS	mass spectrometry
NI	non-inferior
NSAIDs	non-steroidal anti-inflammatory drugs
NVAF	non-valvular atrial fibrillation
NYHA	New York Heart Association
PCI	percutaneous coronary intervention
PD	pharmacodynamic
PE	pulmonary embolism
PK	pharmacokinetic
PO	by mouth
POC	point of care
PPK	population pharmacokinetic
QC	quality control
QD	once daily

Abbreviation	Meaning
QTc	corrected QT interval
RBC	red blood cell count
RR	relative risk
RRR	relative risk reduction
SAE	serious adverse event
SBP	systolic blood pressure
SC	subcutaneous
SE	systemic embolism
TEAE	treatment emergent adverse event
TIA	transient ischaemic attack
TIMI	thrombolysis in myocardial infarction
TTR	time in therapeutic range
UFH	unfractionated heparin
ULN	upper limit of normal
ULQ	upper limit of quantitation
US	ultrasound
VKA	vitamin K antagonist
VTE	venous thromboembolism
TIA	transient ischaemic attack
WBC	white blood cells
WOCBP	women of childbearing potential

1. Clinical rationale

Apixaban is an orally active, potent, direct, selective inhibitor of coagulation factor Xa. It directly and reversibly binds to the active site of FXa and exerts anticoagulant and antithrombotic effects by reducing the conversion of prothrombin to thrombin. At a dose of 2.5 mg PO BID, it has been approved for VTE prophylaxis in patients who have undergone elective knee and hip replacement. As an alternative to warfarin, it is also being developed as an anticoagulant for prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation.

Atrial fibrillation is a common cardiac arrhythmia associated with a five-fold increase in the risk of stroke (1,2). In patients with AF, anticoagulant agents such as warfarin or other VKAs (see note below) are recommended for prevention of stroke and systemic embolisation (3). These compounds exert their anticoagulant effect by antagonizing the vitamin K-dependent clotting cycle and they are monitored by means of the international normalized ratio (INR). Current therapies for stroke prevention include warfarin, ASA and more recently, dabigatran. Antiplatelet therapy with low dose aspirin is recommended in patients with AF who are at low risk for stroke. ASA is also recommended for some patients at moderate risk for stroke if they are at high risk of bleeding, or in patients who have no access to adequate anticoagulation monitoring (4). Warfarin provides effective protection against stroke but it is not prescribed in up to 50% of AF patients, due mainly to bleeding concerns, low risk of embolus, difficulty of use, or patient refusal. Moreover, INRs are in the therapeutic range in only ~60% of the time during chronic warfarin therapy (5). An oral FXa inhibitor which prevents stroke and reduces bleeding and death with a similar efficacy and safety profile compared with warfarin would significantly improve the long-term care and outcome of patients with AF.

Note: For simplicity, 'warfarin' therapy is assumed to include other VKAs when used in this evaluation to describe non-study drug anti-coagulation therapy.

2. Contents of the clinical dossier

2.1. Scope of the clinical dossier

The submission contained the following clinical information:

Module 5

- 3 clinical pharmacology studies, including 3 that provided pharmacokinetic data and 1 that provided pharmacodynamic data.
- 1 population pharmacokinetic analyses.
- Two pivotal Phase 3 efficacy/safety studies (CV185030 and CV185048) and one supportive Phase 2b study (CV185068) were conducted:
- Module 1- Application letter, application form, draft Australian PI and CMI, FDA-approved product label, European Summary of Product Characteristics.

Module 2

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

Additional Materials provided by Sponsor

- Supplementary data for Apixaban ADOPT study, CV185036.

- Apixaban (BMS-562247) Module 2.7.2 Erratum to Summary of the Clinical Pharmacology.
- Report into suspected misconduct at investigator site 1200 in China during Apixaban ARISTOTLE study, CV185030.

2.1.1. Guidance

The proposed Phase 3 program, including apixaban dose selection, comparator selection, efficacy and safety endpoints, and statistical analyses, were discussed in depth with the FDA and the EMEA progressively. Pre-submission meetings were held with the FDA and EMEA over 2005-2011, and with the TGA on 26 Sep 2011.

2.2. Paediatric data

The submission did not include paediatric data.

2.3. Good clinical practice

All studies were conducted according to ICH GCP guidelines and complied with the principles of the Declaration of Helsinki. The studies were monitored by BMS and Pharmaceutical Product Development (PPD) Inc.

3. Pharmacokinetics

3.1. Studies providing pharmacokinetic data

Table 1 shows the studies relating to each pharmacokinetic topic.

Table 1. Submitted pharmacokinetic studies.

PK Topic	Subtopic	Study ID	Primary aim of the study
PK in health adults	General PK single dose multi-dose	 N/A Study CV185074	 Assess the multi-dose PK of apixaban and rivaroxaban
	Bioequivalence† single dose multi-dose	 Study CV185029 N/A	 Assess the oral bioavailability of apixaban solution formulation relative to tablets.
	Food Effect	N/A	
PK in special populations	Target population § single dose multi dose	 N/A N/A	
	Hepatic impairment	Study CV185025	Assess stable hepatic impairment on the PK of apixaban
	Renal impairment	N/A	
	Neonates/infants/ children/adolescents	N/A	
	Elderly	N/A	
	Other special populations	PPK Study	To describe the PK of apixaban in healthy subjects and individuals with non-valvular AF
Genetic/ gender-related PK	Males versus females.	PPK study	See above.
PK Interactions	None	None	
Population PK Analyses	Healthy subjects	PPK Study	See above.
	Target Population	PPK Study	See above
	Other	N/A	

† Bioequivalence of different formulations.
§ Subjects who would be eligible to receive the drug if approved for the proposed indication.

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

3.2. Summary of pharmacokinetics

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

3.2.1. Pharmacokinetics in healthy subjects

Study CV185074 examined the multi-dose PK of apixaban and rivaroxaban following oral administration in healthy subjects. Apixaban and rivaroxaban achieved steady-state exposure by Day 4, based on an assessment of trough (Cmin) concentrations. Apixaban exhibited a relatively longer half life (t½) than that of rivaroxaban (8.65 and 7.89 hours, respectively). The more frequent dosing (BID vs. once daily) and relatively longer half life of apixaban compared to rivaroxaban resulted in the steady state plasma concentration peak to trough ratio (Cmax/Cmin) of apixaban being smaller than that of rivaroxaban; there was an approximate 3.6-fold higher geometric mean Cmax/Cmin ratio observed for rivaroxaban than for apixaban (3.60; 90% CI 2.82 - 4.61). The lower Cmax/Cmin ratio, for apixaban implies that, at steady state, the subjects exposure to apixaban is more consistent over a 24 hour period than for rivaroxaban. Possibly suggesting that apixaban may have an improved safety profile compared to rivaroxaban.

3.2.1.1. Absorption

No new information.

3.2.1.1.1. Absolute bioavailability

Not applicable.

3.2.1.1.2. Bioavailability relative to an oral solution or micronised suspension

Study CV185029 examined the bioavailability of apixaban solution formulation relative to apixaban Phase 3 tablets. The bioavailability of apixaban of the solution and tablet formulations were similar (Frel=105%), suggesting that the solution and tablet formulations may be used interchangeably.

3.2.1.1.3. Bioequivalence of clinical trial and market formulations

The Phase 3 and commercial tablets are identical in their core composition. The differences are in the shape and dimensions of the tablet and the non-functional film coat composition (change in colorant composition) and the sponsor does not expect that these changes will impact on product performance. Therefore, no studies have been provided that directly examine the Phase 3 and commercial tablets and in their stead the sponsor has provided justification for not submitting a bioequivalence study. This document provides information on the *in vitro* dissolution of the Phase 3 and commercial formulations at three pHs, which indicates that the formulation changes from the Phase 3 to the commercial tablet have minimal impact on the tablet dissolution profile and thus support bioequivalence of the two formulations. In addition, the sponsor provides evidence that different formulations with similar dissolution profiles are bioequivalent.

Table 2. Results for statistical analysis for abixaban Cmax, AUC_{0-t}, and AUC_{inf} in the relative bioavailability study (CV185024)

Pharmacokinetic Parameter	Formulation	Adjusted Geometric Mean	Ratios of Geometric Means		
			Ratio	Point Estimate	90% CI
Cmax (ng/mL)	A	101.5			
	B	88.3	B vs A	0.870	(0.788, 0.960)
	C	109.0	C vs A	1.074	(0.973, 1.185)
AUC(INF) (ng.h/mL)	A	1078.8			
	B	1027.9	B vs A	0.953	(0.891, 1.019)
	C	1160.9	C vs A	1.076	(1.006, 1.151)
AUC(0-T) (ng·h/mL)	A	1045.4			
	B	988.5	B vs A	0.946	(0.883, 1.013)
	C	1123.3	C vs A	1.075	(1.003, 1.151)

Source: CV185024 Clinical Study Report[7]

A = Apixaban Phase 2 tablet (86% dissolution) 2x 2.5 mg (reference formulation), n=21
B = Apixaban Phase 2 tablet (77% dissolution) 2x2.5 mg (test formulation 1), n=20
C = Apixaban Phase 3 tablet (89% dissolution) 2x2.5 mg (test formulation 2), n=20

The % dissolution was the 30 min value using the method described in Table 1.2C of Module 2.7.1[6].
Statistical analysis for subjects with an evaluable PK profile for the reference (Treatment A) and at least 1 of the test treatments (B or C) were included.

As noted by the sponsor, in the European Union, comparative dissolution on two batches is sufficient to justify a change in tablet coating weight based on the *Guideline on Dossier Requirement for Type IA and IB Notification*. Following U.S. *Scale-Up and Post-Approval Changes (SUPAC)* guideline, the differences identified above are classified as a Level 1 change. This level of the change in film coating for the tablets is considered to be small by other regulatory agencies (including signatories to International Conference on Harmonization). For example, in Canada, the draft *Post-Notice of Compliance Changes* document only requires comparative dissolution using the QC method to support change in composition of a non-functional coating. Comparative *in vitro* dissolution profiles are therefore sufficient to establish the expected bioequivalence between the Phase 3 and commercial tablets of apixaban.

Therefore, the justification for not providing a bioequivalence study is justified.

3.2.1.1.4. Bioequivalence of different dosage forms and strengths

Study CV185029 also examined the bioequivalence of the solution formulation (10 mg / 25 mL) relative to apixaban Phase 3 tablets (10 mg as 2 x 5 mg tablets). In this study the 90% CIs for AUC0-t and AUCinf were within the equivalence limits (80-125%) indicating equivalent absorption of both the tablet and solution formulations of apixaban. For Cmax however, although the 90% CI extended just beyond the usual equivalence criteria (75-126%), the point estimate for Cmax was close to 1, suggesting that the Cmax for both formulations was similar.

3.2.1.1.5. Bioequivalence to relevant registered products

No new information was provided regarding the bioequivalence of the registered 2.5 mg tablet and the proposed 5 mg tablet.

3.2.1.1.6. Influence of food

No new information was provided.

3.2.1.1.7. Dose proportionality

No new information was provided.

3.2.1.1.8. Bioavailability during multiple-dosing

No new information was provided.

3.2.1.1.9. Effect of administration timing

The population PK (PPK) study, which examined data from 4385 healthy subjects and patients with AF indicated that administration of apixaban in the evening resulted in a 43% decrease in absorption rate constant (ka) relative to administration in the morning or afternoon.

3.2.1.2. Distribution

No new information was provided.

3.2.1.3. Metabolism

No new information was provided.

3.2.1.4. Excretion

No new information was provided.

3.2.1.5. Intra- and inter-individual variability of pharmacokinetics

Study CV185074 provides evidence that the inter-subject variability, as indicated by a lower CV%, was smaller for apixaban across all PK parameters compared with rivaroxaban.

3.2.2. Pharmacokinetics in the target population

No information regarding the PK in the target population was provided in the Phase I and Phase II studies relating to the new indication. However, the pivotal Phase 3 trial ARISTOTLE (CV 185030, of this report) provided PK data on the peak and trough concentrations following 2.5 mg and 5 mg doses of apixaban in 958 patients with AF. The peak geometric mean peak/ trough ratios were approximately 1.33 and 1.54 for the 2.5 and 5 mg BID doses, respectively.

Compared to 2.5 mg BID dosing in healthy subjects (Cmax/Cmin ratio = 4.7,) the results indicate that exposure to apixaban was more consistent over a 24 hour period in patients with AF than in healthy subjects.

In addition, the PPK study, which included data from 3071 patients with AF from both ARISTOTLE and an earlier Phase II study (CV 185067) not included in the current application, indicated that AF patients had decreased apixaban CL/F (13.9%) compared to non-Asian healthy subjects.

3.2.3. Pharmacokinetics in other special populations

3.2.3.1. Pharmacokinetics in subjects with impaired hepatic function

Study CV185025, which examined the PK of a single oral 5 mg dose of apixaban in patients with mild and moderate hepatic impairment and healthy subjects indicated that although there were slight decreases in Cmax and increases in AUC in hepatically impaired patients compared to healthy subjects these differences did not achieve significance. No PK data was provided concerning patients with severe hepatic impairment.

