CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202155Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Clinical Pharmacology/Biopharmaceutics Review
(Addendum to Previous Review – DARRTS date: 02/15/2012)

PRODUCT (Generic Name):	Apixaban
NDA:	202-155
PRODUCT (Brand Name):	ELIQUIS®
DOSAGE FORM:	Tablets
DOSAGE STRENGTHS:	2.5 mg and 5 mg
INDICATION:	Prevention of stroke, systemic embolism, (b) (4) in patients with non-valvular atrial fibrillation
SUBMISSION DATE:	Study report submission on 8/14/2012
SPONSOR:	Bristol-Myers Squibb and Pfizer
REVIEWERS:	Ju-Ping Lai, Ph.D.
TEAM LEADER:	Rajanikanth Madabushi, Ph.D.
OCP DIVISION:	DCP 1
OND DIVISION:	HFD 120

TABLE OF CONTENTS

1.0 EXECUTIVE SUMMARY

The sponsor submitted a study report on August 14, 2012: *Effect of Activated Charcoal on the Pharmacokinetics of Apixaban in Healthy Subjects*, to support NDA 202155 (NME) for apixaban while the original NDA was submitted on September 30, 2011 as a final submission of a series of rolling submissions.

Since there is no antidote for apixaban while high systemic exposure increases bleeding. This study evaluated whether activated charcoal could be used to reduce apixaban exposure following oral administration of apixaban. The key findings are as follows:

- Administration of activated charcoal 2 and 6 hours after ingestion of apixaban reduced apixaban exposure (AUC) by approximately 50% and 27%, respectively.
- Peak exposure (Cmax) of apixaban was not affected by the administration of activated charcoal at 2 hours or 6 hours after apixaban administration.

1.1 RECOMMENDATION

The Office of Clinical Pharmacology (OCP/DCP I) has reviewed the study CV185104 with activated charcoal. The submission is acceptable from a Clinical Pharmacology and Biopharmaceutics point of view. Based on the information reviewed in this study, labeling recommendations are provided in the sections 5.2, 10 and 12.3 of the label.

2.0 DETAILED LABELING RECOMMENDATIONS

The text in Blue colored font represents the labeling statements proposed in this review.

5.2 Bleeding

There is no established way to reverse the anticoagulant effect of apixaban, which can be expected to persist for about 24 hours after the last dose, i.e., for about two half-lives. A specific antidote for ELIQUIS is not available. Because of high plasma protein binding, apixaban is not expected to be dialyzable *[see Clinical Pharmacology (12.3)]*. Protamine sulfate and vitamin K would not be expected to affect the anticoagulant activity of apixaban. There is no experience with antifibrinolytic agents (tranexamic acid, aminocaproic acid) in individuals receiving apixaban. There is neither scientific rationale for reversal nor experience with systemic hemostatics (desmopressin and aprotinin) in individuals receiving apixaban. Use of procoagulant reversal agents such as prothrombin complex concentrate, activated prothrombin complex concentrate, or recombinant factor VIIa may be considered but has not been evaluated in clinical studies. Activated oral charcoal reduces absorption of apixaban thereby lowering apixaban plasma concentrations *[see Overdose (10)]*.

10 OVERDOSAGE

There is no antidote to ELIQUIS. Overdose of ELIQUIS increases the risk of bleeding *[see Warnings and Precautions (5.2)]*.

In controlled clinical trials, orally administered apixaban in healthy subjects at doses up to 50 mg daily for 3 to 7 days (25 mg twice-daily for 7 days or 50 mg once-daily for 3 days) had no clinically relevant adverse effects.

In healthy subjects, administration of activated charcoal 2 and 6 hours after ingestion of a 20-mg dose of apixaban reduced mean apixaban area under plasma-concentration time curve (AUC) by 50% and 27%, respectively. Mean apparent half-life of apixaban decreased from 13.4 hours when apixaban was administered alone to 5.3 hours and 4.9 hours, respectively, when activated charcoal was administered 2 and 6 hours after apixaban indicating that charcoal reduced the extent of absorption of apixaban from the gut. *[see Clinical Pharmacology (12.3)]*. Thus, administration of activated charcoal may be useful in the management of apixaban overdose or accidental ingestion, and may also facilitate discontinuation of drug in the event of bleeding *[see Warnings and Precautions (5.2)]*.

Reviewer's Note: Above labeling recommendations were provided based on the information obtained from activated charcoal study. Detail review of the study is provided in the individual study review in section 3.0 of this review.

12.3 Pharmacokinetics

The pharmacokinetics of apixaban are complicated by prolonged absorption. Thus, despite a short clearance half-life of about 6 hours, the apparent half-life during repeat dosing is about 12 hours, which allows BID dosing to provide effective anticoagulation, but also means that when the drug is stopped for surgery, anticoagulation persists for at least a day.

Absorption

Maximum concentrations (C_{max}) of apixaban appear 3 to 4 hours after oral administration of ELIQUIS. Apixaban is absorbed throughout the gastrointestinal tract. The distal small bowel and ascending colon contribute to ~55% of apixaban absorbed via oral route.

Elimination

Following intravenous administration, ~98% of apixaban is eliminated within 24 hours, with a dominant half-life of ~ 5 hours. (b) (4) Following oral administration, the apparent half-life is ~12 hours because of prolonged absorption.

Reviewer's Note:

- ***This information is provided to clarify the prolonged absorption of apixaban which facilitate the effect of activated charcoal to prevent additional absorption of apixaban from later part of the GI tract.***
- ***The second point is to clarify that the apparent half-life of ~12 hours is because of prolonged absorption. When the continued absorption is stopped, the elimination half-life from systemic is ~ 5 hours.***

Other Labeling Changes:

During the labeling communication, the sponsor proposed to (b) (4) **in order to be consistent with the labeling recommendations of apixaban and enoxaparin. While a dedicated DDI study with enoxaparin was conducted and revealed no PK interaction and expected PD interaction of ~50 % increase in anti-FXa activity, the results didn't lead to recommend** (b) (4)**. The sponsor's proposal is based solely on clinical considerations. The sponsor's proposal is considered acceptable.**

Apixaban VS Activated Charcoal

Report # CV185104	**Study Period** 05/06/11 05/17/11	**EDR Link** \\cdsesub1\EVSPROD\NDA202155\\0070\m5\53-clin-stud-rep\533-rep-human-pk-stud\5331-healthy-subj-pk-init-tol-stud-rep\cv185104\cv185104.pdf
Title	Effect of Activated Charcoal on the Pharmacokinetics of Apixaban in Healthy Subjects	
Objectives	To assess the effect of activated charcoal on the pharmacokinetics of apixaban, when administered 2 hours or 6 hours following the dose of apixaban in healthy subjects.	

Rationale: There is no antidote for apixaban while high systemic exposure could increase bleeding. Activated charcoal has been used in the routine management of oral drug overdose including digoxin, phenytoin. This study hence evaluated whether activated charcoal could be used to reduce apixaban exposure following oral administration of apixaban.

Study Design Single-Dose Randomized Open-Label Crossover Single-Center 3-Treatment 3-Period Healthy Vonuteers

Subjects were admitted to the clinical facility on Day -1. Subjects were randomized on Day 1 of Period 1 to 1 of 6 treatment sequences. Each subject received all 3 treatments (showed below) with 1 treatment given on Day 1 of Periods 1, 2, and 3.

Sequence	Period 1	Period 2	Period 3
ABC	A	B	C
ACB	A	C	B
BAC	B	A	C
BCA	B	C	A
CAB	C	A	B
CBA	C	B	A

Screening: -21days	**Washout:** at least 4 days
Sequence	Showed in the table above

Treatments: (Fasted)

A: single oral dose of 20-mg apixaban (4 × 5 mg tablets)

B: single oral dose of 20-mg apixaban followed by administration of an aqueous suspension of activated charcoal (50 g of activated charcoal and 96 g of sorbitol in 240 mL water) 2 hours after dosing with apixaban.

C: single oral dose of 20-mg apixaban followed by administration of an aqueous suspension of activated charcoal (50 g of activated charcoal and 96 g of sorbitol in 240 mL water) 6 hours after dosing with apixaban.

Study medication

Apixaban (BMS-562247) 20 mg (4 x 5 mg tablets), single dose administered orally, batch number 0E56753.

Actidose® (activated charcoal) with sorbitol suspension, 50 g activated charcoal and 96 g sorbitol, single dose administered orally, lot number 0372802.

PK Sampling (Blood) for Apixaban:

Pre-dose, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 6.5, 8, 10, 12, 18, 24, 36, 48, and 72 hours post-dose on Day 1 through 4 of each treatment period

Analytical Method

The performance of the assay method during study sample analysis is acceptable and is summarized in the table below.

Analyte	**Apixaban**
Method	LC-API/MS/MS
Matrix	Plasma
LOQ (ng/mL)	1.00
Range (ng/mL)	1.00 to 1000
QCs (ng/mL)	3.00, 35.0, 400, 800
Accuracy/Bias	7.14%
Precision (CV%)	5.58%

Statistical Method: Geometric means were included for AUC(INF), AUC(0-T), and Cmax. Point estimates and 90% CIs for the differences on the log scale were exponentiated to obtain estimates for ratios of geometric means and 90% CIs on the original scale. Treatment comparisons included Treatment B compared with Treatment A (B/A) and Treatment C compared with Treatment A (C/A).

Study Population :

Enrolled/**Dosed/Completed**/ Discontinued Due to AE	18/**18/18**/0
Age [Median (range)]	30.5 (18-45) yr
Male/Female	10/8
Race (White/Black or African American)	14/4

Results

Pharmacokinetics of apixaban

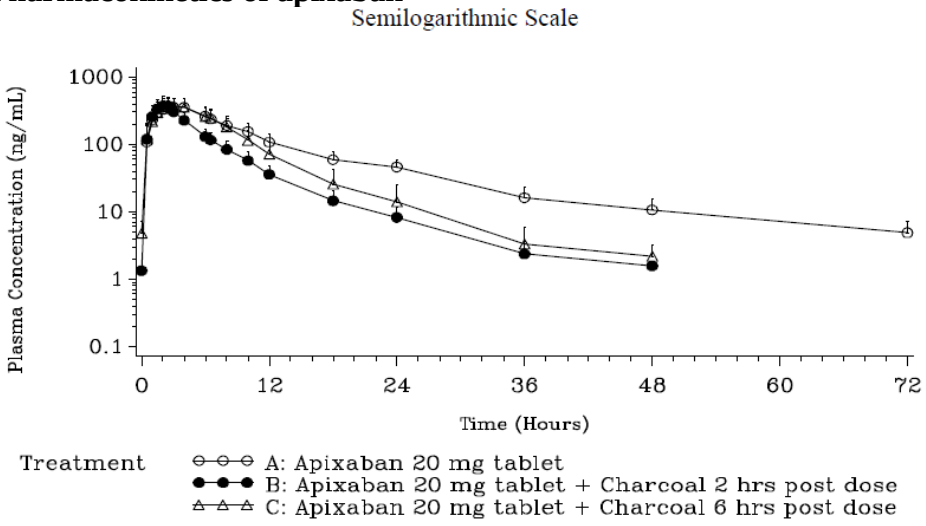

Table 11–3 Plasma Pharmacokinetic Parameters of Apixaban

Parameter (unit)	Treatment: 20-mg Apixaban (N=18)	Treatment: 20-mg Apixaban + Activated Charcoal 2 Hours After Apixaban Dose (N=14)	Treatment: 20-mg Apixaban + Activated Charcoal 6 Hours After Apixaban Dose (N=17)
AUC(0-T) (ng·h/mL)	4080 (27)	2007 (30)	2954 (32)
AUC(INF) (ng·h/mL)	4185 (26)	2034 (30)	2976 (32)
Cmax (ng/mL)	380 (30)	366 (34)	383 (30)
Tmax (h)[a]	2.50 (1.00, 4.00)	2.50 (1.50, 2.50)	2.50 (1.50, 4.00)
T-HALF (h)[b]	13.4 (5.1)	5.3 (1.1)	4.9 (1.2)

Abbreviation: CV, coefficient of variation.
Note: Geometric mean (arithmetic mean CV) is presented for AUC(0-T), AUC(INF), and Cmax.
[a] For Tmax, the median (minimum, maximum) values are presented.
[b] For T-HALF, mean (SD) values are presented.

- Similar apixaban Cmax and median Tmax were observed across the 3 treatments.
- Apixaban mean apparent T-HALF was 5.3 hours, 4.9 hours, and 13.4 hours, respectively, when activated charcoal was administered 2 and 6 hours after dosing with apixaban, and after apixaban administration alone.