3.2.3.2. Pharmacokinetics in subjects with impaired renal function

No new information was provided.

3.2.3.3. Pharmacokinetics according to age

The PPK analysis indicated that the subject's age was a predictive covariate on CLNR/F. For example, a 50 year old subject would have a 11.9% increase and an 80 year old subject would have a 8.5% decrease in CLNR/F relative to the typical 65 year old subject.

3.2.3.4. Pharmacokinetics related to genetic factors

In addition, gender was also a predictive covariate of CLNR/F with female subjects having a 21.6% reduction in CLNR/F relative to male subjects.

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

The PPK study also identified that body weight and patient population were found to influence Vc/F. The effect of baseline body weight on Vc/F was less than directly proportional with a 23.3% reduction for a 50 kg subject and a 19.2% increase for a 90 kg subject relative to the typical 70 kg individual. Patients with recent ACS had an 18% decrease in Vc/F while patients with AF had a 4% decrease in Vc/F relative to healthy subjects.

In addition, a number of covariate effects influenced CL/F. Asian race, AF patients, recent ACS patients, and strong or moderate CYP3A4/p-gp inhibitors resulted in decreases of 11.9%, 13.9%, 21.5%, and 14.6%, respectively, compared to non-Asian subjects, healthy subjects, and subjects that did not receive concurrent administration of a CYP3A4/p-gp inhibitor.

3.2.4. Pharmacokinetic interactions

No new information was provided.

3.3. Evaluator's overall conclusions on pharmacokinetics

Following 4 days of oral dosing of 2.5 mg (Q12h) apixaban in healthy subjects the Cmax, Tmax, AUC_{TAU} and t½ of apixaban were 80.5 ng/mL, 2 hours, 527 ng.h/mL and 8.65 hours, respectively.

The bioavailability of 10 mg of the solution and tablet formulations were similar (Frel=105%), suggesting that the solution and tablet formulations may be used interchangeably.

The AUC of 10 mg of the solution and tablet formulations were equivalent, whereas the Cmax was similar.

No studies directly compared apixaban PK in patients with non-valvular atrial fibrillation and healthy subjects.

Mild and moderate hepatic impairment did not significantly affect the PK of a single 5 mg oral dose of apixaban.

No studies examined the PK of apixaban in subjects with severe hepatic impairment.

PPK analysis indicated that the subject's age and gender were predictive covariates on CLNR/F. Body weight and patient population were found to influence Vc/F and Asian race, AF patients, recent ACS patients, and strong or moderate CYP3A4/p-gp inhibitors resulted in decreased CL/F compared to non-Asian subjects, healthy subjects, and subjects that did not receive concurrent administration of a CYP3A4/p-gp inhibitor.

4. Pharmacodynamics

4.1. Submitted pharmacodynamic studies.

Table 3 shows the studies relating to each pharmacodynamic topic.

Table 3. Studies relating to pharmacodynamics.

PD Topic	Subtopic	Study ID	Primary aim of the study
Primary Pharmacology	Anti-FXa effect	Study CV185074	To assess the multi-dose anti-FXa activity of apixaban in healthy subjects.
Secondary Pharmacology	NA	NA	
Gender other genetic and Age-Related Differences in PD Response	Effect of gender	N/A	
PD Interactions	None provided.	None	
Population PD and PK/PD analyses	Healthy subjects	N/A	Characterisation of the relationships between apixaban plasma concentration and anti-FXa activity.
	Target population	N/A	See above.

§ Subjects who would be eligible to receive the drug if approved for the proposed indication.
‡ And adolescents if applicable.

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

4.2. Summary of pharmacodynamics

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

4.2.1. Mechanism of action

Apixaban is a reversible, direct and highly selective inhibitor of factor Xa. It does not require antithrombin III for antithrombotic activity. Apixaban inhibits free and clot-bound factor Xa, and prothrombinase activity. Apixaban has no direct effects on platelet aggregation, but indirectly inhibits platelet aggregation induced by thrombin. By inhibiting factor Xa, apixaban prevents thrombin generation and thrombus development.

4.2.2. Pharmacodynamic effects

4.2.2.1. Primary pharmacodynamic effects

Study CV185074 examined the multiple-dose PD (anti-Factor Xa activity) of apixaban and rivaroxaban following oral administration in healthy subjects. The results for anti-FXa activity were similar to the results for rivaroxaban and apixaban plasma concentrations with a median Tmax of 2 hours following treatment with either compound. The geometric mean peak anti-FXa

activity was approximately 2.5-fold higher following rivaroxaban than following apixaban treatment, whereas the geometric mean trough anti-FXa activity for rivaroxaban was about 71% of that for apixaban. There was a close temporal relationship between changes in apixaban and rivaroxaban plasma concentrations and changes in AXA, with no delay of onset observed. For both compounds, a linear relationship between plasma concentration and AXA was observed. Thus, the difference in AXA peak to trough ratio for rivaroxaban compared to apixaban closely followed what was observed for plasma concentration and the geometric mean anti-FXa activity peak to trough ratio was approximately 3.5-fold higher following rivaroxaban than following treatment apixaban. When for apixaban this ratio was calculated over a 24-hour interval, a similar result was obtained (geometric mean Peak/Trough anti-FXa ratio over 24 hours of 4.7 [CV% 19.1]). The between-subject variability in Peak/Trough anti-FXa ratio was smaller for apixaban, as shown by a lower CV%. The geometric mean anti-FXa activity $AUC_{0\text{-}24h}$ for apixaban (13.3 IU.h/mL [CV% 22%]) was slightly lower than the AUC_{TAU} for rivaroxaban. Rivaroxaban anti-FXa t½ could not be estimated because anti-FXa activities in the terminal phase were below the lower limit of quantification of the anti-FXa assay.

In the pivotal Phase 3 trial ARISTOTLE (CV 185030) following apixaban 2.5 mg BID and 5 mg BID dosing, the mean peak/trough anti-FXa activity ratios were approximately 1.4 and 1.44, respectively. As in the PK studies (described in the "PK in the target population" section of this report) the Cmax/Cmin ratios in healthy subjects and patients with AF indicated that anti-FXa activity was more consistent over a 24 hour period in the patients with AF.

PPK analysis indicated that the relationship of apixaban exposure with AXA could be described by a linear model. However, this model systematically over-predicted AXA at lower apixaban concentrations and under-predicted AXA at higher apixaban concentrations for the subjects in CV185030.

Study 185025, which examined the PD of a single oral 5 mg dose of apixaban in patients with mild and moderate hepatic impairment and healthy subjects indicated that the effects of apixaban on INR, aPTT and anti-Xa activity were not affected by either mild or moderate hepatic impairment.

4.2.2.2. Secondary pharmacodynamic effects

No new data provided.

4.2.3. Time course of pharmacodynamic effects

Study CV 185030 indicated that following apixaban 2.5 mg BID and 5 mg BID in patients with AF peak anti-FXa activity occurred 2-5 hours post-dose, whereas, trough activity occurred 10-14 hours post-dose.

4.2.4. Relationship between drug concentration and pharmacodynamic effects

In the pivotal Phase 3 trial ARISTOTLE (CV 185030) there appeared to be a good correlation between anti-FXa activity and apixaban plasma concentration for the 2.5 mg BID and 5 mg BID dose groups of apixaban.

4.2.5. Genetic-, gender- and age-related differences in pharmacodynamic response

No new data provided.

4.2.6. Pharmacodynamic interactions

No new data provided.

4.3. Evaluator's overall conclusions on pharmacodynamics

In healthy subjects:

- there was a close temporal relationship between changes in apixaban and rivaroxaban plasma concentrations and changes in AXA, with no delay of onset observed.
- for both apixaban and rivaroxaban, a linear relationship between plasma concentration and AXA was observed. However, further PPK modelling indicated that a linear relationship between concentration and AXA was not sufficient to accurately predict the effects of apixaban at both low and high concentrations in patients with non-valvular atrial fibrillation.
- Rivaroxaban and apixaban induced AXA with a median Tmax of 2 hours; however, the geometric mean peak AXA was approximately 2.5-fold higher following rivaroxaban than following apixaban treatment.

No studies directly compared apixaban PD in patients with non-valvular atrial fibrillation and healthy subjects.

Following a single 5 mg oral dose of apixaban, mild and moderate hepatic impairment had no effect on the ability of the drug to modify INR, aPTT and anti-Xa activity.

5. Dosage selection for the pivotal studies

The dose of warfarin was adjusted to an INR of 2.0-3.0, a range universally accepted for DVT treatment and stroke prevention in patients with AF. The ASA dose was selected at the discretion of the investigator within the range 81-324 mg once daily to accommodate differences in local and international usage guidelines for low dose aspirin prophylaxis.

The dose of apixaban was selected from the Phase 2 study (CV185010) which compared daily apixaban doses of 5, 10 and 20mg, given both once daily and BID, against blinded enoxaparin 30mg SC q12h and open-label warfarin. Study CV185010 was fully evaluated in the initial apixaban submission of 2011 for the indication of elective knee and hip replacement surgery. For all apixaban groups, VTE/all-cause death rates were at least 21% lower compared with the rate on enoxaparin, and at least 53% lower than the rate in subjects on warfarin. All doses of apixaban had favourable efficacy but the higher doses, 10 and 20 mg/day, had similar or higher rates of bleeding than enoxaparin. Apixaban had lower rates of bleeding compared with enoxaparin at the lower doses of 2.5 mg BID and 5 mg once daily. There was also a significant efficacy advantage in favour of BID dosage compared with once daily dosage. The event rate was 8.4% for the apixaban 2.5 mg BID regimen, and 13.1% for the apixaban 5 mg once daily regimen for the primary endpoint.

A Phase 2 study (CV185017) of DVT prevention compared three apixaban groups (5mg BID, 10 mg BID and 20 mg BID) with an open-label warfarin group in subjects who had undergone elective hip or knee replacement surgery. Study CV185017 has not been reviewed as the CSR was not included in the data package. A brief study design and outcome was recorded in a commentary provided by the sponsor in the current submission. VTE rates were low in all groups and there was no excess bleeding in any apixaban group.

For the proposed indication of AF, stroke prevention was considered to outweigh the risk of bleeding and an apixaban dose of 5 mg BID was selected to provide the optimum balance of efficacy and safety. However, patients considered at high risk of bleeding[1] by the investigators

[1] Sponsor clarification: those at high risk of bleeding were defined as those meeting at least 2 of the following criteria: age ≥80 years, body weight ≤60 kg or serum creatinine ≥133 μmol/L.

were given the lower apixaban dose of 2.5 mg BID. No dose ranging studies were performed in subjects with AF.

6. Clinical efficacy

To reduce the risk of stroke, systemic embolism and death in patients with non-valvular atrial fibrillation with at least one additional risk factor for stroke

6.1. Pivotal efficacy studies

6.1.1. Study CV185030

6.1.1.1. Study design, objectives, locations and dates

This was an active-controlled (warfarin), randomized, double-blind, double-dummy, parallel group study comparing apixaban to warfarin, with titration of warfarin based on central monitoring of the INR. Patients were enrolled at 1,053 sites in 40 countries (424 sites in Europe, 316 sites in North America, 176 sites in Asia Pacific and 137 sites in Latin America). First subject first visit was on 19 Dec 2006 and last subject last visit was on 25 May 2011.

Subjects with AF and at least one additional risk factor for stroke were randomized 1:1 to receive either apixaban 5 mg BID or warfarin titrated to INR 2.0-3.0 with matched placebo tablets. There was a screening period of up to 14 days or until their INR was stabilised within the acceptable range. This was followed by a treatment phase lasting until the earlier of subject discontinuation or the recording in the study population of approximately 448 primary efficacy events, with a post-treatment follow-up period of 30 days.

Apixaban (or matching placebo) was given 5 mg BID. It was given 2.5 mg BID if any two[2] of the following criteria applied at baseline: age ≥80 years, body weight ≤60 kg or serum creatinine ≥133 μmol/L. Dosing of warfarin or matching placebo employed a standard algorithm with central monitoring of INR measurements using encrypted point-of-care devices. Monitoring was conducted monthly once a stable INR was attained. In addition to the monthly visits for INR and safety assessments, there were quarterly visits during the treatment period (Months 3, 6, 9, 12, 15, 18, 21, 27, 30, 33, 39, 42, 45, 51, 54, and 57). Physical measurements and ECGs were obtained at yearly visits during the treatment period (Months 12, 24, 36 and 48).

All subjects were followed for the development of stroke (haemorrhagic, ischaemic or unspecified), SE, MI, death, bleeding, hospitalisation or treatment discontinuation until the end of the study. All efficacy and safety endpoints were evaluated by an independent, external, blinded Events Adjudication Committee.

6.1.1.2. Inclusion and exclusion criteria

Key inclusion criteria were: males or females ≥18 years of age; ECG documented AF or atrial flutter not due to a reversible cause; one additional risk factor for stroke including: age ≥75 years; prior stroke, TIA or SE; decompensated congestive cardiac failure; diabetes; treated hypertension.

Key exclusion criteria were: AF due to reversible causes; clinically significant mitral stenosis; contra-indication to anticoagulation; ALT/AST >2xULN or total bilirubin >1.5xULN; creatinine clearance <25 ml/min; platelet count <100,000; persistent, uncontrolled hypertension; infective endocarditis; planned major surgery; planned AF or flutter ablation surgery.

[2] Sponsor clarification: subjects were required to meet at least two of the stated criteria.

6.1.1.3. Study treatments

Apixaban 5 mg PO BID or matching placebo; apixaban 2.5mg PO BID (in selected high risk subjects) or matching placebo; or warfarin or matching placebo dosed at the discretion of the investigator.

6.1.1.4. Efficacy variables and outcomes

The primary efficacy outcome was to determine if apixaban was non-inferior (NI) to warfarin (INR target range 2.0-3.0) for the combined endpoint of stroke (haemorrhagic, ischaemic or unspecified) or systemic embolism (SE) in subjects with AF and at least one additional risk factor for stroke.

Other efficacy outcomes were to determine if apixaban was superior to warfarin for:

- the combined endpoint of stroke or SE
- major bleeding
- all cause death

6.1.1.5. Randomisation and blinding methods

Subjects eligible to receive blinded study drug were randomly assigned 1:1 by IVRS to receive either apixaban or warfarin. At least 40% of subjects at each site were required to be warfarin naive. Subjects, investigators, adjudicating committees and the sponsor's study staff had no access to individual treatment assignments.

6.1.1.6. Analysis populations

- Enrolled subjects data set: all subjects who signed informed consent.
- Randomized subjects data set: subset of the enrolled population who were randomized.
- Evaluable subjects data set: subset of the randomized population, excluding those with significant protocol deviations.
- Treated subjects data set: subset of the enrolled population who received at least one dose of blinded study drug.

6.1.1.7. Sample size

Regulatory agencies have different requirements for establishing non-inferiority. Some agencies require a more stringent NI margin with the upper bound of the two-sided 95% CI for HR to be less than 1.38, compared with 1.44 for other agencies. The most stringent regulatory definition required non-inferiority of apixaban relative to warfarin to be demonstrated if the upper bound of the two-sided 99% CI for relative risk was less than 1.44. Some agencies requiring an upper bound for HR of 1.44 require the type I error to be controlled at the stringent one-sided 0.005 level rather than the one-sided 0.025 level. With 448 subjects with strokes or SE, the study had at least 90% power to meet all regulatory definitions of NI. Based on a sample size of 18,000 subjects allocated 1:1 to receive apixaban or warfarin, assuming a primary efficacy endpoint rate of 1.20 per hundred subject-years, an average follow-up of ~2.1 years was required to reach the target number of primary efficacy events.

6.1.1.8. Statistical methods

There was one planned interim analysis for efficacy to be performed after approximately 50% of the primary efficacy endpoint events had been confirmed by the Adjudicating Committee. The objective was to confirm superiority to warfarin and no testing for NI was performed. Following the interim analysis the DMC recommended that the study continue as planned.

The planned analysis was:

- NI for the primary endpoint was to be assessed first.

- If NI for the primary efficacy endpoint using a NI margin of 1.44 was demonstrated, the superiority for the primary efficacy endpoint was to be tested at the one-sided α=0.005.
- If the superiority for the primary efficacy endpoint was demonstrated, then superiority for ISTH major bleeding (primary safety endpoint) was to be tested at the one sided α=0.005[3].
- If superiority for major bleeding was demonstrated, then superiority for all-cause death was to be tested at the one-sided α=0.005[4].

All statistical analyses were performed using SAS version 8.2 or higher. Except as noted above, hypotheses were tested using two-sided tests at the 5% significance level. Continuous variables were summarized using descriptive statistics including means, standard deviations, minima, maxima and quartiles. Qualitative or discrete variables were summarized using absolute and relative frequencies.

Analysis of the primary endpoint was performed on the Randomized Population (ITT) after appropriate censoring. Tests using each NI margin and significance level described above were performed using a Cox proportional hazards model including treatment group as a covariate and stratified by investigative site and prior warfarin status. The treatment effect was measured by the estimated RR and the two-sided CIs for RR. Event rates were estimated and plotted over time using Kaplan-Meier methodology. The proportion of time in which subjects had an INR in the ranges INR <2.0, 2.0-3.0 and >3.0 were summarized. The frequency of subjects with INR in the 2.0-3.0 range for ≥60%, ≥65%, ≥70%, ≥75% or ≥80% were also summarized.

6.1.1.9. Participant flow

A total of 20,998 subjects were enrolled in the study and 18,201 (86.7%) were randomized to receive study treatment. Of the 2,797 (13.3%) subjects who were not randomized, 1,575 (7.5%) subjects no longer met the study criteria and 951 (4.5%) subjects withdrew consent. Approximately 40% of the randomized subjects were in Europe, 19% in USA, 6% in Canada, 19% in Latin America and 16% in Asia Pacific.

6.1.1.9.1. Major protocol violations/deviations

The frequency of protocol deviations was approximately similar in each treatment group, 24.7% in the apixaban group and 19.4% in the warfarin group. Numerically the most significant deviations were the use of antithrombotic agents (7.9% in the apixaban group and 7.6% in the warfarin group); and non-compliance with apixaban (6.2% in the apixaban group) or apixaban-placebo (6.3% in the warfarin group). Similar rates were observed when analysed by prior warfarin status. Protocol deviations likely to affect the primary efficacy endpoint were pre-specified and occurred in 13.6% in the apixaban group and 7.8% in the warfarin group. However, a sensitivity analysis showed that they had no impact on the primary study results.

Comment: The sponsor has notified regulatory authorities of a GCP breach at site 1178[5] in China, detected after database lock. In the view of the sponsor, there may have been delayed or absent reporting of one or more AEs and SAEs. However, most of the breaches were related to documentation discrepancies, informed consent and retrospective signatures. The sponsors did not think this warranted a sensitivity analysis with and without data from this site. This is not unreasonable given that the site recruited only 37 of the 20,000[6] patients enrolled in the study.

[3] Erratum: α=0.025
[4] Erratum: α=0.025
[5] Erratum. The correct site ID is 1200.
[6] Sponsor clarification: 20,998 patients were recruited.

6.1.1.10. Baseline data

A total of 9,120 subjects were randomized to treatment with apixaban and 9,081 were randomized to receive warfarin. Approximately 93% of subjects in each group were evaluable after receiving at least one dose of study treatment. In the apixaban group, 2,310 (25.3%) subjects discontinued treatment compared with 2,493 (27.5%) subjects in the warfarin group. The reasons for discontinuation are shown in the CSR.

Baseline characteristics were well balanced between the treatment groups. Mean age was approximately 69 years and approximately 31% of the total population were aged ≥75 years. Approximately 65% were male and 83% were white. Baseline disease characteristics were also similar in both groups. Overall, 41.3% of subjects had normal renal function, 41.7% had mild renal impairment, 15.1% had moderate renal impairment and only 1.5% had severe renal impairment.

Baseline risk factors for stroke were similar in both treatment groups. Approximately 67% of subjects had ≥2 risk factors at baseline. The most common risk factors were treated hypertension (87.4%), symptomatic CHF (35.4%), age ≥75 years (31.2%) and 19.4% with a prior history of stroke, TIA or SE.

Other baseline characteristics including medical history, physical examination and prior medications were similar in each group. Approximately 57% of randomized subjects were warfarin experienced and 43% were naive in each treatment group, while 45.7% of the subjects had received prior warfarin for more than 6 months. The mean duration of exposure to randomized treatment was approximately 1.7 years in each treatment group, approximately 15,534 and 15,184 subject-years in the apixaban and warfarin groups respectively. Duration of exposure to apixaban was similar in the warfarin naive and experienced groups.

6.1.1.11. Results for the primary efficacy outcome

Apixaban was non-inferior to warfarin for the composite endpoint of prevention of stroke or SE (one-sided p<0.0001) with HR=0.79 in favour of apixaban. There were 212 (2.32%) events in the apixaban group compared with 265 (2.92%) in the warfarin group. The great majority of events in both groups related to stroke. SE events were infrequent in both groups, 15 (0.16%) in the apixaban group and 16 (0.18%) in the warfarin group.

6.1.1.12. Results for other efficacy outcomes

Apixaban was superior to warfarin for reduction in stroke (haemorrhagic, ischaemic and unspecified) and SE (two-sided p=0.0114, HR=0.79, CI 0.66-0.95). The incidence of each individual endpoint (haemorrhagic stroke, ischaemic or unspecified stroke, SE) was numerically lower on apixaban than warfarin. The study was not powered to demonstrate superiority within subject subgroups. However, the HR was <1 in favour of apixaban in all except one of the subgroups of clinical interest. The only subgroup with HR ≥1 was age group <65 years (HR 1.16, 95% CI 0.77-1.73). Of note, the benefit in favour of apixaban was apparent even in high-risk subjects given 2.5 mg BID. The difference in favour of apixaban was apparent at 3 months and was sustained throughout the intended treatment period.

Apixaban was superior to warfarin for the secondary endpoint of all-cause death. There were 603 (6.61%) deaths in the apixaban group compared with 669 (7.37%) deaths in the warfarin group (two-sided p=0.0465, HR=0.89, CI 0.80-1.0). The difference was of borderline statistical significance and driven largely by a reduction in fatal stroke in the apixaban subjects. Cardiovascular and non-cardiovascular death rates were otherwise similar in the apixaban and warfarin treatment groups.

The primary analysis of subjects who received warfarin was based on ITT, including all INRs irrespective of the titration period or warfarin interruption. Overall, the median time in therapeutic range (TTR) was 60.5% in all subjects randomized to warfarin, and 66.0% excluding the first 7 day titration period and warfarin interruptions. TTR was analysed further

by grouping all warfarin-treated subjects by site. The clinical sites were then ranked and placed in quartiles based on their median warfarin INR. The reduction in stroke/SE in favour of apixaban was similar for study sites with INR control below and above the median TTR, as well as in each quartile interval.

Comment: The analysis of primary events stratified by INR reinforces the significance of the increased efficacy of apixaban compared with warfarin. There was an efficacy benefit in favour of apixaban even in subjects with the best INR control. This suggests a real treatment benefit rather than one based on poor compliance, poor adherence or other reasons for sub-optimal INR control in subjects treated with warfarin.

During the 30 day follow-up at the end of the intended treatment period, there were 27 stroke/SE events in the apixaban group and 10 events in the warfarin group. However, most subjects (23 on apixaban, 7 on warfarin) were not on study drug and had started on other therapies at the time of the event.

Comment: The excess events during the wash-out period might represent a delayed effect of apixaban, or an offset, rebound phenomenon. Alternatively it might represent suboptimal anti-coagulant control as physicians switched subjects from one therapy to another. The sponsors claim the latter and point out that subjects prescribed apixaban will be unlikely to be switched from an oral FXa inhibitor to warfarin. This view is not unreasonable and the potential for harm is addressed in the PI.

Following evaluation of this submission, the sponsor has provided further information relating to study CV185030. In section 4.3 of the CSR, an unusually high incidence of potential dosing errors was documented. At some point in the study, 7.3% of subjects in the apixaban group and 1.2% of subjects in the warfarin group received a study medication container of the incorrect type. A sensitivity analysis was performed which showed that the primary efficacy and safety endpoint analyses and conclusions were not influenced by the outcomes in this subset of subjects. The sponsor has investigated the root cause of these errors and provided a comprehensive 24 page report of the findings. The conclusion of this report is that the true incidence of medication errors was <0.1% of study dispensations in <1% of subjects overall. The root cause of the original errors was related to data entry, mainly incorrect apixaban and warfarin container numbers entered into the dispensed medication fields of the eCRF. The sponsor has performed another sensitivity analysis including the revised, much lower estimates for dosing error. The conclusions of this analysis did not affect the original overall study conclusion, namely the statistically significant benefit in favour of apixaban for stroke and systemic embolism, major bleeding and all-cause death. A summary of the sensitivity analyses for the primary endpoints were provided.

Comment: The conclusion is that the primary outcomes of study CV185030 are valid, with or without this additional analysis. The overall conclusions of the clinical evaluation also remain valid, with or without the inclusion of the post hoc analysis.

6.1.2. Study CV185048

6.1.2.1. Study design, objectives, locations and dates

This was a randomized, double-blind, double-dummy, parallel-group study comparing apixaban and acetylsalicylic acid for the prevention of stroke in AF subjects who have failed or are unsuitable for warfarin treatment. A total of 6421 subjects were enrolled in the study and 5598

(2798 on apixaban and 2780 on ASA) were randomized to receive study treatment.[7] Subjects were enrolled at 526 sites in 36 countries. Approximately 45% of randomized subjects were in Europe, 21% in Latin America, 20% in Asia Pacific, and 14% in North America. The countries with the greatest numbers of randomized subjects were Russia (12.5%), USA (9.5%), Brazil (7.4%), Mexico (6.2%) and Germany (5.8%). First subject first visit was on 31 August 2007 and last subject last visit was on 20 September 2010.