Reviewer's Note:

- *The half-lives observed were apparent half-lives and not elimination half-lives. While activated charcoal should act on direct contact with drugs in GI, administration of activated charcoal should only prevent additional absorption and should not be expected to change the elimination half-life. The apparent half-life after apixaban alone (13.4 hrs) represents a combination of elimination and continuous absorption while the apparent half-lives after charcoal treatment (~5 hrs) represent real elimination phase.*
- *From the intravenous study (Study CV185020) where there is no absorption phase, the half-life of apixaban 5 mg dose is 8 hrs. However it should be noted that by 24 hrs, ~98 % is eliminated with a dominant half-life of ~5 hrs. This is consistent with the finding in the activated charcoal study when continuous absorption is prevented. The apparent half-life of apixaban is prolonged after oral dosing due to continuous absorption of apixaban throughout the GI tract.*
- *It should be also noted that from a dedicated regional gastrointestinal absorption study (Study CV185007), apixaban is shown to be absorbed throughout the GI tract. The distal small bowel and ascending colon contribute to ~55% of apixaban absorbed via oral route. This further confirms that the decreased exposure of apixaban by avtivated charcoal is by preventing further absorption of apixaban from the GI.*

Statistic summary

Parameter (unit)	Treatment[a]	N	Adjusted Geometric LS Means	Ratio of Geometric LS Means (B/A or C/A) and 90% CI of the Ratio (B/A or C/A)
AUC(0-T) (ng·h/mL)	A	18	4080.31	–
	B	14	2050.53	0.503 (0.456 – 0.554)
	C	17	3007.71	0.737 (0.674 – 0.806)
AUC(INF) (ng·h/mL)	A	18	4185.27	–
	B	14	2075.98	0.496 (0.450 – 0.547)
	C	17	3028.00	0.723 (0.661 – 0.792)
Cmax (ng/mL)	A	18	379.77	–
	B	14	379.43	0.999 (0.903 – 1.105)
	C	17	391.04	1.030 (0.939 – 1.130)

Abbreviations: CI, confidence interval; LS, least squares.
Note: A linear mixed-effects model analysis was performed on the natural logarithms of AUC(0-T), AUC(INF), and Cmax with treatment, period, and sequence as fixed effects and measurements within subject as repeated measurements.
[a] Treatment A = Single oral dose of 20-mg apixaban.
Treatment B = Single oral dose of 20-mg apixaban + activated charcoal 2 hours after dosing with apixaban.
Treatment C = Single oral dose of 20-mg apixaban + activated charcoal 6 hours after dosing with apixaban.

- Following activated charcoal administration 2 hours after apixaban administration, the ratio of the geometric least squares (LS) means (90% CI) for AUC(0-T) and AUC(INF) of apixaban was 0.503 (0.456 – 0.554) and 0.496 (0.450 – 0.547), respectively.
- Following activated charcoal administration 6 hours after apixaban administration, the ratio of the geometric LS means (90% CI) of AUC(0-T) and AUC(INF) of apixaban was 0.737 (0.674 – 0.806) and 0.723 (0.661 – 0.792), respectively.
- Peak exposure (Cmax) of apixaban was not affected by the administration of activated charcoal at 2 hours or 6 hours after apixaban administration as the ratio of the geometric LS means for Cmax was 0.999 (0.903 – 1.105) and 1.030 (0.939 – 1.130), respectively.

Safety

- Was there any death or serious adverse events? ☐ Yes ☒No ☐ NA

Overall AEs are summarized in the following table:

	Treatment			
No. of subjects (%)	20-mg Apixaban (N=18)	20-mg Apixaban + Activated Charcoal 2 Hours After Apixaban Dose (N=18)	20-mg Apixaban + Activated Charcoal 6 Hours After Apixaban Dose (N=18)	Overall (N=18)
Total number of AEs	4	54	44	102
Number of subjects with at least 1 AE	3 (16.7)	13 (72.2)	14 (77.8)	15 (83.3)

Abbreviation: AE, adverse event.

- Higher percentages of subjects reported AEs after receiving apixaban and activated

charcoal administered 2 hours or 6 hours after dosing with apixaban (72.2% and 77.8%, respectively) compared with apixaban alone (16.7%).

- The highest percentages of subjects reported AEs classified as gastrointestinal disorders (83.3%) and nervous system disorders (33.3%) (diarrhea: 11 subjects (61.1%) each, nausea: 9 and 8 subjects (50.0% and 44.4%, respectively), abdominal pain: 6 subjects each (33.3%), vomiting: 4 and 3 subjects (22.2% and 16.7%, respectively), and headache: 4 subjects each (22.2%)).

Reviewer's note: *Based on the sponsor, the majority of AEs were largely consistent with the known tolerability profile of activated charcoal.*

Conclusion

- Administration of activated charcoal 2 and 6 hours after ingestion of apixaban reduced apixaban exposure (AUC) by approximately 50% and 27%, respectively.
- Peak exposure (Cmax) of apixaban was not affected by the administration of activated charcoal at 2 hours or 6 hours after apixaban administration.

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/s/

JU PING LAI
12/17/2012

RAJANIKANTH MADABUSHI
12/17/2012

BIOPHARMACEUTICS REVIEW

Office of New Drug Quality Assessment

Application No.:	NDA 202-155 (000)	**Reviewer:** Sandra Suarez Sharp, Ph.D.	
Division:	DPARDP		
Applicant:	Bristol Myers Squibb	**Acting Biopharmaceutics Supervisory Lead:** Angelica Dorantes, Ph.D .	
Trade Name:	Eliquis		
Generic Name:	Apixaban (BMS-562247) film-Coated IR Tablets	**Date Assigned:**	Rolling NDA- Oct , 2011
Indication:	Antithrombotic/anticoagulant agent	**Date of Review:**	Feb 19, 2012
Formulation/strength	Immediate Release Tablet/2.5 mg and 5 mg		
Route of Administration	Oral		

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Submission Dates	Date of informal/Formal Consult	PDUFA DATE
Rolling NDA Sep 29, 2011 Original NDA Nov 3, 2011 Dec 9, 2011 Dec 29, 2011 Feb 14, 2012	Oct 2011	March 28, 2012

Type of Submission:	Rolling NDA
Type of Consult:	1. Dissolution method and acceptance criterion 2. Acceptability of [redacted] (b) (4) 3. Acceptability of the lower strength 4. Acceptability of data supporting the bridging throughout the apixaban development 5. Role of dissolution on QbD

SUMMARY OF BIOPHARMACEUTICS FINDINGS:

Apixaban (BMS-562247) is a novel, orally active, selective, direct, reversible inhibitor of the coagulation factor Xa (FXa). It was developed as an antithrombotic/anticoagulant agent. Apixaban immediate release film coated tablets, 2.5 mg and 5 mg are intended to be given [redacted] (b) (4)

The product and process development of apixaban was conducted under a Quality by Design (QbD) paradigm to ensure desired product performance in terms of quality, safety, and efficacy. Dissolution was identified as one of the Critical Quality Attributes (CQAs) for the drug product.

This review focuses on the evaluation of: **1)** The acceptability of the dissolution method and acceptance criterion; **2)** Data supporting the acceptability of the 2.5 mg strength, **3)** The acceptability of data supporting the bridging throughout the apixaban clinical development, **4)** The acceptability of the proposed use of [redacted] (b) (4); and **5)** The role of dissolution on the [redacted] (b) (4) for the proposed drug product.

1) Dissolution Method and Acceptance Criterion:
The following dissolution method and acceptance criterion for apixabn IR tablets, 2.5 mg and 5 mg are being proposed by the Applicant:

USP Apparatus	Spindle Rotation	Medium Volume	Temperature	Medium	Acceptance Criterion
II	75 rpm	900mL	37°C	pH 6.8 phosphate buffer, 0.05% SLS	Q=(b) (4) at 30 min

The proposed dissolution method and acceptance criterion are deemed acceptable. The Applicant submitted sufficient information to support the discriminating ability of the dissolution method. The dissolution acceptance criterion was based on the mean dissolution profiles of clinical and stability batches and on the ability of the specification to reject batches that were shown not to be bioequivalent.

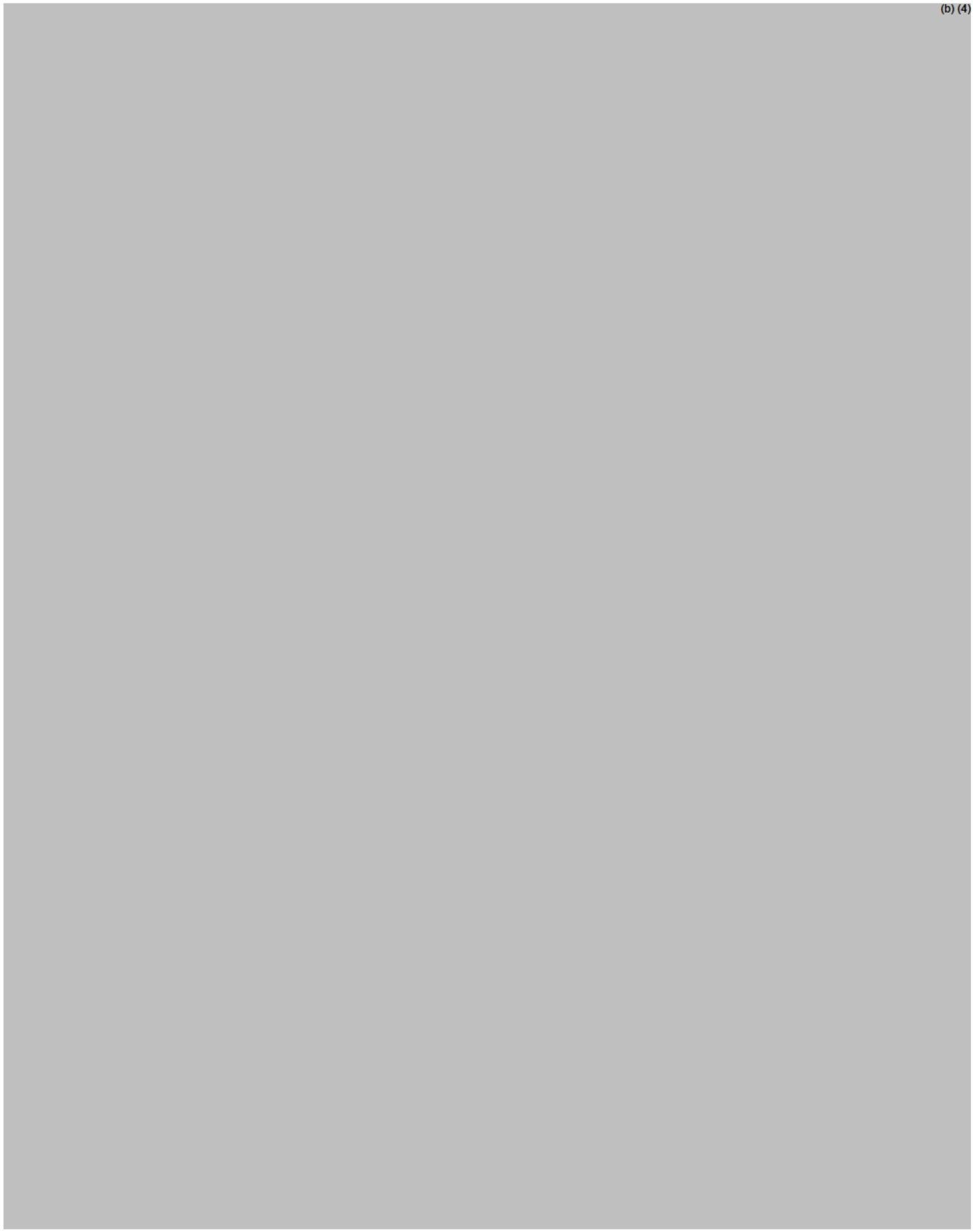
2) Data Supporting the Acceptability of the 2.5 mg strength
Two tablet strengths, 2.5 mg and 5 mg, as immediate-release film-coated tablets have been developed for commercialization. The two tablet strengths are (b) (4) The acceptability of the lower strength is based on the following information included in the present submission:

- The 2.5 mg strength and the 5 mg strength have the same dosage form;
- The 2.5 mg strength is (b) (4) in its active and inactive ingredients to the 5 mg strength product;
- Dissolution profile comparisons in three different media between the 5 mg and 2.5 mg strengths were close to super imposable suggesting similar in vitro dissolution performance despite the act that the f2 similarity factor could not be calculated due to existence of rapid dissolution profiles;
- Apixaban (b) (4) was assessed in an intra-subject dose escalation study (CV185013) using single doses of 2.5, 10, 25, and 50 mg in a double-blinded, randomized trial. According to the Applicant, apixaban showed (b) (4) exposure up to doses of ≤ 10 mg

3) Acceptability of data supporting the bridging throughout the apixaban development
There were some major process and formulation changes implemented to the Phase 3 clinical trial formulation. These changes are supported by the result of two BA/BE study linking the phase 2 and phase 3 formulation. These studies are being reviewed by OCP.