The trial required subjects who had at least one additional risk factor for stroke, and who had previously used or were unsuitable for warfarin. They were screened during a 28 day period and then randomized 1:1 to receive apixaban or ASA. Following randomization, visits were scheduled at Months 1 and 3, and then every 3 months until completion of the double-blind phase of the study. Subjects who discontinued study treatment were followed for outcome events until the end of the double-blind period. The double-blind treatment period was to end after at least 226 primary efficacy endpoints were recorded. Subject numbers and study duration were based on event rates from similar studies. However, following a planned interim analysis the DMC stopped the study early because of superior efficacy in the apixaban group.

All subjects were followed for the development of stroke (haemorrhagic, ischaemic or unspecified), SE, MI, death, bleeding, hospitalisation or treatment discontinuation until the end of the study.

6.1.2.2. Inclusion and exclusion criteria

Key inclusion criteria were: males or females ≥ 50 years of age; documented permanent, paroxysmal or persistent AF; not currently receiving warfarin therapy; at least one risk factor for stroke including: prior stroke or TIA, age ≥ 75 years, treated hypertension, diabetes mellitus, heart failure NYHA Class 2 or greater, LVEF ≤ 35%, or documented peripheral arterial disease.

Key exclusion criteria were: AF due to reversible causes; valvular disease requiring surgery; ALT/AST >2xULN or bilirubin >1.5xULN; creatinine clearance <25 ml/min; platelet count <100,000; planned AF ablation to be performed within 3 months.

6.1.2.3. Study treatments

Subjects were randomized 1:1 to receive either:

- Apixaban 5 mg BID (or 2.5 mg for at risk subjects) or matching placebo.
- ASA 81 to 324 mg once daily or matching placebo.

Apixaban (or matching placebo) was given as a 5 mg tablet BID, or as a 2.5 mg tablet BID for subjects at increased risk of bleeding; namely age >80 years, body weight ≤ 60 kg or serum creatinine ≥ 133 µmol/L.[8]

The ASA dose was selected at the discretion of the investigator. More than 90% of subjects were receiving a dose of either 81 mg or 162 mg on the day of randomization.

6.1.2.4. Efficacy variables and outcomes

The main efficacy outcome was to determine if apixaban 5 mg BID (2.5 mg BID in selected at risk subjects) is superior to ASA (81 to 324 mg once daily) for preventing the composite outcome of stroke or systemic embolism in subjects with AF and at least one additional risk factor for stroke who failed or are unsuitable for warfarin therapy.

Other efficacy outcomes included:

[7] Sponsor clarification: Number of patients randomised: 5598 (2807 on apixaban and 2791 on ASA); number treated: 5578 (2798 on apixaban and 2780 on ASA).
[8] Sponsor clarification: subjects meeting at least 2 of the pre-specified criteria received 2.5 mg BID.

- To determine if apixaban is superior to ASA for prevention of the composite endpoint of stroke, SE, MI, or vascular death (major vascular events).
- To determine if apixaban is superior to ASA for all-cause death.
- To compare apixaban and ASA with respect to: the composite outcome of stroke, SE, MI, vascular death, or major bleeding (net clinical benefit); the composite endpoint of all-cause death, stroke, or SE; vascular death; or major bleeding.

6.1.2.5. Randomisation and blinding methods

At screening, subjects were randomized 1:1 in blocks of four by IVRS to receive apixaban or ASA. At the time of randomization, the IVRS assigned each subject a container number which was recorded in the CRF and used for drug re-supply throughout the study. To maintain blinding of study treatment, study medications were prepared in a double-dummy design using placebo matching the active treatments. Subjects, investigators, members of the administrative and adjudicating committees and sponsor staff did not have access to individual subject treatment assignments. A total of 19 subjects were un-blinded by the investigators during the conduct of the study.

6.1.2.6. Analysis populations

- Enrolled subjects data set: all subjects who signed informed consent.
- Randomized subjects data set: subset of the enrolled population who were randomized by IVRS regardless of whatever treatment they received.
- Evaluable subjects data set: subset of the randomized population, excluding those with protocol deviations likely to affect the primary efficacy endpoint.
- Treated subjects data set: subset of the enrolled population who received at least one dose of blinded study drug.

6.1.2.7. Sample size

The study included two planned interim efficacy analyses:

- The first analysis was planned to occur when approximately 113 (50%) of the total 226 subjects with adjudicated primary events had accrued.
- The second analysis was planned to occur when approximately 170 (75%) of the total 226 subjects with adjudicated primary events had accrued.

Assuming an average 1.6 years follow-up and a stroke rate of 3.3/hundred subject-years in ASA-treated subjects, the study would have at least 90% power to detect a 35% RRR of apixaban versus ASA at the one-sided α=0.025 level if there were 226 subjects with adjudicated strokes or SE. A total of 5600 subjects were required to be randomized to study treatment, assuming a 1% incidence of loss to follow-up. Event rates and between-group assumptions were based on ITT analyses of previous studies.

6.1.2.8. Statistical methods

All statistical analyses were carried out using SAS. For the interim analysis, the primary endpoint was assessed using a modified Haybittle-Peto boundary of four SD (two-sided p-value <0.00006), the boundary referring to a treatment difference greater than the prescribed number of SE and which favoured apixaban. For the second interim analysis, the primary endpoint was assessed using a modified Haybittle-Peto of three SD (two-sided p-value <0.0026). If the observed HR for the primary endpoint at either analysis crossed the critical value obtained using the corresponding Haybittle-Peto boundary, a confirmatory interim analysis was required 3 months later. If the observed HR again crossed the critical value, the DMC was allowed to be terminated for apixaban superiority after taking into account overall risk-benefit.

The DMC recommended stopping the study after a confirmatory analysis of the first scheduled interim analysis. The two-sided p-value for the primary efficacy endpoint was <0.00006 at the scheduled and confirmatory analyses.

6.1.2.9. Participant flow

A total of 6421 subjects were enrolled and 5598 subjects were randomized to study treatment. Of the 823 (12.8%) subjects who were not randomised, 435 (6.8%) no longer met the study criteria. Fewer subjects discontinued study treatment in the apixaban group than in the ASA group. The most common reasons for discontinuing study treatment were AEs and subjects' request.

6.1.2.10. Major protocol violations/deviations

In the randomized subject set, there were 167 subjects [in each of the treatment groups] with significant protocol deviations, 5.9% in the apixaban group and 6.0% in the ASA group. The predetermined significant protocol deviations related mainly to eligibility criteria and the use of prohibited concomitant medications. The number of protocol deviations was relatively small, balanced between the treatment groups and unlikely to have impacted on the interpretation of the study results. Site 127 was closed because of persistent GCP non-compliance after the randomization of 16 subjects. None of the subjects had a primary efficacy endpoint so there was no impact on the final study results. A total of 57 sites were audited by the sponsor or its representatives.

6.1.2.11. Baseline data

Baseline demographic characteristics were well balanced between the two groups. Approximately 59% of subjects were male and 79% were White. Mean age was approximately 70 years and approximately 34% of subjects were aged ≥75 years. The treatment groups had similar baseline disease characteristics. Overall, 33.5% of subjects had normal renal function; 38.4% had mild impairment (CrCL >50 to ≤80 mL/min), 17.3% had moderate renal impairment (CrCL >30 to ≤50 mL/min), and 2.1% had severe renal impairment (CrCL ≤30 mL/min).

Baseline risk factors for stroke were evenly balanced between the two treatment groups, with an average CHADS2 score of 2 in each group. More than 61% of randomized subjects had at least two risk factors. The most common risk factors were treated hypertension (86.4%), heart failure (NYHA class ≥2) or LVEF ≤35% (33.7%), prior stroke or TIA (13.6%) and age ≥75 years (33.8%). There were no clinically relevant differences between treatment groups in the distribution of baseline risk factors.

Overall, 6.4% of subjects at risk were given the lower dose of apixaban 2.5 mg BID. Medical history findings were similar for the apixaban and ASA groups. Non-study medications were also similar in both groups. Approximately 76% of subjects were taking ASA and 15% were taking oral anticoagulants before the first dose of study drug. Overall, 40% of randomized subjects had previously used warfarin.

6.1.2.12. Results for the primary efficacy outcome

Apixaban was superior to ASA for the prevention of stroke or SE in subjects with AF and at least one additional risk factor for stroke, and who had failed or were expected to be unsuitable for warfarin treatment (two-sided p-value <0.00001). The event rates were 1.62 and 3.63 per 100 subject-years for apixaban and ASA respectively with unadjusted HR 0.45 (95% CI 0.23-0.88[9]). The difference in event rates was apparent within the first month of the study and was sustained throughout the study period. The majority of primary outcome events were strokes. There were only 2 (0.07%) SE in the apixaban group compared with 13 (0.47%) in the ASA group.

[9] Sponsor clarification: the 95% CI shown is the adjusted CI; the unadjusted 95% CI is 0.32-0.62.

Analyses for the primary efficacy endpoint were performed for subgroups of clinical interest, although the study was not designed to ensure adequate power for subgroup analyses. The upper bounds of the 95% CIs for the HR were <1 for most of the 49 subgroup categories suggesting a benefit in favour of apixaban in all subgroups. Of note, subjects who received apixaban 2.5 mg BID had a similar outcome benefit compared with those who received 5 mg BID. Subjects who were considered unsuitable for warfarin also had a substantial benefit in favour of apixaban.

6.1.2.13. Results for other efficacy outcomes

Subjects who received apixaban had a significant reduction in major vascular events (composite of stroke, SE, MI, or vascular death) compared with subjects who received ASA (two-sided p-value = 0.00026, HR 0.66 (95% CI 0.53-0.83). Apixaban reduced the incidence of all-cause death although the difference was not statistically significant. The incidence of each individual efficacy endpoint was lower on apixaban than ASA, including MI. In addition, apixaban significantly reduced the incidence of non-fatal strokes of all severities compared to ASA.

The pre-specified net-clinical benefit tertiary endpoint (the composite of stroke, SE, MI, vascular death and major bleeding) combined the primary and secondary efficacy endpoints, and the primary safety endpoint. The analysis included all endpoints occurring during the intended treatment period in the randomized (ITT) population. The incidence of this composite endpoint was reduced in subjects who received apixaban compared with subjects who received warfarin [163 (5.81%) and 220 (7.88%)] events respectively (HR 0.73, 95% CI 0.60-0.90, p<0.003). The benefit in favour of apixaban was an absolute reduction of 1.9%/year in this composite efficacy endpoint.

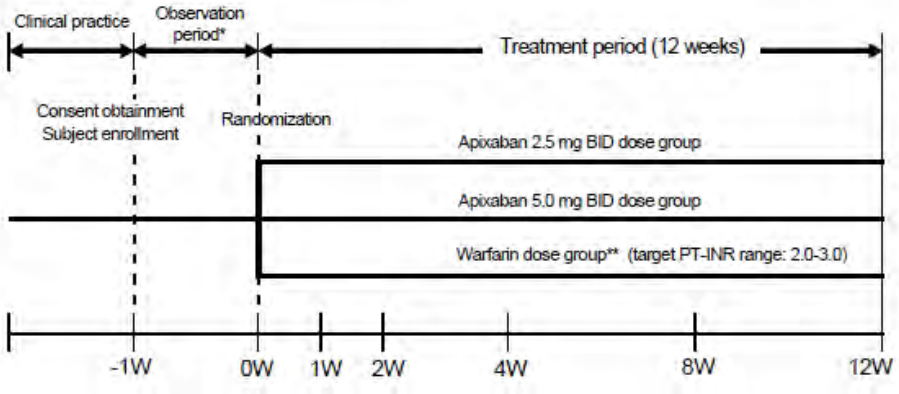
6.2. Other efficacy studies

6.2.1. Study CV185067

6.2.1.1. Study design and objectives

This was a Phase 2b, randomized, partially blind (double-blind apixaban, open-label warfarin), active controlled (warfarin), multicentre study to evaluate the safety and dose-response relationship of two doses (2.5 mg BID and 5 mg BID) of apixaban compared to warfarin (controlled INR 2.0 -3.0) administered for 12 weeks in Japanese subjects with NVAF (schema below):

Figure 1. Study CV185067: Schema



The study was conducted by Pfizer Global R&D and was supervised by a Study Steering Committee, a Clinical Event Committee and a DSMC. It was conducted in 23 centres in Japan.

The primary objective was to assess the effects of two doses of apixaban (2.5 mg BID and 5 mg BID) compared with warfarin on the composite endpoint of major and clinically relevant non-major bleeding events during the treatment period.

Secondary objectives included:

- To compare the effects of two doses of apaixaban and warfarin on all bleeding events (major bleeding, clinically relevant non-major bleeding and minor bleeding).
- To compare the effects of two doses of apixaban on major bleeding events.
- To assess the overall safety and tolerability of apixaban and warfarin.
- To compare the effects of two doses of apixaban and warfarin on efficacy endpoints (stroke, SE, all-cause death and MI).
- PK, PD and biomarker data to characterize the profile of apixaban in Japanese subjects.

Key inclusion criteria included: males and females with NVAF; one additional risk factor for stroke (defined in the study reports above), and documented AF not due to a reversible cause. Key exclusion criteria included: recent stroke, TIA or MI; bleeding or thrombotic tendencies; warfarin treatment contraindicated; refractory or severe hypertension, and severe heart failure (NYHA Grade IV).