The definitive food effect study was conducted with the Phase 2 formulation. The Applicant included dissolution profiles comparisons between the Phase 2 formulation and the Phase 3 formulation. The f2 similarity testing values were > 50 indicating no difference in the in vitro performance between the Phase 2 and Phase 3 formulations. In addition, according to the Applicant, the results from relative BE study CV185024 conducted under fasting conditions indicate that the phase 2 formulation and the phase 3 formulation were BE. These data indicate that the conclusions made under the food effect study conducted with the phase 2 formulation can be extrapolated to the Phase 3 and commercial formulations.

The Phase 3 clinical trial and commercial tablets are IR film coated tablets that differ only in the shape or tablet dimensions and film coat color/composition. Specifically, the differences between the commercial vs. clinical film coats are in their color, weight of film coat (b) (4) % w/w) and lactose/HPMC (Hydroxypropyl methylcellulose) ratio (b) (4)). It was established through dissolution testing in three different media that these changes are minor and do not affect the release of apixaban from the drug product.


(b) (4)

(b) (4)

The Applicant stated on submission dated Feb 14, 2012, that changes to the manufacturing process that may have the potential to impact the quality of the drug product will be assessed within BMS internal quality control system.

RECOMMENDATION:

The ONDQA-Biopharmaceutics team has reviewed NDA 202-155 for Apixaban IR tablets, 2.5 mg and 5 mg. The following dissolution method and dissolution acceptance criterion have been found acceptable.

USP Apparatus	Spindle Rotation	Medium Volume	Temperature	Medium	Acceptance Criterion
II	75 rpm	900mL	37°C	pH 6.8 phosphate buffer, 0.05% SLS	Q=(b) (4) at 30 min

From the Biopharmaceutics perspective, NDA 202-155 for Apixaban Tablets is recommended for approval.

Additionally, the Applicant agreed to perform dissolution testing for release and stability as recommended by the Agency. The Applicant may (b) (4) . In addition, the Applicant stated that changes to the manufacturing process that may have the potential to impact the quality of the drug product will be assessed within BMS internal quality control system.

Sandra Suarez Sharp, Ph. D.
Biopharmaceutics Reviewer
Office of New Drug Quality Assessment

Angelica Dorantes, Ph.D.
Acting Biopharmaceutics Supervisory Lead
Office of New Drug Quality Assessment

BIOPHARMACEUTICS ASSESSMENT

INTRODUCTION

Apixaban (BMS-562247) is a novel, orally active, selective, direct, reversible inhibitor of the coagulation factor Xa (FXa). It is being developed as an antithrombotic/anticoagulant agent. Apixaban is intended to be given (b) (4) The dose used in Phase 3 studies in adults for prevention of stroke and systemic embolism in subjects with AF was 5 mg administered orally twice daily (BID), with an option to use 2.5 mg BID in select subjects at increased risk of bleeding.

The Clinical Pharmacology and Biopharmaceutics program of this NDA is based primarily on three key apixaban Clinical Pharmacology/Biopharmaceutics studies, a bioequivalence study (CV185019), a relative bioavailability study (CV185024), and a food effect study (CV185008). These studies provide the data that bridge findings from tablets utilized in early clinical development (Phase 1 and Phase 2) with those used in later clinical development (Phase 1 and Phase 3) and their application to understanding the expected pharmacokinetics (PK), safety and efficacy profile of the proposed commercial (hereafter "commercial") tablet formulation.

This review focuses on the evaluation of: **1)** the acceptability of the dissolution method and acceptance criterion; **2)** Acceptability of the lower strength, **3)** Acceptability of data supporting the bridging throughout the apixaban development, **4)** The acceptability of the proposed use of (b) (4); and **5)** the role of dissolution on the (b) (4) for the proposed drug product.

Drug Substance

Apixaban drug substance is a white to yellow, nonhygroscopic, crystalline powder. Apixaban is a non-ionizable compound; thus, the aqueous solubility is not affected by changes in pH. The aqueous solubility of apixaban is 0.04 mg/mL at 37°C over a pH range 1.2 to 6.8.

The Applicant classified Apixaban as a Biopharmaceutics Classification System (BCS) Class III compound (high solubility/low permeability). The proposed dose of apixaban (b) (4). According to BCS classification criteria, apixaban is classified as highly soluble at doses ≤ 10 mg, since the dose/solubility ratio is ≤ 250 mL (10 mg/0.04 mg/mL = 250 mL).

Drug Product

Two tablet strengths, 2.5 mg and 5 mg, as immediate-release film-coated tablets have been developed for commercialization. The two tablet strengths are (b) (4) The components and composition of apixaban are summarized in Table 1.

Table 1. Composition of apixaban Tablets, 2.5 mg and 5 mg

Component	Function	2.5mg	5mg
(b) (4)		mg/tablet	mg/tablet
Apixaban (BMS-562247-01),	Active	2.50	5.00
Lactose Anhydrous	(b) (4)		
Microcrystalline Cellulose			
Croscarmellose Sodium			
Sodium Lauryl Sulfate			
Magnesium Stearate			
(b) (4)			
Croscarmellose Sodium	(b) (4)		
Magnesium Stearate			
Core Tablet Weight			
Film Coat			
(b) (4)			
Total Tablet Weight		104.00	208.00

Formulation Development

Nine oral formulations (five tablets and four oral solutions) and a solution formulation for intravenous (IV) administration were developed to support the apixaban clinical development program.

Four immediate-release tablet formulations were developed for clinical studies as follows:

- The apixaban (b) (4) tablet formulation (Phase 2 tablet, at 2.5, 5, 10 and 20 mg strengths): This formulation was developed and used in Clinical Pharmacology studies conducted early in the development program and in most of the Phase 2 safety/efficacy clinical studies of apixaban.
- Two Phase 3 prototype tablets (20 mg): These formulations were developed to support formulation development. The (b) (4) Phase 3 prototype tablet (20 mg) was similar in composition to the Phase 3 tablets (2.5 and 5 mg) except for the percent active in the tablets. These two prototype tablets were used only in the bioequivalence study (CV185019). The (b) (4) tablet was selected for further development based on the results of this study.
- The apixaban film-coated (b) (4) tablet formulation (Phase 3 tablet, at 2.5 and 5 mg strengths): This formulation was developed and used in all Phase 3 and additional Clinical Pharmacology studies including the relative BA assessment, CV185024.
- An immediate-release, (b) (4), film-coated tablet formulation (at 2.5 and 5-mg strength): This formulation was identical to the Phase 3 tablet

formulation with the exception of the tablet shape (2.5 mg tablet) or dimensions (5 mg tablet) and film coat, was developed for commercialization.

The commercial tablet formulation had minor modifications when compared to the Phase 3 tablet. The Phase 3 and commercial tablets are immediate release film coated tablets that differ only in the shape or tablet dimensions and film coat color/composition. These changes are considered minor differences that will not affect tablet performance. Therefore, pivotal bioequivalence or dose strength equivalence studies were not needed to qualify the commercial formulation from the Phase 3 tablet. Figure 1 shows the main BE studies conducted to bridge changes implemented to the Phase 3 clinical trial formulations. These BE studies are being reviewed by OCP.

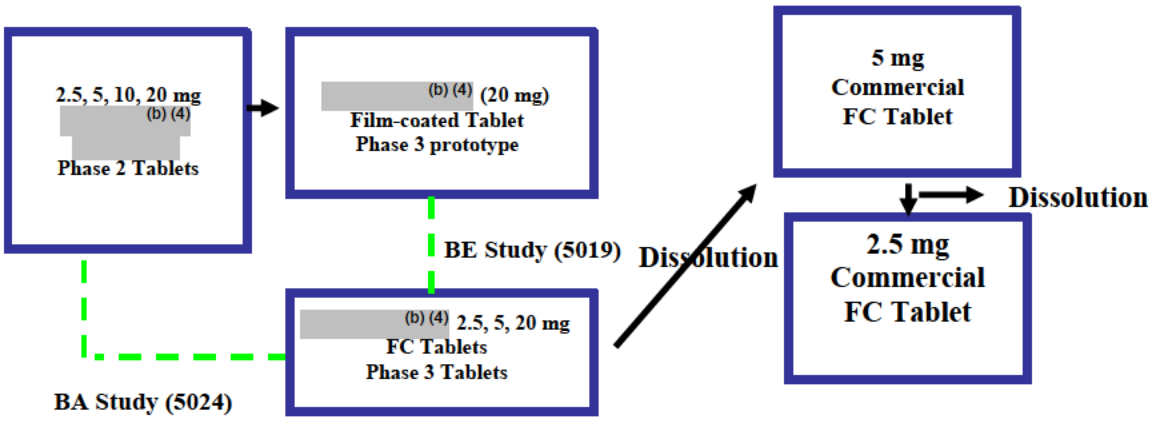


Figure 1. Schematic Overview of the apixaban oral formulation development and studies supporting the changes implemented.

1) DISSOLUTION METHOD AND DISSOLUTION ACCEPTANCE CRITERION

Dissolution Method

The dissolution method proposed as a quality control tool for apixaban film-coated IR tablets, 2.5 and 5 mg is summarized below:

USP Apparatus	Spindle Rotation	Medium Volume	Temperature	Medium
II	75 rpm	900mL	37°C	50 nm Phosphate Buffer pH 6.8 0.05% (w/v) SLS

Dissolution Method Development

a. Dissolution Medium Selection

According to the Applicant, at the proposed dosage strengths of 2.5 mg and 5 mg, apixaban has high aqueous solubility (Dose Strength/Solubility ≤ 250 mL) as defined by

the BCS. It is a non-ionizable compound and its aqueous solubility is independent of pH as shown in Table 2. The aqueous solubility of apixaban (0.04 mg/mL) indicated that the three different buffer media (pH 1.2, 4.5 and 6.8) provide sink conditions (of greater than five times) with a medium volume of 900 mL. In addition, Figure 2 shows that the dissolution profiles are independent of pH.

Table 2. Aqueous Solubility of Apixaban as a Function of pH at 37°C

pH	Buffer/Media	Solubility (mg/mL)	Dose strength/ Solubility of Apixaban (mL)	
			2.5-mg	5-mg
1.2	0.1N HCl	(b) (4)		
4.5	0.05 M Sodium Citrate			
6.8	0.05 M Sodium Phosphate			

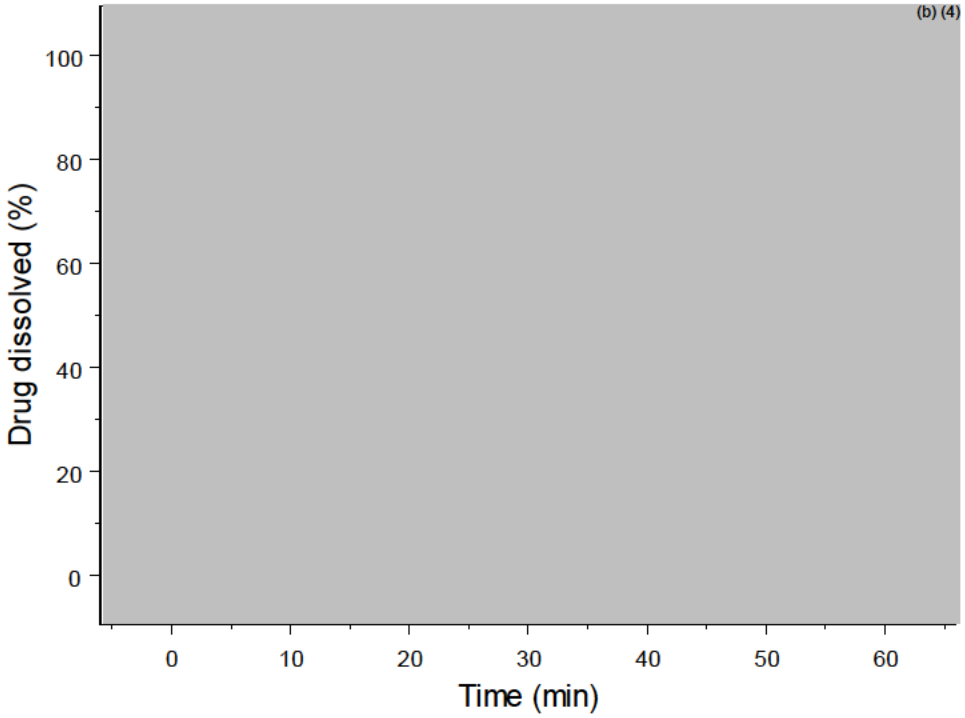


Figure 2. Effect of pH/media on Dissolution of Apixaban FC Tablets, 2.5 g (50 rpm). Generated using Applicant provided data.