6.2.1.2. Results for the efficacy outcome

A total of 245 subjects were enrolled and 222 subjects were assigned to treatment with warfarin (74 subjects), apixaban 2.5 mg BID (74 subjects) or apixaban 5 mg BID (74 subjects). Four subjects were not treated with study medication and 23 subjects withdrew from the study during the observation period. There were no obvious differences in baseline demographics among the three treatment groups. Overall, mean age was 70.3 years, 82.9% were male, all were Asian (Japanese) and mean BMI was 24.7 kg/m2. More than 80% of subjects in each group had previous experience of warfarin. More than 50% of subjects had ≥2 risk factors for stroke. Most patients had mild or moderate renal impairment and the mean duration since the first diagnosis of AF was approximately 7 years.

The primary outcome was related to safety as described below. All efficacy endpoints were secondary. In the warfarin group, 3 subjects (4.1%) had adjudicated stroke events and one subject had a TIA. There were no subjects with stroke, SE, MI or all-cause death in either of the apixaban groups.

In the apixaban groups, there was a dose dependent increase in exposure at each time point. There were weak correlations between apixaban dose or plasma concentrations and PT, PT-INR and aPTT. Anti-Xa activity increased dose dependently and the correlation with plasma apixaban concentrations was higher than those observed with the other PD markers.

Comment: The study was well balanced and controlled. Over a 12 week period there were no adjudicated stroke events in either apixaban group compared with three in the warfarin group. The study was not powered to detect a difference between the groups but the results support the benefit observed in subjects (mostly Caucasian) treated with apixaban in the Phase 3 studies. The PK/PD results confirmed that subjects had adequate exposure to apixaban.

6.2.2. Study CV185036

CV185036 (ADOPT) was a Phase 3 randomized, double-blind, parallel-group, multi-centre study of the safety and efficacy of apixaban for prophylaxis of venous thromboembolism (VTE) in acutely ill medical subjects during and following hospitalization (a study summary is provided

in Appendix 1[10]). A total of 6528 subjects were randomized 1:1 to receive either enoxaparin 40 mg SC once daily while in hospital or oral apixaban 2.5 mg BID for 30 days. The primary efficacy endpoint was the composite of adjudicated total VTE (fatal and non-fatal PE, and symptomatic or asymptomatic proximal and distal DVT) and VTE-related death during the intended treatment period. Superiority of apixaban for the primary efficacy endpoint was not demonstrated. Event rates were 2.71% in the apixaban group compared with 3.06% in the enoxaparin group and the trend in favour of apixaban was not statistically significant (HR 0.87 [95% CI 0.62-1.23, p<0.44]).

Comment: This was a study of a lower dose of apixaban with a different comparator given for a shorter duration for a different indication. The study failed its primary endpoint but it is included in this evaluation for its additional safety data in relation to apixaban.

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

None performed.

6.4. Evaluator's conclusions on clinical efficacy

Conclusion regarding efficacy in the indication to reduce the risk of stroke, systemic embolism and death in patients with non-valvular atrial fibrillation with at least one additional risk factor for stroke

Two large Phase 3 studies demonstrated a statistically significant superiority for apixaban compared to warfarin and ASA for the composite endpoint of stroke (haemorrhagic and ischaemic) and SE. The great majority of events were stroke with fewer SE, consistent with other studies of anticoagulation in subjects with AF. No formal analyses of pooled data were performed but the results in both studies were internally consistent. In study CV185030, stroke or SE occurred in subjects on apixaban at a rate of 1.27%/yr compared with 1.6%/yr in subjects on warfarin (p=0.0114, HR 0.79 [95% CI 0.66-0.95]). In study CV185048 the rates were 1.62% in subjects who were given apixaban, and 3.63%, in subjects given ASA (p<0.0001, HR 0.45 [95% CI 0.32-0.62]). All cause death rates were also lower in subjects who received apixaban in both studies, although the difference was statistically significant only in study CV185030 (p<0.0465, HR 0.89 [95% CI 0.80-1.00]). In both studies, individual event rates for ischaemic and undetermined stroke, haemorrhagic stroke, SE, and MI were numerically less frequent in the apixaban groups compared with the warfarin and ASA groups.

Study CV185048 was stopped early by the DMSC because of clear superiority for the primary endpoint in favour of apixaban compared with aspirin. It is possible that superiority for secondary endpoints such as all-cause death might have achieved statistical significance if the trial had run its full course. Apixaban was statistically superior to ASA for prevention of stroke (haemorrhagic or ischaemic) and SE (HR 0.45 (95% CI 0.23-0.88[11]). It was also associated with a reduction in major vascular events (composite of stroke, SE, MI and vascular death). The incidence of individual endpoints including haemorrhagic stroke, ischaemic stroke, unspecified stroke, vascular death and MI was lower in the apixaban group compared with the warfarin group.

The studies were designed in compliance with EMEA and FDA guidelines for thrombotic therapy. The studies were adequately powered and conducted, randomized, double-dummy, double-blind, active controlled and parallel group. The studies were well balanced for baseline characteristics including medical history, age, gender and race, and the study population

[10] Not included as part of the extract of the CER
[11] Sponsor clarification: the 95% CI shown is the adjusted CI; the unadjusted 95% CI is 0.32-0.62.

represented the target population for apixaban in this submission. Study withdrawals and significant deviations from the protocol were not excessive. The efficacy and safety endpoints were appropriately monitored and confirmed by an independent, external adjudicating committee. The key objective in the pivotal study CV185030 was non-inferiority of apixaban compared with warfarin. This objective was not only achieved but statistically significant superiority of apixaban over warfarin was also demonstrated. The percentage benefit was small but clinically meaningful given the major consequences of the efficacy outcomes in question.

Apixaban was superior to warfarin in subjects considered suitable for warfarin therapy. Apixaban was also superior to ASA for subjects considered unsuitable for warfarin therapy. The benefit was apparent in subgroups including age, gender, race and renal function. A similar benefit was observed in at risk subjects (age ≥80 years, body weight ≤60 kg or serum creatinine ≥133 μmol/L) who received a lower dose of apixaban 2.5 mg BID.

Comment: Apixaban was superior to warfarin and ASA for all efficacy endpoints but most of the benefit was driven by a reduction in stroke. There were numerical benefits in favour of apixaban for individual endpoints such as SE but the numbers were small and the differences were not statistically significant. The practice is widespread but it is a moot point whether claims for such infrequent events should be captured in composite endpoints.

7. Clinical safety

7.1. Studies providing evaluable safety data

The following studies provided evaluable safety data:

Pivotal efficacy studies: The pivotal Phase 3 studies CV185030 and CV185048 provided the main safety data in the target population treated for up to 2.1 years. AEs could be reported spontaneously or during open-ended questioning, examination, or evaluation of subjects at each study visit. To prevent bias, subjects were not questioned about the specific occurrence of AEs.

Pivotal studies that assessed safety as a primary outcome

None submitted.

Dose-response and non-pivotal efficacy studies

Not applicable.

Other studies evaluable for safety only

The non-pivotal Phase 2 efficacy study CV185067 provided limited safety data.

Additional safety data were evaluated in the unrelated study CV185036. Major bleeding occurred in 0.47% in the apixaban group and 0.19% in the enoxaparin group. The adjusted difference between groups was 0.29% (95% CI 0.01-0.57, p<0.44). The frequency of AEs, SAEs, deaths, and discontinuations due to AEs was similar in both treatment groups. The frequency of hepatic events and marked laboratory abnormalities was also similar in both treatment groups.

Comment: Major bleeding events were infrequent in both treatment groups but numerically more frequent in the apixaban group. Some of the excess bleeding events in the apixaban group can be attributed to the longer treatment duration (approximately 30 days for apixaban and 7 days for enoxaparin). Overall, the safety profile of apixaban in this study is compatible with the profile observed in the AF pivotal studies discussed below.

7.2. Patient exposure

Total exposure was high in the 23,718 subjects included in two pivotal Phase 3 studies. Exposure in study CV185030 was 15,534 and 15,184 subject-years for apixaban and warfarin respectively, with an average duration of treatment of ~1.7 years. Exposure in study CV185048 was 3,193 and 3,150 subject-years for apixaban and ASA respectively in study, with an average duration of treatment of ~1.1 years. In eight completed Phase 2 and 3 studies in other indications, safety data are available for an additional 11,929 subjects who received apixaban. Of these, 4,452 subjects received apixaban 10 mg/day, either as 5 mg BID or 10 mg once daily.

7.3. Adverse events

7.3.1. All adverse events

7.3.1.1. Pivotal studies

General adverse events (AEs): Most AEs were mild to moderate in severity in both pivotal studies. In study CV185030, the safety profile of apixaban was similar to warfarin. AEs occurred in approximately 82% of subjects in each treatment group. The most common AEs were infections, mainly respiratory and urinary tract infections, which occurred in 37.6% and 38.6% in the apixaban and warfarin groups, respectively. Gastrointestinal disorders occurred in 27.2% and 29.2% of the apixaban and warfarin groups, respectively (diarrhoea occurred in 6.4% and 6.5%, respectively). Respiratory disorders (mainly dyspnoea, epistaxis and cough) occurred with similar frequency in each group (23.3% and 24.8%, respectively). Cardiac disorders (mainly AF and cardiac failure) occurred in 22.6% and 21.9% in the apixaban and warfarin groups, respectively. AEs related to bleeding were less frequent in the apixaban group (25.2%) compared with the warfarin group (32.7%).

In study CV185048, the frequency of adverse events with onset during the treatment period was similar in both treatment groups; 65.5% and 69.2% in the apixaban and ASA groups respectively. Overall, the most common events were dizziness and dyspnoea. Infections (mainly respiratory and urinary tract) occurred in 19.2% and 20.2% respectively; cardiac disorders (mainly AF and cardiac failure) occurred in 16.4% and 17.3% respectively; gastrointestinal disorders (mainly diarrhoea, abdominal pain, gastritis and nausea) occurred in 16.2% and 17.9% respectively; and nervous system disorders (mainly dizziness, headache and syncope) occurred in 13.2% and 17.7% respectively. Neurologic events were AEs of special interest because of one case of amyotropic lateral sclerosis (ALS) and one case of Guillain-Barre syndrome (GBS) which occurred in a Phase 2 study of VTE following TKR. There were no cases of ALS or GBS in the studies submitted in this application.

7.3.1.2. Other studies

In study CV185067, there were no clinically meaningful differences in the frequency of AEs among the treatment groups (46.7% in the warfarin group, 51.4% in the apixaban 2.5 mg BID group, and 59.2% in the apixaban 5.0 mg BID group).

7.3.2. Treatment-related adverse events

7.3.2.1. Pivotal studies

The primary safety endpoint in both pivotal Phase 3 studies was major bleeding defined variously below:

Major Bleeding: the definition was adapted from the ISTH definition as acute clinically overt bleeding accompanied by one of the following:

- A decrease in Hgb of 2 g/dl or more over a 24 hour period.
- A transfusion of 2 or more units of packed red blood cells.

- Bleeding into at least one of the following critical sites: intracranial, intraspinal, intraocular, pericardial, intra-articular, intramuscular with compartment syndrome or retroperitoneal.
- Fatal bleeding.

Clinically Relevant non-Major Bleeding (CRNM): CRNM was defined as acute clinically overt bleeding that is not associated with any additional criteria to be defined as major bleeding, and meeting at least one of the following criteria:

- Hospital admission for bleeding
- Medical or surgical treatment for bleeding
- Change in anticoagulant or antiplatelet therapy

Major bleeding was adjudicated by the independent adjudicating committee: CRNM and minor bleeding events were not adjudicated.

Bleeding endpoints: In the pivotal efficacy study CV185030, apixaban was superior to warfarin for the primary safety endpoint of adjudicated ISTH major bleeding. Event rates were 3.60% and 5.10% in the apixaban and warfarin groups respectively (HR 0.69 [95% CI 0.60-0.80], p<0.0001). Event rates were also significantly lower in the apixaban group compared with the warfarin group for the composite of major or CRNM bleeding, all bleeding and for all endpoints using GUSTO and TIMI criteria (p<0.0001 for all comparisons). Reduced bleeding was apparent soon after dosing and the difference was sustained throughout the treatment period (Figure 2). The components of ISTH major bleeding are shown in Table 4.