Although, the equilibrium solubility of apixaban indicates sink condition in USP media, the tablets of both 2.5-mg and 5-mg strengths showed incomplete dissolution at 50 rpm during the paddle speed study. Therefore, a low level of surfactant (0.05% SLS) was added to the dissolution medium to ensure the complete dissolution of 5-mg tablets

(Table 3). A buffered dissolution medium of pH 6.8 was selected to avoid low pH instability of SLS.

Table 3. Dissolution of Apixaban 5-mg Proposed Commercial Tablets and Phase 3 Tablets at 75 rpm in 50 mM Phosphate Buffer with 0.05% SLS, pH 6.8

Time (min)	% Dissolved			
	Batch 77483-006D (Drug substance (b) (4) = (b) (4) µm)		Batch 64490-047-CTD* (Drug substance (b) (4) = (b) (4) µm)	
	% Dissolved	%RSD	% Dissolved	%RSD
10	(b) (4)		(b) (4)	
20				
30				
45				
60				

b. Effect of Surfactant

The solubility of apixaban was studied in the pH 6.8 phosphate buffer containing SLS at various concentrations. Figure 3 shows that the solubility of apixaban was not significantly enhanced when the SLS concentration is ≤ 0.05%.

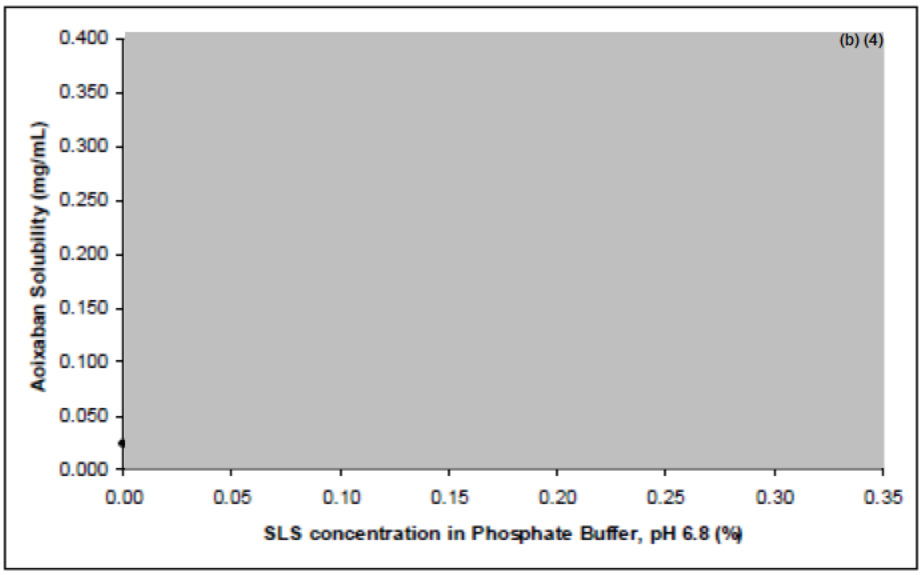


Figure 3. Effect of SLS Concentration on Solubility of apixaban

c. Selection on Apparatus

The effect of different dissolution apparatus on the drug release for both 2.5-mg and 5-mg tablets was also evaluated. The Basket method (Apparatus I) at 100 rpm yielded similar dissolution profiles to the Paddle method at 75 rpm for 2.5 mg tablets manufactured using drug substance of (b) (4) particle size (b) (4) µm). However, 5-mg tablets

manufactured using drug substance of (b) (4) µm particle size exhibited incomplete dissolution (< (b) (4) dissolved in 60 minutes) when the basket method was used (Figure 4).

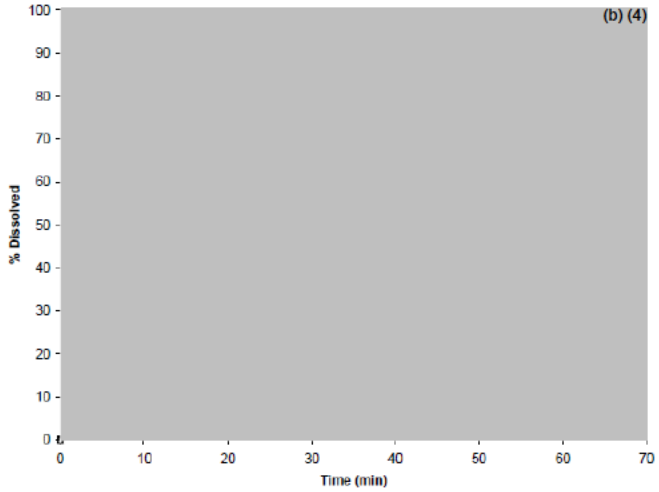


Figure 4. Dissolution Profiles of Commercial Apixaban Film- Coated Tablets (2.5 mg and 5 mg) in Phosphate Buffer with 0.05% SLS, pH 6.8 Using Paddle at 75 rpm and Basket at 100 rpm

d. Selection of paddle rotation speed

Dissolution of 2.5-mg and 5-mg proposed commercial tablets at 50 rpm paddle speed using three dissolution media at different pH (pH 1.2: 0.1 N HCl; pH 4.5: 50 mM acetate buffer; and pH 6.8: 50 mM phosphate buffer) was studied (Table 4). The data provided showed incomplete dissolution profiles (< 95% dissolved at 60 min) using a 50 rpm paddle speed for both dosage strengths. Although, 60 rpm provided complete dissolution at 60 min for the 2.5-mg tablets; the 5-mg tablets showed incomplete dissolution at 60 rpm. These tablets showed incomplete dissolution even at 75 rpm using the above dissolution media. The paddle speed of 75 rpm was selected to avoid possible tablet mounding at lower paddle speeds. In order to obtain a complete dissolution profile for 5-mg tablets, dissolution medium with surfactant was evaluated.

Table 4. Dissolution of Apixaban Commercial Film-Coated Tablets (5-mg) at 50 rpm Paddle Speed in Three Media

Time (min)	Batch 77483-006D (Drug substance, (b) (4)- (b) (4) µm)					
	pH 1.2 0.1N HCl		pH 4.5 Acetate Buffer, 50 mM		pH 6.8 Phosphate Buffer, 50 mM	
	% Dissolved	%RSD	% Dissolved	%RSD	% Dissolved	%RSD
10	(b) (4)					
15						
20						
30						
45						
60						
90*						

e. Discriminating Power of the Dissolution Method

The discriminating power of the dissolution method was tested against material attributes and tablet properties that could affect product performance, namely drug substance particle size and disintegrant level.

In order to evaluate the dissolution method for its discriminating ability, 2.5-mg and 5-mg tablets were made using various drug substance particle size and disintegrant level. Table 5 shows that, when the drug substance of (b) (4) particle size (b) (4) = (b) (4) µm) is used to produce the 2.5-mg tablets, the dissolution rate is significantly slower compared to that of the tablets made using drug substance with a particle size within the specification limit (b) (4) = (b) (4) µm). The F2 value is 37 comparing the two dissolution profiles, indicating the method is discriminating for particle size of the drug substance used to manufacture the tablets. In addition, when the disintegrant is absent from the 2.5 mg and 5 mg tablets but other formulation/process parameters are within the proposed specifications, the dissolution rate is significantly slower compared to that of the tablets within the formulation/process (b) (4)

Table 5. Dissolution Profiles of Commercial Apixaban Tablets (2.5-mg) Using Drug Substance of Different Particle Size

Time* (min)	% Dissolved			
	77507-044-2.5mg-C Drug substance (b) (4) = (b) (4) µm		77507-046-2.5mg-C Drug substance (b) (4) = (b) (4) µm	
	Average	%RSD	Average	%RSD
5	67	3.5	48	4.8
10	81	1.2	63	2.3
15	88	1.4	71	1.1
20	92	1.5	76	0.8
30	96	1.3	82	0.9
60	101	1.2	91	0.6

* Additional timepoints were added for investigational purpose

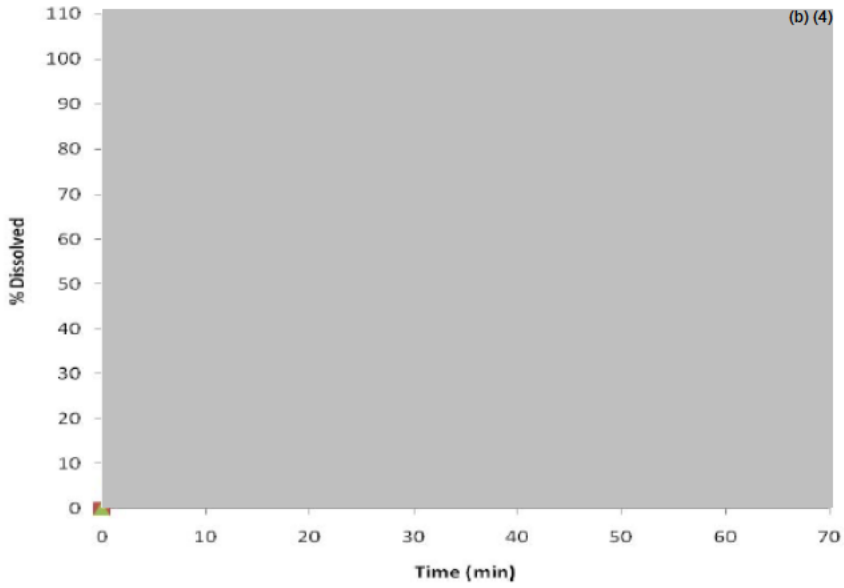
F2=37, calculated using first three timepoints, n=6.

In addition the method is considered bio-relevant, because it is able to reject batches that were found not bioequivalent. The results from BE study CV185024 indicate that the dissolution method is able to discriminate for batches that are inequivalent (Table 6, Figure 5). For example, batch 4K90273 with a (b) (4)% release at 30 min was found not BE to the phase 3 clinical batch and the f2 testing was <50. On the other hand batch 4E83425 with a (b) (4)% release at 30 min was BE to the clinical batch and the f2 testing was >50, indicting that the method is bio-relevant.

Table 6. Results of Statistical Analyses for Apixaban Cmax, AUC(0-T), and AUC(INF) in Study CV185024

Pharmacokinetic Parameter	Formulation	Adjusted Geometric Mean	Ratios of Geometric Means		
			Ratio	Point Estimate	90% CI
Cmax (ng/mL)	(b) (4)	101.5 88.3 109.0	(b) (4) vs (b) (4) vs	0.870 1.074	(0.788, 0.960) (0.973, 1.185)
AUC(INF) (ng h/mL)		1078.8 1027.9 1160.9	vs vs	0.953 1.076	(0.891, 1.019) (1.006, 1.151)
AUC(0-T) (ng·h/mL)		1045.4 988.5 1123.3	vs vs	0.946 1.075	(0.883, 1.013) (1.003, 1.151)

(b) (4) = Apixaban Phase 2 tablet (b) (4) % dissolution) 2x 2.5 mg (reference formulation), n=21
= Apixaban Phase 2 tablet % dissolution) 2x2.5 mg (test formulation 1), n=20
= Apixaban Phase 3 tablet % dissolution) 2x2.5 mg (test formulation 2), n=20



Method: Apparatus 2 (paddle), 75 RPM, 0.05% SLS, pH 6.8 phosphate buffer, 37°C, 900 mL
Treatment definitions for CV185024: Treatment (b) (4) (Reference Phase 2 tablet, 2x 2.5 mg tablet, Batch 4E83425, 2x 2.5 mg tablet, (b) (4) % dissolution by 30 min); Treatment (b) (4) (Phase 2 tablet, 2x 2.5 mg tablet, Batch 4K90273, (b) (4) % dissolution by 30 minutes); Treatment (b) (4) (Phase 3 tablet, 2x 2.5 mg tablet, Batch 6E17717, (b) (4) % dissolution by 30 minutes)

Figure 5. Dissolution profiles of bathes tested in BE study CV105024. The oval highlights the batches that were BE and have f2 > 50.

Reviewer's Comments
The Applicant provided adequate information to support the acceptability and discriminating power of the proposed dissolution method. In addition, the method can be considered bio-relevant, because it is able to reflect the in vivo performance of the product.