Figure 2. Kaplan-Meier plot for ISTH major bleeding during the treatment period – Treated subjects (Study CV185030)

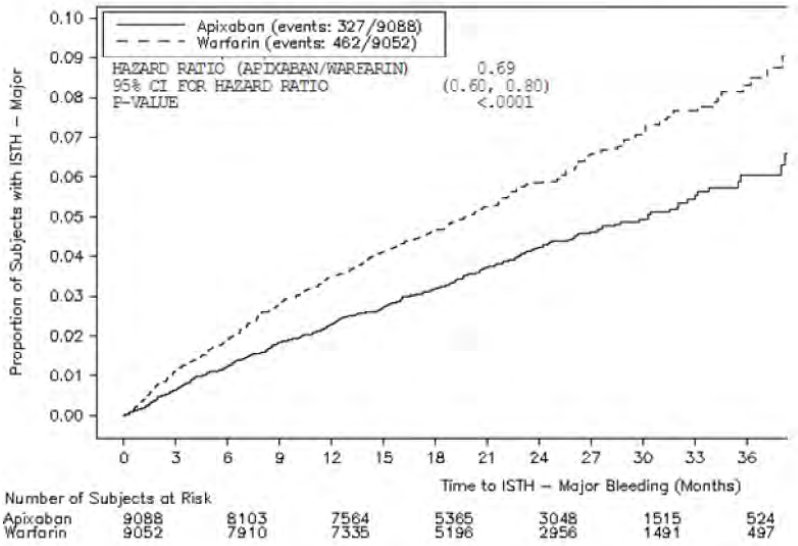


Table 4. Summary of components of ISTH major bleeding during the treatment period – Treated subjects (Study CV185030)

	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

The denominator to calculate each percentage is the total number of treated subjects within each treatment group
Each type of event was only counted once per subject but subjects could be counted in multiple categories

Fatal haemorrhage (including adjudicated haemorrhagic stroke) occurred in 10 subjects (0.06%/yr) in the apixaban group compared with 37 subjects (0.24%/yr) in the warfarin group. Intracranial haemorrhages, including all adjudicated haemorrhagic strokes, occurred in 52 subjects in the apixaban group compared with 122 subjects in the warfarin group (HR 0.42 [95% CI 0.3-0.58], p<0.0001). Major bleeding into critical sites occurred in 91 subjects in the apixaban group compared with 158 subjects in the warfarin group. With the exception of intraocular bleeding, major bleeding at other critical sites was less frequent or similar in the apixaban group compared with the warfarin group. There were 49 (28 serious) cases of adjudicated intraocular bleeding events in the apixaban group compared with 63 (19 serious) in the warfarin group.

Comment: All bleeding events, including intraocular bleeding, were reduced in subjects treated with apixaban compared with warfarin. The numerical excess of serious intraocular bleeding in apixaban subjects is possibly a chance finding. A post hoc analysis showed that most events in both groups occurred in elderly subjects with known risk factors for ocular haemorrhage such as diabetes.

Adjudicated major GI bleeds (upper GI, lower GI and rectal) were less frequent in the apixaban group (118 subjects) compared with the warfarin group (130 subjects).

As discussed in the section on *Efficacy Results for other efficacy parameters* regarding this study (above), the median TTR for subjects randomized to warfarin was 66% excluding the first 7 days of titration and warfarin interruptions. As discussed above, there was a reduction in ISTH major bleeding in the apixaban group compared with the warfarin group. Similar reductions were apparent for study sites with INR control below and above the median TTR as well as in

the four quartile intervals. There was no evidence that the benefit in favour of apixaban was related to excessive anticoagulation in a limited proportion of warfarin subjects.

In study CV185048, major bleeding occurred in 45 subjects (1.61%) in the apixaban group compared with 29 subjects (1.04%) in the ASA group. The HR was 1.54 (95% CI 0.96-2.45, p=0.07) in favour of ASA. The composite of major or CRNM bleeding occurred more frequently in the apixaban group (5.0%) than in the ASA group (3.63%) (HR 1.38 [95% CI 1.07-1.78] p=0.014). In addition, all bleeding events occurred more frequently in the apixaban group (11.62%) group compared with the aspirin group (8.99%) (HR 1.30 [95% CI 1.10-1.53] p=0.0017). In each treatment group, there were five fatal bleeds and 11 intracranial haemorrhages.

7.3.2.2. Other studies

In study CV185067, the proportion of subjects with major or CRNM bleeding events was 5.3% in the warfarin group and 1.4% in both the apixaban 2.5mg BID and 5.0mg BID groups. The proportion of subjects with total bleeding events was 12.5% in the apixaban 2.5 mg BID group, 23.9% in the apixaban 5.0 mg BID group and 17.3% in the warfarin group. Epistaxis was the most frequent bleeding event in all groups. There were no major bleeding events in either of the apixaban groups.

Comment: Clinically significant bleeding was less frequent in subjects treated with apixaban 2.5 mg BID or 5.0 mg BID compared with subjects who received warfarin. The results of this study in 222 Japanese subjects treated for 12 weeks are consistent with the conclusions of the pivotal Phase 3 study CV185030.

7.3.3. Deaths and other serious adverse events

7.3.3.1. Pivotal studies

In study CV185030, death was analysed as an efficacy endpoint (adjudicated all-cause death). There were 429 (4.7%) deaths in the apixaban group compared with 468 (5.2%) in the warfarin group (HR 0.89 p<0.05). The most common Serious AEs resulting in death for apixaban subjects were: sudden death (0.6%), cardiac failure (0.4%), myocardial infarction (0.3%), sudden cardiac death (0.3%), cardiac arrest (0.3%), pneumonia (0.3%), death (0.2%) and ischaemic stroke (0.2%). In study CV185048, adjudicated all-cause death was also analysed as an efficacy endpoint. During the treatment period, there were 91 (3.3%) deaths in the apixaban group compared with 115 (4.1%) in the ASA group. All-cause death was numerically lower for apixaban compared with ASA but the difference was not statistically significant (HR 0.79 p<0.07). The most common serious AEs resulting in death for apixaban subjects were: death (0.5%), sudden death (0.3%), cerebrovascular accident (0.3%), pneumonia (0.3%), congestive cardiac failure (0.2%), cardiac failure (0.2%), and myocardial infarction (0.2%).

In study CV185030, the frequency of SAEs was similar in the apixaban (35.0%) and warfarin (36.5%) groups. Most were related to cardiac, infectious or nervous system disorders, including stroke (Table 5). In study CV185048, the incidence of SAEs was lower in the apixaban group (23.5%) than the ASA group (28.9%). The most common SAEs were atrial fibrillation and cardiac failure in both groups.

Table 5. Summary of Serious Adverse Events Reported in >1.0% of Subjects with onset during the treatment period. (Study CV185030)

System Organ Class (SOC) (%) Preferred Term (PT) (%)	Apixaban N = 9088	Warfarin N = 9052
TOTAL SUBJECTS WITH AN EVENT	3182 (35.0)	3302 (36.5)
CARDIAC DISORDERS	1278 (14.1)	1231 (13.6)
CARDIAC FAILURE	310 (3.4)	301 (3.3)
ATRIAL FIBRILLATION	301 (3.3)	287 (3.2)
CARDIAC FAILURE CONGESTIVE	171 (1.9)	175 (1.9)
ANGINA UNSTABLE	112 (1.2)	87 (1.0)
INFECTIONS AND INFESTATIONS	598 (6.6)	622 (6.9)
PNEUMONIA	202 (2.2)	231 (2.6)
NERVOUS SYSTEM DISORDERS	458 (5.0)	465 (5.1)
ISCHAEMIC STROKE	91 (1.0)	76 (0.8)

7.3.3.2. Other studies

In study CV185067, there were 4 (5.3%) SAEs in the warfarin group, compared with 1 (1.4%) in the apixaban 2.5 mg BID group, and 5 (7.0%) in the apixaban 5 mg BID group. There were no deaths during the study.

7.3.4. Discontinuation due to adverse events

7.3.4.1. Pivotal studies

In study CV185030, the incidence of AEs leading to discontinuation of study drug was lower in the apixaban group (7.6%) than the warfarin group (8.4%). In warfarin-naive subjects, the incidence of AE leading to discontinuation of study drug was 7.8% in the apixaban group compared with 8.8% in the warfarin group. In study CV185048, the incidence of AEs leading to discontinuation of study drug was lower in the apixaban group (8.5%[12]) than the ASA group (13.0%).

7.3.4.2. Other studies

In Study CV185067 twelve subjects discontinued the study because of AEs during the treatment period: 4 (5.3%) in the warfarin group and 4 (5.6%) in each of the apixaban groups.

7.3.5. Laboratory tests

7.3.5.1. Liver function

7.3.5.1.1. Pivotal studies

Three independent hepatologists provided blinded assessments of subjects with concurrent elevation of ALT >x3 ULN and total bilirubin >x2 ULN and /or pre-defined SAEs (jaundice, hepatitis and hepatic failure) related to elevated LFTs. The frequency of significant LFT elevations was low and similar in the apixaban and comparator groups in both pivotal studies CV185030 and CV185048. Most significant LFT abnormalities were transient and associated with identifiable causes such as cholelithiasis. Liver-related deaths occurred mainly in subjects with underlying liver disease including malignancy.

7.3.5.1.2. Other studies

In Study CV185067 the proportion of subjects with elevated LFTs during the treatment period was low and comparable across the three treatment groups. No subjects had ALT >x3ULN and no subjects had elevated ALT >x3ULN and total bilirubin >x1.5ULN on the same day in any treatment group. No subjects discontinued study drug because of elevated LFTs.

[12] Erratum. Correct value is 9.5%

7.3.5.2. Kidney function

7.3.5.2.1. Pivotal studies

The incidence of marked abnormalities of renal function was low and similar in both pivotal studies (CV185030 and CV185048 pooled data). Treatment-emergent significant elevations of serum creatinine occurred in 54 (2.2%) subjects in the apixaban groups and 58 (2.6%) [13] subjects in the comparator groups.

7.3.5.2.2. Other studies

In study CV185067, significant elevations in serum creatinine occurred in 1 (1.4%) subject in the warfarin group, 2 (2.9%) subjects in the apixaban 2.5 mg BID group, and 1 (1.4%) subject in the apixaban 5.0 mg BID group.

7.3.5.3. Other clinical chemistry

7.3.5.3.1. Pivotal studies

Marked laboratory abnormalities occurred infrequently for most parameters and they were similar in the apixaban and warfarin groups in CV185030, and the apixaban and ASA groups in CV185048. Overall, there were no marked differences in the frequencies of MA of liver function, kidney function or creatinine kinase in the pooled pivotal studies.

7.3.5.3.2. Other studies

In study CV185067 marked laboratory abnormalities occurred in 21.6% of the warfarin group, 23.6% of the apixaban 2.5 mg BID group and 21.1% of the apixaban 5.0% BID group. There were five AEs related to LFT abnormalities, all in the apixaban groups. None were serious or lead to treatment discontinuation.

7.3.5.4. Haematology

7.3.5.4.1. Pivotal studies

In the pooled studies CV185030 and CV185048, the frequency of thrombocytopaenia (platelets <100,000) during the treatment period was low and similar in the apixaban group (1.1%) and comparator groups (1.1%). Five subjects (<0.1%) in the apixaban group and four subjects (<0.1%) in the comparator group had platelet counts <50,000 during the treatment period. In study CV185030, MA relating to RBC and platelets were similar in the apixaban (17.7%) and warfarin (17.0%) groups. MA relating to WBC were reported in 11.1% of subjects in the apixaban group compared with 11.5% in the warfarin group. In study CV185048, MA relating to RBC and platelets were similar in the apixaban (6.7%) and ASA (6.3%) groups. MA relating to WBC were reported in 0.7% of subjects in the apixaban group compared with 0.8% in the ASA group.

7.3.5.4.2. Other studies

There were no clinically meaningful differences between treatment groups in haematological parameters in study CV185067.

7.3.5.5. Electrocardiograph

7.3.5.5.1. Pivotal studies

In studies CV185030 and CV185048, ECGs at baseline were similar in the apixaban and comparator groups. No clinically relevant differences between treatment groups were observed over time. Apixaban had no significant effects in a thorough QTc study conducted previously.

[13] Sponsor comment: these values are for BUN elevations. The analogous figures for creatinine elevations are 589 (5.5%) and 606 (5.7%).

7.3.5.5.2. Other studies

In study CV185067, only one subject in each treatment group had a significant change in ECG from baseline.

7.3.5.6. Vital signs

7.3.5.6.1. Pivotal studies

In the Phase 3 studies, mean changes from baseline in systolic and diastolic blood pressure and heart rate were similar in the apixaban and warfarin groups in CV185030 and in the apixaban and ASA groups in CV185048. The frequencies of AEs (BP decreased, BP increased, SBP increased, heart rate decreased and heart rate increased) were <1.0% of subjects in each treatment group.

7.3.5.6.2. Other studies

In study CV185067 there were no clinically relevant changes in vital sign measurements in the three treatment groups during the treatment period.

7.3.6. Post-marketing experience

Apixaban has not been approved for the proposed indication so no post-marketing experience is available. The date of first launch of apixaban for the prevention of VTE was 15 Jun 2011 and no meaningful data were available for this submission. The first PSUR was scheduled to be distributed in Jan 2012.

7.3.7. Safety issues with the potential for major regulatory impact

7.3.7.1. Liver toxicity

None identified.

7.3.7.2. Haematological toxicity

None identified.

7.3.7.3. Serious skin reactions

None identified.

7.3.7.4. Cardiovascular safety

None identified.

7.3.7.5. Unwanted immunological events

Not applicable.

7.4. Other safety issues

7.4.1. Safety in special populations

Safety related to bleeding endpoints was analysed extensively in multiple subgroups defined by age, gender, race, geographical region, body weight, BMI, prior warfarin and ASA status, and others. These are discussed in the individual study evaluations above. Overall, there were no clinically meaningful differences in any subgroup compared with the general populations and no specific medical risk factors were identified.