Dissolution Acceptance Criterion
The following dissolution acceptance criterion is being proposed by the Applicant as a QC for the release of apixaban IR, tablets:

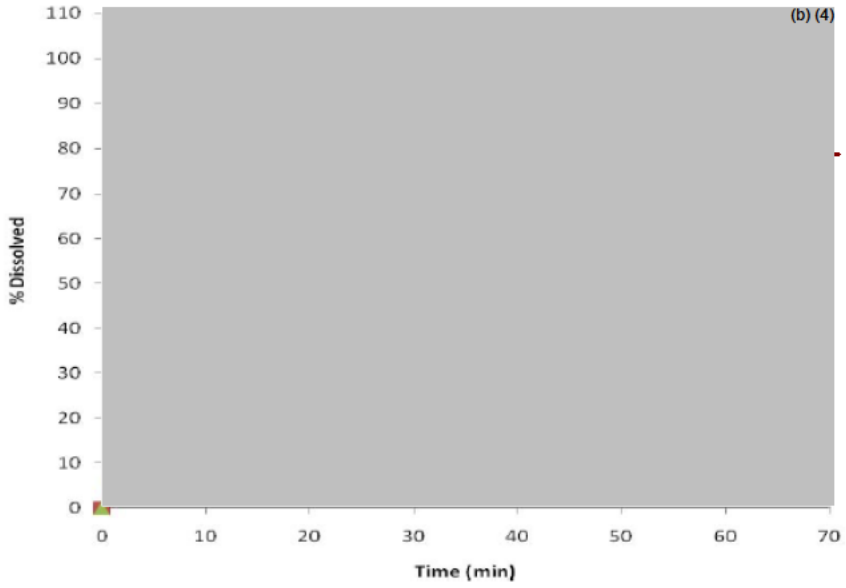
Dissolution Acceptance criterion
Q= (b) (4) at 30 min

According to the Applicant, this criterion is being proposed since the 30 min time ensures solution-like in-vivo absorption. In other words, this proposed specification was set based on the dissolution profile of a batch that was BE to the clinical batch and to an oral solution in terms of AUC.

Reviewer's Recommended Dissolution Acceptance Criterion
The proposed dissolution acceptance criterion is acceptable. However, not precisely for the reason stated by the Applicant since the product can not be considered a solution-like product since Cmax failed the BE requirements.

This reviewer considers that the Q= (b) (4) at 30 min is a biorelevant dissolution specification because it allows the rejection of batches that were shown to be not BE to the clinical batch. Figure 6 (similar to Figure 5 above) shows that an earlier time point (i.e. 20 min) would reject batches shown to be bioequivalent.

In addition, all the clinical batches and the batches under stability testing meet the recommended dissolution acceptance criterion (*refer to data included on December 29, 2011, submitted upon the Division's request*).



Method: Apparatus 2 (paddle), 75 RPM, 0.05% SLS, pH 6.8 phosphate buffer, 37°C, 900 mL
Treatment definitions for CV185024: Treatment (b) (4) (Reference Phase 2 tablet, 2x 2.5 mg tablet, Batch 4E83425, 2x 2.5 mg tablet, (b) (4) % dissolution by 30 min); Treatment (b) (4) Phase 2 tablet, 2x 2.5 mg tablet, Batch 4K90273, (b) (4) % dissolution by 30 minutes); Treatment (b) (4) Phase 3 tablet, 2x 2.5 mg tablet, Batch 6E17717, (b) (4) % dissolution by 30 minutes)

Figure 6. Dissolution profiles of bathes tested in BE study CV105024. The blue oval highlights the rejection of the green profile (BE batch 4E83425) if Q= (b) (4) % at 20 min.

2) DATA SUPPORTING THE ACCEPTABILITY OF THE 2.5 MG STRENGTH

Two tablet strengths, 2.5 mg and 5 mg, as immediate-release film-coated tablets were developed for commercialization. The two tablet strengths are (b) (4)

The acceptability of the lower strength is based on the following information included in the present submission:

- The 2.5 mg strength and the 5 mg strength have (b) (4)
- The 2.5 mg strength is (b) (4) in its active and inactive ingredients to the 5 mg strength product (refer to Table 1 above);
- Dissolution profile comparisons in three different media between the 5 mg and 2.5 mg strengths were close to super imposable suggesting similar in vitro dissolution performance despite the fact that *f2* similarity could not be calculated due to existence of rapid dissolution profiles (Table 7).

Table 7. Summary of Dissolution Profiles Established for 2.5 mg and 5 mg Commercial Tablets in Three Media a (n=12)

Time (min)	10	15	20	30	45	60
Product	**Average Percent of Label Dissolved in Medium 1 [b] (pH 6.8)**					
2.5 mg	87		97	99	99	99
5 mg	74	88	92	96	98	98
Product	**Average Percent of Label Dissolved in Medium 2 [c] (pH 4.5)**					
2.5 mg	85		96	99	99	99
5 mg	72	86	91	95	97	98
Product	**Average Percent of Label Dissolved in Medium 3 [d] (pH 1.2)**					
2.5 mg	78		93	95	96	96
5 mg	73	85	89	92	94	94

a Dissolution method: Apparatus II, paddle speed 75 rpm in a volume of 900 mL at 37°C in different media
b Medium 1: 0.05 M sodium phosphate buffer with 0.05% SLS, pH 6.8 (current quality control method)
c Medium 2: 0.05 M sodium acetate buffer with 0.05% SLS, pH 4.5
d Medium 3: 0.1 N HCl with 0.05% SLS, pH 1.2

3) DATA SUPPORTING THE CHANGES IMPLEMENTED THROUGHOUT DRUG PRODUCT DEVELOPMENT

There were some major process and formulation changes implemented to the Phase 3 clinical trial formulation. These changes are supported by the result of two BA/BE study linking the phase 2 and phase 3 formulation. These studies are being reviewed by OCP. The definitive food effect study was conducted with the Phase 2 formulation. The Applicant included dissolution profiles comparisons between the Phase 2 formulation and the Phase 3 formulation. The f2 similarity testing values were > 50 indicating no difference in the in vitro performance between the Phase 2 and Phase 3 formulations (Table 8).

Table 8. Summary of dissolution similarities established for the 5mg Phase 3 tablets and 5mg Phase 2 tablets (n=6)

Time (min)	10	20	30	45	60	
Product	**% dissolved**					**F2[a]**
Phase 2, 1x5 mg	(b) (4)					Reference
Phase 3,[b] 1x5 mg						55

[a] % dissolved at 10, 20 and 30 min were used for the calculation of the similarity factor F2.
[b] Dissolution was conducted in 12 vessels.

Reviewer's Comments

The f2 similarity testing values were >50 indicating no difference in the in vitro performance between the Phases 2 and Phase 3 formulations. In addition, according to the Applicant, the results from relative BE study CV185024 conducted under fasting conditions indicate that the phase 2 formulation and the phase 3 formulation are BE. These data indicate that the conclusions made under the food effect study conducted with

the phase 2 formulations can be extrapolated to the Phase 3 and commercial formulations.

Changes Implemented to the Commercial Formulation

The Phase 3 and commercial tablets are IR film coated tablets that differ only in the shape or tablet dimensions and film coat color/composition. Specifically, the differences between the commercial vs. clinical film coats are in their color, weight of film coat (b) (4) w/w) and lactose/HPMC (Hydroxypropyl methylcellulose) ratio ((b) (4)). It was established through dissolution testing that these changes are minor and do not affect the release of apixaban from the drug product. Table 9 summarizes the results of the dissolution comparisons between the commercial vs. Phase 3 tablets conducted in three different media. Figure 7 shows the dissolution profiles of a commercial batch vs. a Phase 3 batch.

Table 9. Summary of Dissolution Similarities Established for 5 mg Tablets in Three Media[a] (n=12)

Time (min)	10	15	20	30	45	60
Product	**Average Percent of Label Dissolved in Medium 1 (pH 6.8)**					
Phase 3	74	87	92	96	98	99
Commercial	74	88	92	96	98	98
Product	**Average Percent of Label Dissolved in Medium 2 (pH 4.5)**					
Phase 3	72	86	91	96	98	99
Commercial	72	86	91	95	97	98
Product	**Average Percent of Label Dissolved in Medium 3 (pH 1.2)**					
Phase 3	71	83	88	92	95	96
Commercial	73	85	89	92	94	94

[a] Dissolution method: Apparatus II, paddle speed 75 rpm in a volume of 900 mL at 37°C in different media
[b] Medium 1: 0.05 M sodium phosphate buffer with 0.05% SLS, pH 6.8 (current quality control method)
[c] Medium 2: 0.05 M sodium acetate buffer with 0.05% SLS, pH 4.5
[d] Medium 3: 0.1 N HCl with 0.05% SLS, pH 1.2

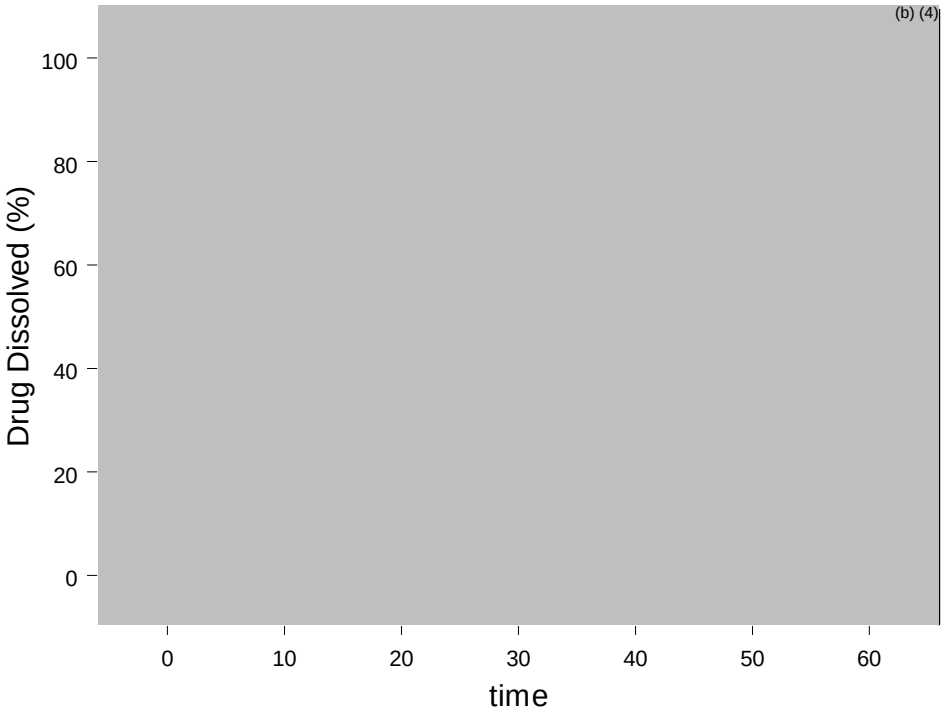


Figure 7. Dissolution of Apixaban 5-mg Proposed Commercial Tablets (batch 0006D) and Phase 3 Tablets (batch 047CTD) at 75 rpm in 50 mM Phosphate Buffer with 0.05% SLS, pH 6.8. Generated using Applicant provided data.

Reviewer's Comments

The dissolution comparisons between the commercial and phase 3 tablets presented in Table 9 and the profiles shown in Figure 7 suggest that a change of film coating from (b) (4) *between the Phase 3 and commercial batches is of not clinical relevance.*

(b) (4)

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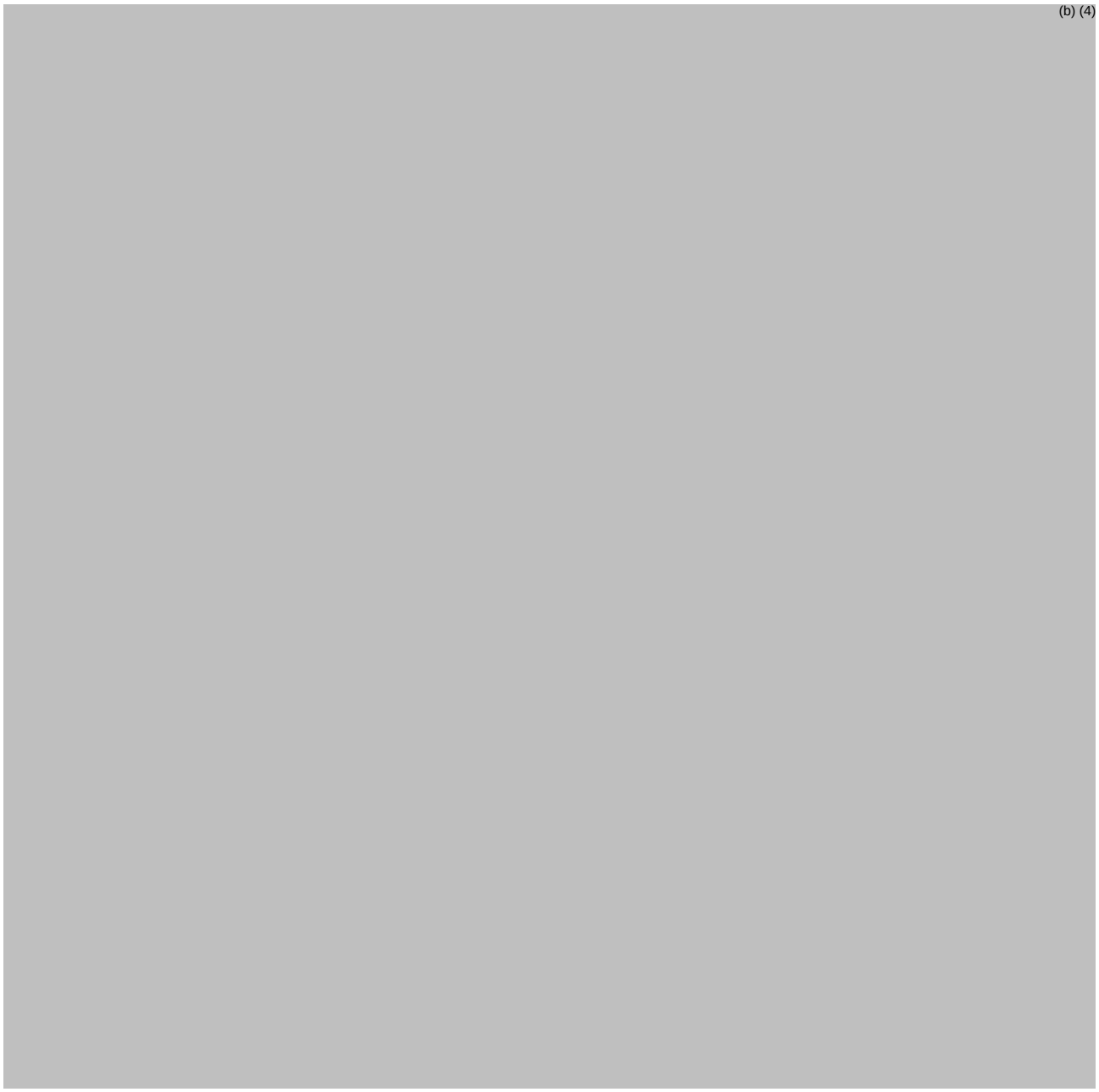

Reviewer's Comments

During the discussion at the teleconference that took place on Jan 8, 2012, the Applicant agreed to perform dissolution testing at release and during stability testing of apixaban batches (see also section 4 for more details). This agreement was documented on the submission dated Feb 14, 2012. Changes to the manufacturing process that may have the potential to impact the quality of the drug product will be assessed within BMS internal quality control system.

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/s/

SANDRA SUAREZ
02/24/2012

ANGELICA DORANTES
02/24/2012

Clinical Pharmacology/Biopharmaceutics Review

PRODUCT (Generic Name):	Apixaban
NDA:	202-155
PRODUCT (Brand Name):	ELIQUIS®
DOSAGE FORM:	Tablets
DOSAGE STRENGTHS:	2.5 mg and 5 mg
INDICATION:	Prevention of stroke, systemic embolism, (b) (4) in patients with non-valvular atrial fibrillation
NDA TYPE:	Priority
SUBMISSION DATE:	Final rolling submission on 9/30/2011
SPONSOR:	Bristol-Myers Squibb and Pfizer
REVIEWERS:	Ju-Ping Lai, Ph.D. Divya Menon-Andersen, PhD
TEAM LEADER:	Rajnikanth Madabushi, Ph.D.
PHARMACOMETRICS REVIEWER:	Tzu-Yun McDowell, Ph.D. Dhananjay Marathe, Ph.D.
PHARMACOMETRICS TEAM LEADER:	Pravin Jadhav, Ph.D
PHARMACOGENOMICS REVIEWER:	Hobart Rogers, Ph.D.
PHARMACOGENOMICS 2nd REVIEWER:	Michael A Pacanowski, Ph.D
OCP DIVISION:	DCP 1
OND DIVISION:	HFD 120

TABLE OF CONTENTS

1.0 EXECUTIVE SUMMARY

This is an original NDA 202155 (NME) submitted on September 30, 2011 as a final rolling submission seeking for approval of ELIQUIS ® (Apixaban, BMS-562247) for the prevention of stroke, systemic embolism, (b) (4) in patients with non-valvular atrial fibrillation. This NDA is under the priority review classification.

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

In this submission, there are 31 human study reports submitted to support the dosing and the proposed claim for apixaban, including 29 clinical pharmacology studies as well as population pharmacokinetic study and exposure response analysis based on Phase 2 and 3 trials. The proposed product is a film-coated tablet, with two proposed strength of 2.5 mg and 5 mg. The recommended dosing regimen is 5 mg twice-daily administered orally and 2.5 mg twice-daily for high risk patients with at least 2 of the following 3 characteristics, age ≥80 years, body weight ≤ 60 kg, or serum creatinine ≥ 1.5 mg/dL.

1.1 RECOMMENDATION

The Office of Clinical Pharmacology (OCP/DCP I) has reviewed the clinical Pharmacology and Biopharmaceutics sections of the NDA 202-155. The submission is acceptable from a Clinical Pharmacology and Biopharmaceutics point of view provided the sponsor agrees with the Agency's labeling recommendations.

Labeling discussions are ongoing. Draft labeling recommendations are outlined in the Detailed Labeling Recommendations section of the review.

1.2 OVERALL SUMMARY OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FINDINGS

Apixaban is the active moiety and the main drug-related moiety in the circulation. Absorption of apixaban is approximately 50 %. Following oral administration, peak plasma concentrations are observed at ~3-4 hours post dose. . Apixaban is 87 % bound to plasma proteins. Apixaban is not extensively metabolized (~ 20 % metabolized primarily by CYP3A4). None of the metabolites exhibit relevant pharmacological activity. About 25% of the radioactivity is recovered in urine and ~ 50 % recovered in feces with the parent drug contributes to the majority of the content. The average apparent terminal half-life for apixaban is 12 hours.

Steady-state PK:
Accumulation ratio for apixaban following twice daily administration for 7 days is < 2. Peak to trough ratio (C_{max}/C_{trough}) at steady state is ~ 3.

Dose proportionality:
Apixaban exhibits dose-proportional PK following oral administration of 2.5 to 10 mg. At doses higher than 10 mg, apixaban exhibits less than dose proportional increase in C_{max} and AUC_{inf}.

Dose Selection:
There is no dedicated study for dose selection in AF program. The dose selection was based on DVT program where BID regimen showed a better trend on efficacy and a 10 mg daily dose balanced the safety profile when compared with the active control, warfarin. In phase III, the dosing regimen was 5 mg twice-daily administered orally. For high risk patients with at least 2 of the following 3 characteristics, age ≥ 80 years, body weight ≤ 60 kg, or serum creatinine ≥ 1.5 mg/dL, the dosing regimen was 2.5 mg twice-daily.
Based on the clinical outcome, the 5 mg BID dose demonstrated superior efficacy and safety than active control, warfarin. For 2.5 mg BID in subgroup, a 25 % lower exposure was observed, however the efficacy still holds based on the exposure-outcome relationship analysis by OCP. The dose selection is therefore considered acceptable.

Intrinsic Factors:
- Exposure to apixaban increased by 50% in subjects with severe renal impairment, while the exposure decreased by 25% in subjects with body weight less than or equal to 50 kg.
- None of the intrinsic factors by themselves significantly impacted the exposure to apixaban that warrants dose adjustment.
- Dosing recommendations for patients with moderate hepatic impairment cannot be provided as the exposure-outcome relationship is not clearly understood in this population.

Extrinsic Factors:
Drug-drug Interactions:
Pharmacokinetic results:
- Exposure to apixaban increases by 100% when co-administered with ketoconazole, a strong CYP3A/P-gp inhibitior. This translates into a increased bleeding risk (70% increase). Hence, a dose reduction of apixaban to 2.5 mg BID is recommended when co-administered with ketoconazole. No dose adjustment is recommended when co-administered with moderate inhibitors.
- Co-adminstration with rifampin, a strong CYP3A/P-gp inducer results in halving of exposure to apixaban. There is no clinical experience at these reduced exposures, concomitant administration of strong CYP3A/P-gp inducers should be avoided.

Pharmacodynamic results:

- **Aspirin and clopidogrel:** Pharmacokinetic or pharmacodynamic interactions were not evident when apixaban was coadministered with aspirin (325 mg once daily) or with clopidogrel (75 mg once daily) or with the combination of clopidogrel 75 mg and aspirin 162 mg once daily.
- **Naproxen:** No changes on platelet aggregation were observed by arachidonic acid-induced platelet aggregation and no clinically relevant prolongation of bleeding time was observed after concomitant administration of apixaban and naproxen.
- **Enoxaparin:** An expected additive effect on anti-FXa activity (40% to 50% increase) was observed while no PK changes were evident when co-administratered with enoxaparin. The observed increase in anti-Xa activity was not associated with clinically relevant bleeding events.

Biopharmaceutics:

- BCS Class: Apixaban is a BCS class III (high solubility, low permeability) drug.
- Relative Bioavailability: The final to-be marketed formulation was used in the pivotal clinical trial.
- Food Effect: Food does not significantly affect systemic exposure to apixaban. Apixaban tablets can be taken without regard to food.
- Analytical Assays: The assays used to measure apixaban and its metabolites are considered validated.

2.0 QUESTION BASED REVIEW

2.1 GENERAL ATTRIBUTES

2.1.1 What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product as they relate to clinical pharmacology and biopharmaceutics review?

Dosage Form/Strengths: 2.5 mg and 5 mg tablets

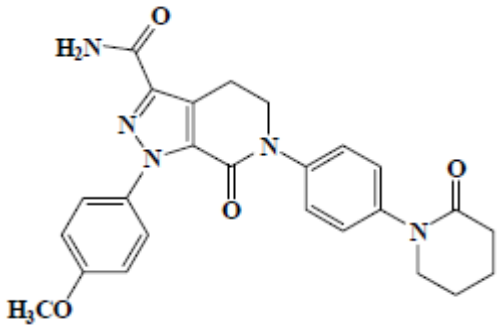
Indication: The proposed indication for ELIQUIS® (Apixaban, BMS-562247) is for prevention of stroke, systemic embolism, (b) (4) in patients with non-valvular atrial fibrillation.

Pharmacologic Class: Selective, direct, reversible inhibitor of the coagulation factor Xa (FXa)

Chemical Name: 1-(4-Methoxyphenyl)-7-oxo-6-[4-(2-oxopiperidin-1-yl)phenyl]-4,5,6,7-tetrahydro-1*H*pyrazolo[3,4-*c*]pyridine-3-carboxamide. Its molecular weight is 459.50.

Molecular formula: $C_{25}H_{25}N_5O_4$

Chemical structure:



Physical Characteristics: Aqueous **s**olubility is 0.028 mg/mL at 24°C. The solubitlity is independent of pH in the range of 1.2 to 6.8. The pH of apixaban solution in water at 24°C is (b) (4). At doses ≤ 10 mg, apixaban is completely soluble in 250 mL of physiological buffer. The pKa can not be estimated since apixaban is a non-ionized compound. The distribution coefficient of apixaban is (b) (4) (log Po/w= (b) (4)) in n-octanol/phosphate buffer at pH 7.4.

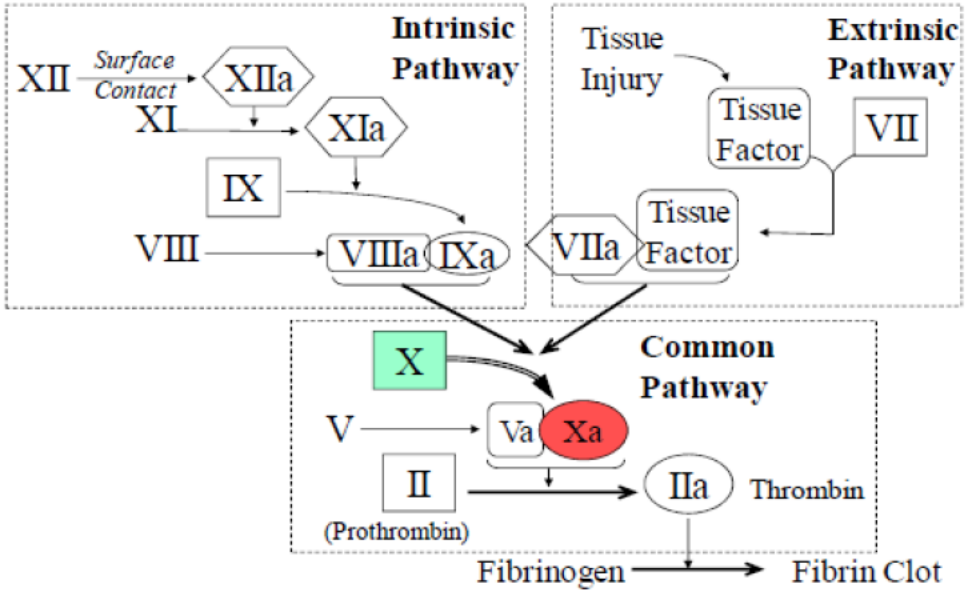
Formulation: Apixaban tablets (2.5 mg and 5 mg) are compositionally (b) (4) The final to-be marketed formulation was used in the pivotal clinical trial.