Safety was specifically assessed in subjects with renal impairment (serum creatinine ≥ 133 µmol/L), the very elderly (age ≥80 years) and subjects with low body weight (≤60 kg). All subjects within these categories received the reduced dose of apixaban 2.5 mg BID. Hazard ratios for major bleeding within these subgroups were similar to those observed in the general treatment population. Moreover, there was no excess of AEs or laboratory MAs in these special

populations. Subjects with suspected or known coagulopathy due to hepatic impairment were specifically excluded from both pivotal studies. Apixaban has not been studied in subjects with severe renal impairment (CrCl ≤15 ml/min) or in pregnant or lactating women.

7.4.2. Safety related to drug-drug interactions and other interactions

Potential PK/PD interactions with concomitant medications were assessed using nonclinical and clinical data, including twelve drug interaction studies. Nonclinical PK data suggested that apixaban has minimal effects on CYP450 induction or inhibition so it is unlikely that apixaban will affect the exposure of other drugs. The potential for other drugs to affect apixaban exposure appeared to be related mainly to the induction or inhibition of CYP3A4 and CYP3A5 metabolism or P-gp mediated efflux. Specific attention was paid to potential PK interactions between apixaban and the anticoagulant or antiplatelet agents enoxaparin, aspirin and clopidogrel. There was an additive effect on anti-Xa activity with co-administration of apixaban and enoxaparin. However, there were no PD interactions between apixaban and aspirin, naproxen or clopidogrel based on template bleeding time, platelet aggregation, clotting tests or anti-Xa activity. Ketoconazole (a strong inhibitor of CYP3A4 and P-gp) and diltiazem (a moderate inhibitor of CYP3A4) increased apixaban exposure 2-fold and by 40%, respectively. Naproxen (a P-gp inhibitor) increased apixaban exposure by 60%. Rifampicin (a strong CYP and P-gp inducer) reduced apixaban exposure by 40-50%.

Comment: *In vitro* and clinical data in healthy volunteers suggest that apixaban is unlikely to affect the metabolism of other drugs. Exposure to apixaban is likely to be affected by concomitant inhibitors and inducers of CYP3A4 and P-gp and appropriate caution should be observed. Despite the limited evidence of significant interactions, care should be observed with the concomitant use of ASA, other NSAIDs and platelet inhibitors.

7.5. Evaluator's overall conclusions on clinical safety

Monitoring of standard safety endpoints (including AEs, SAEs, laboratory investigations, vital signs, ECGs, LFTs and neurologic AEs) demonstrated no clinically significant differences between subjects treated with apixaban and the active comparators, warfarin and ASA. There were no placebo control subjects. However, exposure was high in all treatment groups (15,534 and 15,184 patient-years for apixaban and warfarin respectively in study CV185030; 3,193 and 3,150 patient-years for apixaban and ASA respectively in study CV185048). Duration of treatment averaged ~1.7 years[14] so it is unlikely that a significant, common safety signal for apixaban was overlooked.

The primary safety endpoint in both pivotal studies was bleeding. Bleeding events were categorized a priori, investigated and recorded carefully, and major events were confirmed by an independent adjudicating committee. In study CV185030, the safety profile of apixaban in relation to major and minor bleeding was superior to warfarin. The difference was highly significant and clinically relevant. In contrast, in study CV185048 there was a higher incidence of major bleeding in the apixaban group compared with the ASA group. The difference was not statistically significant and the number of fatal bleeds and intracranial haemorrhages was the same in both groups. However, there was a statistically significant increase in the composite of both Major + CRNM and all bleeding in the apixaban group compared with the ASA group. On balance, the evidence suggests that apixaban is more likely to cause bleeding than ASA (as might be predicted from the pharmacology of the two compounds).

The safety profile of apixaban was similar in subgroups which included the elderly, subjects with renal failure, and both warfarin-experienced and warfarin-naive subjects. Of special note,

[14] Sponsor clarification: 1.7 years for Study CV185030 and 1.1 years for Study CV185048.

apixaban was not associated with an increased risk of MI in either pivotal study although approximately one third of subjects had pre-existing coronary artery disease.

Overall, the safety summary provided by the sponsor is acceptable.

8. First round benefit-risk assessment

8.1. First round assessment of benefits

The lifetime risk of AF in those over 55 years of age is 20-25% in both genders in US and Europe and the incidence will rise as these populations age. AF reduces exercise tolerance and may exacerbate cardiac failure. However, the most significant association is stroke which is increased five-fold in those with AF. More than 15% of strokes are associated with AF and 70% of these are fatal. The risk of stroke is 2.8% in those aged 60-69 years; 9.9% in those aged 70-79; and 23.5% in those aged 80-89 (6). The mortality in subjects with AF is twice that of age-matched subjects with sinus rhythm, due at least in part to the increased risk of stroke (6). The risk of stroke is enhanced by the association with other risk factors encapsulated in the CHADS2 score: congestive heart failure, hypertension, age, diabetes, and stroke (including TIA) (8).

Warfarin is the gold standard for the prevention of stroke in subjects with AF and stroke rates may be reduced by up to 64% compared with subjects treated with placebo (7). However, up to 50% of subjects with AF receive treatment other than warfarin (approximately 30% are treated with ASA and 20% receive no antithrombotic therapy) (9). Antiplatelet agents such as ASA reduce stroke in AF subjects by 20%, but warfarin reduces stroke by 40% compared with anti-platelet agents (10). Several European and US guidelines together advocate the use of warfarin for subjects with two or more risk factors for stroke, and ASA as a less preferable alternative for those with only a single risk factor. Up to 50% of subjects are considered unsuitable for warfarin therapy, mainly due to the risk of bleeding. Moreover, the benefit of warfarin therapy depends on the maintenance of INR within 2.0-3.0 but this is notoriously difficult to achieve, especially in elderly subjects. Treatment is complicated by concomitant illnesses such as hepatic and renal impairment, concomitant medications with the risk of drug-drug interactions, poor treatment compliance and logistic difficulties associated with long-term INR monitoring.

ASA reduces the risk of stroke, but not fatal stroke, in AF patients by up to 22% compared with placebo. However, ASA has been shown to be less effective than warfarin in preventing stroke with event rates of 4.5% and 2.4% respectively (HR 0.55 [95% CI 0.43-0.71])(11).

The primary efficacy endpoint in both pivotal studies was stroke (ischaemic, haemorrhagic or unspecified) or SE. Secondary endpoints were all-cause death in both studies, and major vascular events (stroke, SE, MI, vascular death) in CV185048. The primary endpoint for CV185030 was NI or superiority if NI was demonstrated. NI was demonstrated and apixaban was significantly superior to warfarin and to ASA for the composite endpoint of stroke and SE. The incidence of SE was low compared with stroke as demonstrated in previous AF studies. Apixaban had the largest benefit on haemorrhagic stroke as shown below (Tables 6 and 7):

Table 6. Key efficacy outcomes in subjects with AF in study CV185030

	Apixaban N=9120 n (%/yr)	Warfarin N=9081 n (%/yr)	Hazard Ratio (95% CI)	P-Value
Stroke or systemic embolism*	**212 (1. 27)**	**265 (1. 60)**	**0. 79 (0. 66, 0. 95)**	**0. 0114**
Stroke				
Ischemic or undetermined	162 (0. 97)	175 (1. 05)	0. 92 (0. 74, 1. 13)	
Hemorrhagic	40 (0. 24)	78 (0. 47)	0. 51 (0. 35, 0. 75)	
Systemic embolism	15 (0. 09)	17 (0. 10)	0. 87 (0. 44, 1. 75)	
All-cause death*†	**603 (3. 52)**	**669 (3. 94)**	**0. 89 (0. 80, 1. 00)**	**0. 0465**

Table 7. Key efficacy outcomes in subjects with AF in study CV185048

	Apixaban N=2807 n (%/year)	Aspirin N=2791 n (%/year)	Hazard Ratio (95% CI)	P-Value
Stroke or Systemic embolism*	**51 (1. 62)**	**113 (3. 63)**	**0. 45 (0. 32, 0. 62)**	**<0. 0001**
Stroke				
Ischemic or undetermined	43 (1. 37)	97 (3. 11)	0. 44 (0. 31, 0. 63)	
Hemorrhagic	6 (0. 19)	9 (0. 28)	0. 67 (0. 24, 1. 88)	
Systemic embolism	2 (0. 06)	13 (0. 41)	0. 15 (0. 03, 0. 68)	
Stroke, SE, MI, or vascular death*	**132 (4. 21)**	**197 (6. 35)**	**0. 66 (0. 53, 0. 83)**	**0. 003**
Myocardial infarction	24 (0. 76)	28 (0. 89)	0. 86 (0. 50, 1. 48)	
Vascular Death	84 (2. 65)	96 (3. 03)	0. 87 (0. 65, 1. 17)	
All-cause death*†	**111 (3. 51)**	**140 (4. 42)**	**0. 79 (0. 62, 1. 02)**	

Apixaban significantly reduced all-cause death compared with warfarin, with a trend in favour of apixaban compared with ASA. In CV185048, there was a significant benefit in favour of apixaban on major vascular events. The efficacy benefit was apparent in all subgroups and appeared to be independent of previous warfarin use, age, gender, number of risk factors for stroke, renal function, and apixaban dose reduction in at risk subjects. Apixaban was also superior to warfarin even in subjects whose INR control was in the optimal range.

Comment: The statistical benefit in favour of apixaban was highly significant when compared with both warfarin and ASA. The benefit in favour of apixaban was clinically worthwhile but modest compared with warfarin (HR 0.79 [95% CI: 0.66-0.95] for stroke; HR 0.89 [95% CI: 0.80-1.00] for all-cause death). However, the clinical benefit in favour of apixaban compared with ASA was more marked than that with warfarin (HR 0.45 [95% CI: 0.32-0.62] for stroke; HR 0.66 [95% CI: 0.53-0.83] for major vascular events). Overall, there is strong evidence that apixaban is equally effective or superior to the current gold standard therapies for stroke prevention in AF.

8.2. First round assessment of risk

Standard safety endpoints included AEs, SAEs, death, discontinuations due to AEs, neurologic and laboratory assessments including LFTs were recorded. Overall, the frequency of all the safety indices was acceptable with no evidence to suggest excess risk in the apixaban group compared with the warfarin and ASA groups.

The single greatest risk of apixaban for the proposed indication is bleeding. The frequency of bleeding with apixaban has been compared with warfarin, the most widely used anticoagulant therapy, and ASA, the most widely used antiplatelet agent for prophylaxis in AF. The frequency of bleeding was carefully evaluated and classified according to accepted guidelines such as ISTH,

GUSTO and TIMI. Bleeding endpoint criteria were closely defined and adjudicated by a blinded expert panel for consistent reporting and to avoid bias.

The frequency of major bleeding, fatal haemorrhages, intracranial haemorrhages and all bleeding was less in the apixaban group compared with the subjects on warfarin as shown below (Table 8). The benefit in favour of apixaban was statistically significant, clinically relevant, and was independent of INR control in the warfarin group. Major bleeding at critical sites was similar or lower in the apixaban group compared with the warfarin group, with the possible exception of intraocular bleeding.

Table 8. Bleeding events in subjects with atrial fibrillation in study CV185030

	Apixaban N=9088 n (%/year)	Warfarin N=9052 n (%/year)	Hazard Ratio (95% CI)	P-value
Major*†	327 (2.13)	462 (3.09)	0.69 (0.60, 0.80)	<0.0001
Fatal	10 (0.06)	37 (0.24)		
Intracranial	52 (0.33)	122 (0.80)		
Major + CRNM	613 (4.07)	877 (6.01)	0.68 (0.61, 0.75)	<0.0001
All	2356 (18.1)	3060 (25.8)	0.71 (0.68, 0.75)	<0.0001

* Assessed by sequential testing strategy for superiority designed to control the overall type I error in the study.

Major bleeding occurred more often in the apixaban group compared with the ASA group as shown below (Table 9). The difference was not statistically significant and there was no increase in the number of subjects with fatal or intracranial bleeds. However, there was a statistically significant benefit in favour of ASA for the composite of major and CRNM and all bleeding.

Table 9. Bleeding events in subjects with atrial fibrillation in study CV185048

	Apixaban N=2798 n(%/year)	ASA N=2780 n (%/year)	Hazard Ratio (95%CI)	P-value
Major†	45 (1.41)	29 (0.92)	1.54 (0.96, 2.45)	0.0716
Fatal, n	5 (0.18)	5 (0.18)		
Intracranial, n	11 (0.39)	11 (0.40)		
Major + CRNM	140 (4.46)	101 (3.24)	1.38 (1.07, 1.78)	0.0144
All	325 (10.85)	250 (8.32)	1.30 (1.10, 1.53)	0.0017

Comment: The frequency of bleeding is clearly less in subjects treated with apixaban than with warfarin and the benefit is clinically meaningful. As would be expected, the frequency of bleeding is greater in subjects treated with apixaban compared with ASA. The excess risk is small but clinically meaningful despite the similar frequency of fatal and intracranial bleeds in both treatment groups.

8.3. First round assessment of benefit-risk balance

The benefit-risk balance of apixaban 5 mg BID, given for the proposed usage, is favourable.