2.1.2 What are the proposed mechanism of action and therapeutic indications?

Apixaban is an orally active, selective inhibitor of the coagulation factor Xa (FXa) that directly and reversibly binds to the active site of FXa, and exerts anticoagulant and antithrombotic effects by diminishing the conversion of prothrombin to thrombin. Apixaban is a highly potent inhibitor of human FXa with an inhibition constant (Ki) of 0.08 ± 0.01 nM and a high degree of selectivity over other coagulation proteases and structurally-related enzymes involved in digestion and fibrinolysis.

As a key mediator of both extrinsic and intrinsic activation pathways of coagulation (Figure 1 below), FXa is a key physiological mediator of thrombin formation. Thrombin, through its actions on fibrin formation and platelet activation, is the principal modulator of thrombosis in both the venous and arterial circulation. Inhibition of thrombin generation, therefore, produces antithrombotic effects under a variety of pathological conditions. (b) (4)

Figure 1. Role of Factor Xa in the Clotting Cascade



Source: Sponsor's Report, Clinical Overview, Figure 1.1

The proposed indication for apixaban is reduction of the risk of stroke, systemic embolism (SE), (b) (4) in patients with non-valvular AF, (b) (4)

2.1.3 What are the proposed dosages and route of administration?

The sponsor proposed dose is 5 mg apixaban tablet twice daily by oral. In high risk patients with at least any 2 of the following 3 criteria, age ≥ 80 years, body weight ≤ 60 kg, or serum creatinine ≥ 1.5 mg/dL, the proposed dose is 2.5 mg tablet twice daily.

2.2 GENERAL CLINICAL PHARMACOLOGY

2.2.1 What are the clinical studies used to support dosing or claims and what are their design features?

There are 31 human study reports submitted to support the dosing and the proposed claim for apixaban, including 29 clinical pharmacology studies as well as population pharmacokinetic study, exposure response analysis based on Phase 2 (AF and acute coronary syndrome (ACS) programs) and Phase 3 (ARISTOTLE and AVERROES) trials and 1 thorough QT study. For efficacy and safety, two Phase 3 controlled trials were submitted. The ARISTOTLE program evaluated the efficacy of apixaban against warfarin for stroke prevention in patients with non-valvular atrial fibrillation, while the AVERROES evaluated the efficacy of apixaban versus aspirin to prevent stroke in atrial fibrillation patients who have failed or unsuitable for Vitamin K antagonist treatment. The submission also contains *in vitro* studies regarding protein binding, hepatic metabolism and drug interactions and transporters and bioanalytical validation and assay reports for apixaban and its inactive metabolite, M1.

The apixaban clinical pharmacology program included the following assessments:

- The single- and multiple-dose safety, tolerability, PK and PD profiles of apixaban following PO administration as well as that following a single intravenous (IV) bolus dose.
- The effect of apixaban on clotting time assessments (international normalized ratio (INR), prothrombin time (PT), activated partial thromboplastin time (aPTT) and modified prothrombin time (mPT)), anti-Xa activity (AXA), thrombin generation, template bleeding time, and platelet aggregation, alone and in combination with antiplatelet agents and other anticoagulants.
- The potential for apixaban to prolong the QTc interval at exposures exceeding that anticipated in the intended patient population.
- The effect of food on apixaban PK.
- The effect of concomitant drugs on apixaban PK and PD; both those identified as having a potential mechanism for pharmacokinetic and/or pharmacodynamic interaction with apixaban as well as other commonly administered agents in the intended population.
- The effect of apixaban on the PK of common concomitant medication in the intended population.

Apixaban was administered PO as single and multiple daily doses up to 50 mg and IV as single doses up to 5 mg; the majority of subjects received apixaban PO. Apixaban was administered for up to 10 days in Phase 1 clinical trials. Clinical pharmacology studies evaluated total daily doses up to 5-fold higher (50 mg) than that proposed for this indication, 5-mg BID. The majority of subjects exposed to apixaban in the clinical

pharmacology program were male (83%) and < 65 years of age (93%, range: 18 to 85 years); 59% were Caucasian. On average, subjects weighed 78 kg (range: 38 to 175 kg) and had a body mass index of 26 kg/m2 (range: 17 to 54 kg/m2). The majority of subjects were considered to be healthy based on routine medical examination. Among the subjects described above were those enrolled into specific studies designed to evaluate special populations all of whom received apixaban: 24 subjects with mild to severe renal impairment, 16 subjects with mild to moderate hepatic impairment, 39 subjects 65 years of age and 39 female subjects, 18 subjects weighing 50 kg and 19 subjects weighing ≥ 120 kg, 34 Japanese subjects, and 12 Chinese subjects. A total of 842 subjects participated in Phase 1 apixaban studies; of which 744 received at least 1 dose of apixaban.

2.2.2 What is the basis for selecting the response endpoints and how are they measured in clinical pharmacology and clinical studies?

The following variables were used in the evaluation of pharmacodynamics, effectiveness and safety. Although the variables were similar across studies, every study did not evaluate each variable.

The pharmacodynamic endpoints measured in clinical pharmacology studies were:

Prolongation of clotting time was evaluated by prothrombin time (PT), international normalized ratio (INR), activated partial thromboplastin time (aPTT), and a modified PT test (mPT; a modification of the traditional PT assay employing diluted $CaCl_2$ to provided a broader dynamic range). The specific inhibition of Factor Xa was evaluated with the Rotachrom® heparin assay (anti-Xa activity). Additional methods such as ex vivo thrombin generation, template bleeding time, Diapharm Factor X activity assay, and platelet aggregation were explored only in a limited number of studies.

The primary efficacy and safety endpoints in the clinical studies in AF patients are listed as follows:

The primary efficacy endpoint in both Phase 3 studies was the composite of stroke (ischemic, hemorrhagic, or of unspecified type) and SE.

The primary safety endpoint in the Phase 3 AF studies was major bleeding using the definition adapted from the ISTH guidelines.

2.2.3 Are the active moieties in plasma and clinically-relevant tissues appropriately identified and measured to assess pharmacokinetic parameters and exposure-response relationships?

Yes. The analytical method for apixaban concentration determination is acceptable. The only active moiety in plasma (or any other biological fluid) is apixaban. None of the apixaban metabolites identified across species have relevant pharmacologic activity. Apixaban is also the major drug related component in human plasma.

Concentrations of apixaban in serum were determined using specific LC/MS/MS method. Following administration of apixaban 2.5 mg to 5 mg BID, the apixaban plasma concentrations associated with mean C_{min} and C_{max} range from 19 ng/mL to 162 ng/mL, well within the reportable range of the LC/MS/MS method used to determine apixaban plasma concentration.

Blood samples were collected for up to 72 to 96 h after drug administration allowing full and appropriate characterization of apixaban PK parameters. A summary of related bioanalytical methods used is given in the analytical section 2.6 of this review.

2.2.4 What are the characteristics of exposure-response relationships for efficacy?

The E-R relationship for efficacy was conducted in a subset of apixaban-treated patients (n = 2932) who had available exposure data in ARISTOTLE [steady-state AUC (AUCss), derived from the sponsor's population PK model]. Ischemic stroke, a major component of primary efficacy endpoint, was chosen as the efficacy outcome.

A linear logistic regression was performed to model odds of having an ischemic stroke as a function of AUCss. **Figure 2** shows the probability of ischemic stroke was independent from apixaban exposure at the dose level studied. This relationship remained shallow and insignificant using a Cox proportional hazard (PH) model controlling for potential covariates. The E-R analyses for efficacy may be limited due to narrow exposure range and the small number of ischemic stroke event in the PK subset (n = 27). No further interpretation of the Cox PH model was made.

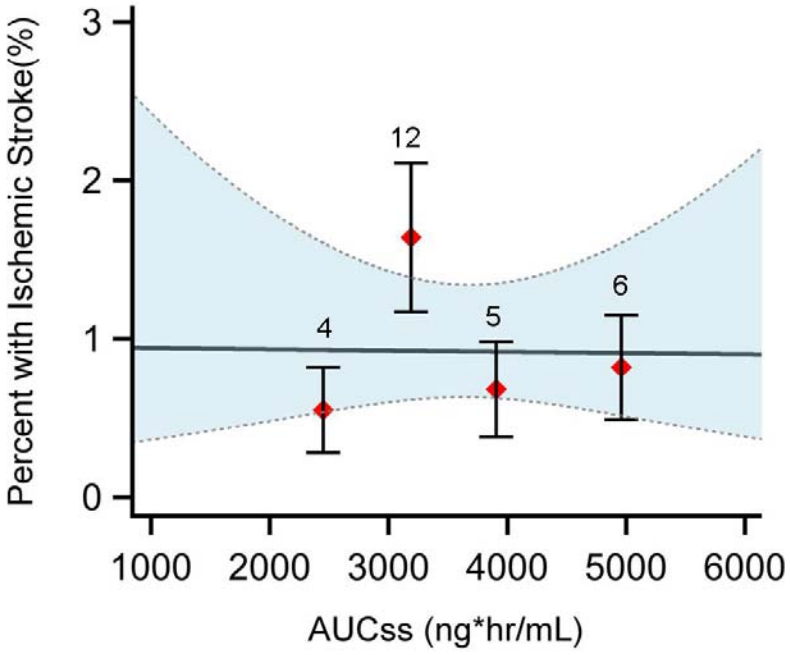


Figure 2. Probability of ischemic stroke is independent of apixaban exposure over the studied dose range. The solid line represents the predicted probability from a linear logistic regression. The red markers represent the observed probability at the median AUCss for a given quartile.

2.2.5 What are the characteristics of exposure-response relationships for safety?

The E-R analyses for safety explored the relationship between apixaban exposure (AUCss) and ISTH major bleed, the primary safety endpoint as defined as clinically overt bleeding accompanied by a decrease in hemoglobin ≥ 2 g/dl and/or a transfusion of ≥ 2 units of packed red blood cells or bleeding at critical sites or a fetal bleeding. A linear logistic regression and Cox PH model were used to characterize the relationship using the same PK subset, as in the E-R analysis for efficacy. The probability for ISTH major bleeding event was found to be increased with an increase in apixaban exposure as show in **Figure 3**. With 2 fold increase in exposure, the probability of a major bleed within 1 year in a typical patient receiving 5 mg BID is predicted to increase from 1.79% to 3.11% (~70 % increase). For details see Pharmacometric Review.