9. First round recommendation regarding authorisation

Authorisation is recommended for apixaban 2.5 mg BID or 5 mg BID for the proposed additional indication *'to reduce the risk of stroke, systemic embolism and death in patients with non-valvular atrial fibrillation with at least one additional risk factor for stroke'*.

10. Clinical questions

The sponsor is requested to provide, in its s31 response, a copy of its responses to all of the questions asked in the US FDA Complete Response Letter addressed to Bristol-Myers Squibb in the USA and signed by Robert Temple on 22/06/2012. This pdf document is the attachment to the sponsor's e-mail to [Information redacted] of the TGA of 26/06/2012 and identified by the code 120626 FDA Complete Response Letter. If there are any questions and/or issues from this Complete Response Letter which are still unresolved by the due date for the s31 response, the sponsor is requested in that response to identify these questions and/or issues so that the delegate can seek to resolve them via the Delegate's Request for ACPM Advice.

10.1. Pharmacokinetics

The sponsor is requested to provide the report of Study CV185025 for review within the Round 2 evaluation phase of this submission.

Other than information contained in the PPK report, have the PK of apixaban in patients with AF and healthy subjects been directly compared in a single study, if so can the sponsor please provide the details?

10.2. Pharmacodynamics

Other than information contained in the PPK report, have the PD of apixaban in patients with AF and healthy subjects been directly compared in a single study, if so can the sponsor please provide the details?

10.3. Efficacy

None.

10.4. Safety

None.

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

Evaluator questions and sponsor responses relating to the first round report on the PK/PD of apixaban.

Question 1. *The sponsor is requested to provide the report of Study 185025 for review within the Round 2 evaluation phase of this submission.*

Sponsor's Response 1. Study CV 185025 was previously submitted in the Category 1 application of 27 May 2010 to register Eliquis for VTE. At the request of the TGA an additional copy of this study was provided on 24 April 2012 (our ref: 120424StudyCV185025). TGA has confirmed that the Clinical Evaluator has received this study report.

Evaluator's Response 1. Study CV 185025, which examined the APIXABAN PK in subjects with mild to moderate hepatic impairment and in healthy subjects, was received just prior to the final submission of the First Round Evaluation; therefore, the results and findings of this study were incorporated into the final version of the First Round Evaluation.

Questions 2 and 3. Other than information contained in the population pharmacokinetics (PPK) report, have the pharmacokinetics of apixaban in patients with atrial fibrillation and in healthy subjects been directly compared in a single study? If so, the sponsor is requested to provide the relevant details.

Sponsor's Response 2 and 3. There is no single study comparing the PK/PDs of apixaban between healthy subjects and patients with atrial fibrillation. All comparisons between healthy subjects and patients with atrial fibrillation have been made on the basis of population pharmacokinetic modeling.

Evaluator's Response 2 and 3. The sponsor has confirmed that no studies directly compared the PK/PD in patients with AF and healthy subjects. The PPK modelling study indicated that AF patients had decreased apixaban CL/F (13.9%) compared to non-Asian healthy subjects, suggesting that apixaban exposure is increased in subjects with AF compared with healthy non-Asian subjects. In addition, Asian race reduced apixaban clearance by 14%; and a 15% to 30% increase in AUC (compared to control) was observed for intrinsic factors such as age (≥ 65 years), gender, and low body weight (≤ 50 kg), whereas, body weight ≥120 kg was associated with an approximately 30% lower AUC_{inf}. Therefore in the absence of clinical trial data that directly examine the effects of these characteristics on apixaban PKs and PDs, the evaluator recommends that the PRECAUTION section of the PI is modified to identify that these characteristics may alter apixaban PKs and PDs.

A copy of the FDA CRL was provided to the TGA on 26 June 2012 and the sponsor's responses have been submitted. The questions relate mainly to dispensing errors in the ARISTOTLE study and potential root cause analyses.

FDA Question 1: The most significant concern was related to dosing errors in the ARISTOTLE study (CV185030) as addressed in the first round assessment under *Efficacy*, above. In a report to the EMA, the sponsors stated that the frequency of drug dispensation errors to patients was <0.1%. However, the FDA requested a more detailed analysis to ensure there was no impact on any primary efficacy or safety endpoints due to patients who may have received two active study drugs (apixaban and warfarin), or no active study at all. Three independent, mutually exclusive audits were conducted on random samples of tear-off dispensing labels attached to the study drug containers. The first audit of an 8% patient sample was initiated by the sponsor and a further 12% sample was analysed at EMA request. The FDA requested a further sample of 20% taking the complete sample to 40% of all study subjects. Legible labels were obtained in 99.2% of the total sample. In the FDA initiated audit, dispensing the wrong study medication occurred in 0.1% of apixaban patients and 0.116% of patients assigned to warfarin. In the initial 20% sample audit the frequencies were 0.048% for apixaban and 0.041% for warfarin. Although the numbers were small, the frequency of detected errors was double in the 40% audit compared with the 20% audit. However, sampling errors become less frequent as sample size increases and the true error rate is unlikely to be significantly different from the rate detected in the 40% sample. The average number of dispensations in each patient was twenty: most errors were isolated and multiple errors did not occur in individual patients. Observed errors were combined with missing data to give an estimate of total error, assuming that the observed and missing error rates were the same. Using this worst case analysis, the overall frequency of incorrect dispensations was up to 0.47% and 0.54% in the apixaban and warfarin groups respectively. Using these worst case assumptions, the frequency of dosing errors was small, and the superiority of apixaban over warfarin for stroke, systemic embolisation, bleeding and all cause death was maintained. Only if errors in missing data were 100-fold higher than the observed rate would the statistical significance of the superiority exceed p=0.05 (p=0.053). As

an example, the results of the sensitivity analysis relating to stroke and systemic embolisation are shown below (Table 10). Hazard ratios and 95% CI were comparable in the different censoring scenarios.

Table 10. Sensitivity analysis for Time to SSE with different censoring scheme – Randomised subjects in combined random sample.

	Hazard Ratio (Apixaban/Warfarin)	95% CI
No Censoring	0.84	(0.62, 1.15)
Censoring Subjects Only Legible Label Errors	0.82	(0.60, 1.13)
Legible Label Errors + 50% Missing Labels	0.84	(0.61, 1.16)
Legible Label Errors + All Missing Labels	0.88	(0.63, 1.23)

These further analyses largely confirm the analysis and conclusions discussed in the first round evaluation. The superiority for apixaban compared with warfarin has been confirmed.

FDA Question2: The FDA requested an estimate of the number of patients unblinded by investigators without reporting them to the sponsor. Based on the random sample audits, the frequency of unreported unblinding was 3/8000 patients. This can be considered trivial.

FDA Question 3: The FDA requested details of the Site Monitoring Plan to understand how dispensing errors were allowed to occur. The sponsor responded that site monitoring was conducted to a high standard in accordance with their SOPs. The processes are described in detail and the sponsors point out that they were good enough to detect the errors in this case. In general, most errors were transcriptional in the eCRF and relatively few actual dispensing errors occurred.

FDA Question 4: The FDA questioned manual changes to the automated IVRS. They were concerned that human error may have contributed to dispensing errors. The sponsors justify this practice which is occasionally necessary and they describe the pre-defined procedures and methods used for manual changes. In the event, there were only 107 manual changes out of over 400,000 study treatment containers so they were unlikely to have contributed to the dispensing error rate.

FDA Question 5: A 'cursory examination' of the study datasets by the FDA revealed that they did not always match the information in the eCRFs. The sponsor replies that the perceived error rate was overstated and that accuracy is ensured by data management and statistical SOPs, the use of validated systems, and the use of additional quality checks and validation procedures.

FDA Question 6: Some patients had a unique AE listed multiple times as both non-serious and serious and the sponsor was requested to prepare a new adverse event analysis dataset. The sponsor offered a variety of legitimate reasons why such apparent dual listings may occur. However, they prepared a new dataset. The minor changes did not impact on the safety profile of apixaban previously noted in the ARISTOTLE study.

In response to the FDA CRL, the TGA had several follow-up questions as shown below:

TGA Questions 14 August 2013:

- Clarification of all analysis conducted (that is, 12%, 20%, 40).
- Confirmation that all of the above audits were mutually exclusive.
- Time of request received and from which regulatory authority.
- Strategy of sample size selection for each analysis conducted.
- Timelines for all analyses conducted and responses/results being made available.

The sponsor confirmed that all the audits were mutually exclusive. The responses to the other questions are summarised in Table 11 below. The responses are satisfactory and the FDA have not raised further concerns.

Table 11. Summary of Responses to TGA Questions of 14 August 2012					
Agency	**Request Date**	**Response Date**	**Analysis Description**	**Strategy for Sample Size**	**Comments See comment above**
FDA	09-Feb-2012	21-Feb-2012	• 8% sample size ("convenience" sample).	• These labels were available centrally at BMS sites; there was no sample size calculation.	• The request came during a meeting with the FDA. • Two analyses were conducted. • The first analysis was of available original product labels. It suggested that a majority of the 3274 discrepancies in container numbers between the IVRS assignment and the eCRF record were due to eCRF transcription errors rather than actual errors in dispensing. • Only 0.12% of all labels re-entered from the original source labels did not match the labels assigned in the IVRS (less than the 0.38% calculation based on all container numbers entered into the web-based eCRF.

Table 11. Summary of Responses to TGA Questions of 14 August 2012					
Agency	**Request Date**	**Response Date**	**Analysis Description**	**Strategy for Sample Size**	**Comments See comment above**
					• The second analysis sought to determine if the container code entries in the eCRF that did not match an IVRS assignment were possibly simple transcription errors. Error logs associated with drug shipment to sites were examined. • Based on this comparison it became apparent that 76% of the incorrect container numbers (defined as those containers that did not match the IVRS assignment) captured in the eCRF were transcription errors (because the container did not exist at the site). • The overall conclusion from these analyses was that the true proportion of errors in medication dispensations was therefore likely even lower than the 0.38% that was derived, based on eCRF entries.

Table 11. Summary of Responses to TGA Questions of 14 August 2012					
Agency	**Request Date**	**Response Date**	**Analysis Description**	**Strategy for Sample Size**	**Comments See comment above**
EMA	15-Mar-2012	17-May-2012	**20% randomized sample** **Main Analyses:** • Frequency of potentials study medication errors estimated based on eCRF entries. • Frequency of potential study medication errors estimated based on eCRF entries after excluding obvious transcription errors. • Estimated Frequency of Study Medication Errors - Sample of IP Labels. **Sensitivity Analyses:** • Excluding endpoints on or after the first suggestion in the eCRF of a dispensing or transcription error and censoring subjects who did not have an endpoint prior to this error. • Excluding all data from subjects who had a container of the incorrect type entered in the eCRF during the analysis period.	• The algorithm for the 12% sampling was agreed by the EMA and is attached as Appendix 1.	• The request came from a revised D120 list of CHMP questions. The revision followed on from proactive communication by the MAH to the EMA on the evolving situation. • A copy of the summary response to the EMA question was submitted to the TGA on 21 May 2012.

Table 11. Summary of Responses to TGA Questions of 14 August 2012					
Agency	**Request Date**	**Response Date**	**Analysis Description**	**Strategy for Sample Size**	**Comments See comment above**
FDA	16-Jul-2012	17-Sep-2012	• Confirmatory sample (20%). • 3 major sets of analysis – Container labels. – eCRF data entries relative to IVRS assignments. – Sensitivity analyses on simulated medication error frequencies for the ARISTOTLE conclusions.	• The SAPs for container label analysis and the sensitivity analyses are presented in Appendix 2. • FDA provided sponsors with a sample of 236 sites selected from the 813 sites with treated subjects that were neither part of the Convenience nor in the First Random Sample.	• Errors in treatment were low and consistent across treatment arms, indicating a well-controlled process. • Sensitivity analyses demonstrate primary outcomes from ARISTOTLE maintained. • Please refer to summary response for CRL1 for detailed response.

Table 11. Summary of Responses to TGA Questions of 14 August 2012					
Agency	**Request Date**	**Response Date**	**Analysis Description**	**Strategy for Sample Size**	**Comments See comment above**
EMA	23-Jul-2012	17-Aug 2012	• Potential for medication errors in the illegible labels in EMA 12% sample.	N/A	• The request was part of the D180 List if Outstanding Issues from the CHMP. • Bar code reader technology was applied to identify illegible labels. • The number of medication errors (17) and the overall medication error rate (0.03%) are unchanged by this additional analysis. • In addition, the EMA inspections of three of the trial sites support that the study was GCP compliant. • The EMA response can be provided upon request. • The Eliquis SPAF application received a positive CHMP opinion on 20 September 2012.

12. Second round benefit-risk assessment

The second round risk-benefit assessment has not changed from the first round assessment.

13. Second round recommendation regarding authorisation

Authorisation is recommended for apixaban 2.5 mg BID or 5 mg BID for the proposed additional indication *'to reduce the risk of stroke, systemic embolism and death in patients with non-valvular atrial fibrillation with at least one additional risk factor for stroke'*.[15]

[15] See the AusPAR for this application for the Indication proposed by the Delegate and the finally approved Indication.

14. References

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