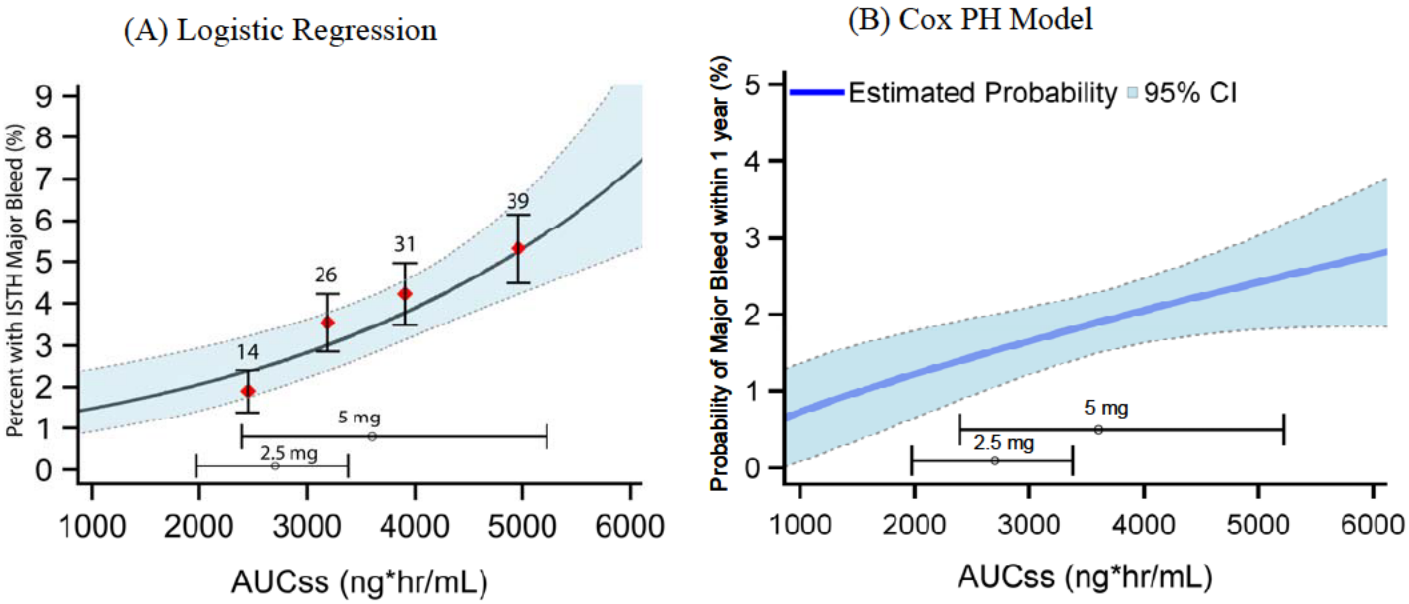


Figure 3. ISTH major bleeding events increased with an increase in apixaban exposure (AUCss) at the dose level studied. Probability of major bleeding by AUCss shown in (A) linear logistic regression model and (B) Cox PH regression model indicating a predicted probability of an event within one year after controlling for other covariates.

2.2.6 Is the dose adjustment of 2.5 mg BID for patients at increased bleeding risk appropriate?

Yes. A dose modification strategy was implemented in ARISTOTLE and AVERROES to minimize the potential for higher exposures in AF patients who are at an increased risk of bleeding. 2.5 mg BID instead of 5 mg BID was given to subject who had any two of the three following criteria: age ≥ 80 years, body weight ≤ 60 kg and serum creatinine ≥ 1.5 mg/dL. Although the dose adjustment was not based on PK matching, there was empirical evidence in ARISTOTLE indicating that apixaban was effective in reducing stroke/SE as well as risk of major bleeding compared to warfarin both within the 2.5 mg BID and the 5 mg BID subgroups (see **Figure 4**).

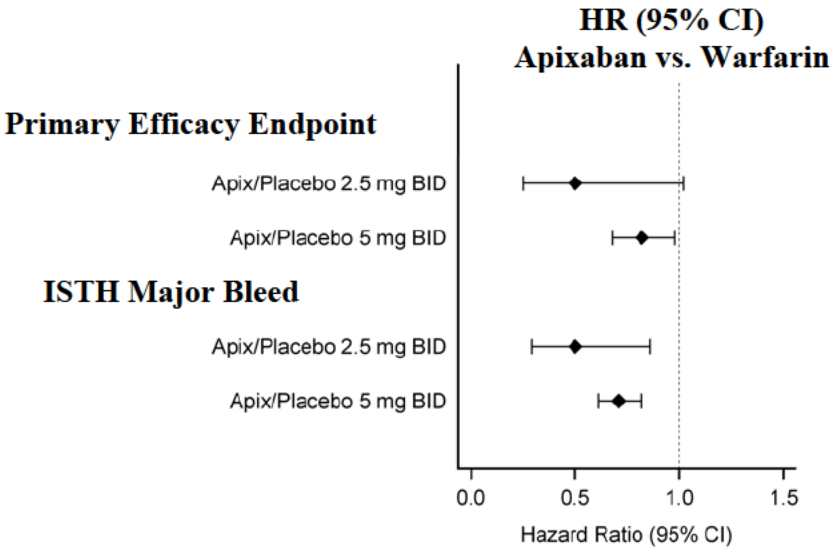


Figure 4. HR and 95% confidence for Primary Efficacy Endpoint and ISTH Major Bleed by dose group (warfarin as the reference)

In addition, based on the established E-R relationship for safety, 2.5 mg BID mitigated the major bleeding risk by about 2 fold in the high risk population. The probability of major bleeding risk within a year is predicted to be 3.55% (2.26-4.62) in high risk patients receiving 2.5 mg BID compared to a predicted 1-year event rate of 6.33% (4.43-8.20) if the same patients were to receive 5 mg (no dose adjustment).

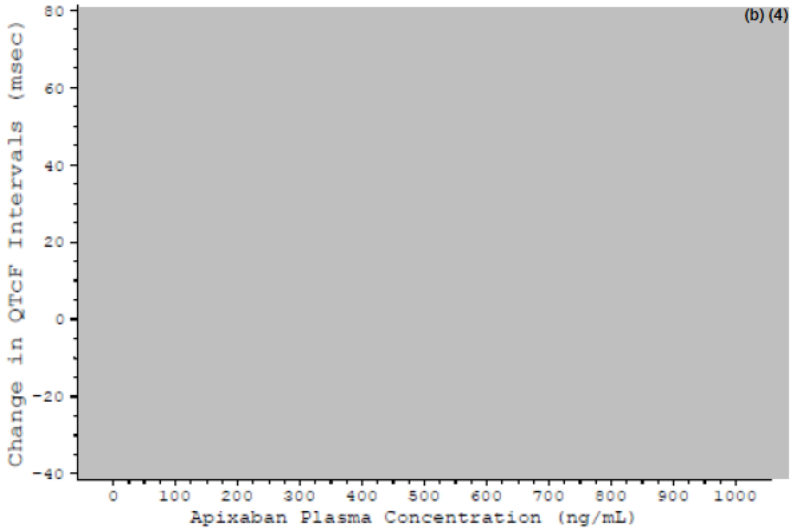
Lastly, a 25% lower apixaban exposure was observed in both 2.5 mg BID group and high body weight (≥ 120 kg) subset in 5 mg BID. In patients with high body weight (receiving 5 mg BID) the efficacy was maintained [HR: 0.34 (0.11-1.06)] which is consistent with the efficacy findings in 2.5 mg BID. These results suggest that a 25% decrease in apixaban exposure might not result in loss of efficacy.

In summary, based on the findings that apixaban 2.5 mg BID reduced major bleeding risk and retained efficacy effect compared to warfarin, dose adjustment of 2.5 mg BID for AF patients at higher bleeding risk based on the sponsor's criteria is acceptable.

2.2.7 Does this drug prolong QT or QTc interval?

Apixaban does not prolong the QTc interval at apixaban plasma concentrations that exceeded those observed in AF patients who received apixaban (**Figure 5** below). The link to the QT-IRT review of the thorough QT study is provided.

Figure 5. Scatter Plot of Δ QTcF versus Apixaban Plasma Concentration



Source: CV185031 Clinical Study Report[19]

Note: The solid horizontal lines represent 30 msec and 60 msec thresholds for QTcF change from baseline.

2.2.8 What are the PK characterstics of apixaban?

2.2.8.1 What are the single and multiple dose PK parameters?

Single and multiple dose PK characteristics of apixaban following oral administration of 0.5 to 50 mg were determined in several studies (**CV185001, CV185002a, CV185013**). Single dose PK characteristics of apixaban following intravenous administration of 0.5 to 5 mg were determined in study **CV185020**.

Following oral administration apixaban exhibited dose proportional PK in the dose range upto 10 mg. At doses higher than 10 mg the increase in systemic exposure (C_{max}, AUC) was less than dose proportional. Following IV administration, apixaban exhibited dose proportional PK in the dose range studied.

Accumulation ratio for apixaban following twice daily administration for 7 days was ~ 2. Mean CL/F was ~ 5 L/h (CL ~3 L/h) and the mean elimination half-life was ~ 12 h. Peak plasma apixaban concentrations are attained at ~ 3 to 4 h post dose. Peak to trough ratio (C_{max}/C_{trough}) at steady state was ~ 3 (**CV185002a**).

Plasma time course of apixaban on days 1 and 7 following twice daily administration presented in **Figure 6**.

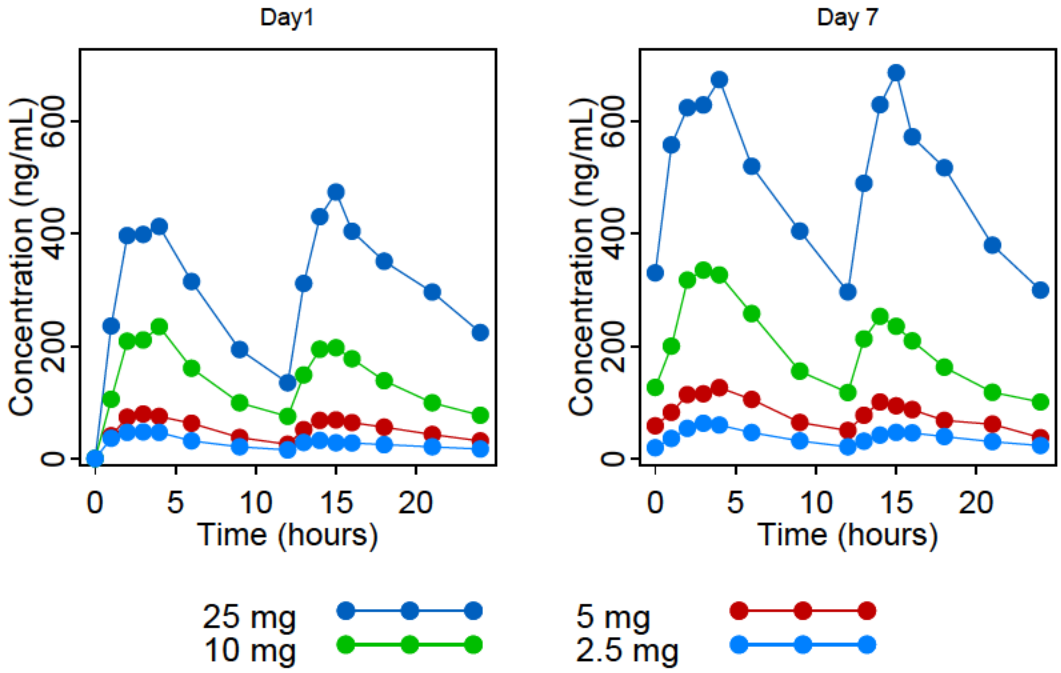


Figure 6. Mean plasma apixaban concentrations following twice daily dosing of apixaban 2.5, 5, 10 or 20 mg.

2.2.8.2 How does the PK of the drug and its major metabolites in healthy adults compare to that in patients?

Based on population pharmacokinetic analyses, the pharmacokinetics of apixaban in patients with atrial fibrillation was similar to that observed in healthy subjects.

2.2.8.3 What are the characteristics of drug absorption?

Following oral administration of apixaban tablets/solution, apixaban was detected in plasma at 0.5 h (earliest sampling time) post administration. Peak plasma concentrations were observed at about ~ 3.5 h and ~ 1 h following administration of the tablet and solution, respectively. The absolute bioavailability of apixaban following administration of apixaban tablets is ~ 50% (**CV185020, CV185045**).

2.2.8.4 What are the characteristics of drug distribution?

The apparent volume of distribution (Vss/F) across PK studies was estimated to be about 50 L (Vss ~ 22 L derived following intravenous administration) in healthy subjects and patients with atrial fibrillation.

Apixaban is ~ 87% bound to plasma proteins, as determined in an *in vitro* study at 1 μM (459.5 ng/mL) apixaban concentration. Plasma apixaban concentrations at therapeutic doses are lower than 1 μM. There was no difference in plasma protein binding of apixaban between healthy subjects and subjects with mild to moderate hepatic impairment (**Table 1**).

Table 1. Plasma protein binding of apixaban in healthy subjects and subjects with hepatic impairment at peak plasma levels following administration of a single dose of 5 mg.

Subject description	**Apixaban concentration range (ng/mL)**	**Mean % fraction unbound (± SD)**
Healthy (n=16)	34.0 - 110.0	7.1 (1.3)
Child-Pugh A (n=8)	36 - 86	6.8 (1.4)
Child-Pugh B (n=8)	37 - 85	7.9 (1.8)

2.2.8.5 Does the mass balance study suggest renal or hepatic as the major route of elimination?

Apixaban is eliminated mainly in urine as unchanged drug.

Following administration of [^{14}C] Apixaban solution, ~ 78% of the administered dose was recovered in 9 days, of which ~ 25% was eliminated in urine (21 % unchanged), ~ 2.4% in bile (~ 0.8% unchanged), and ~ 56 % in feces (34% unchanged).

Factoring in the absolute bioavailability of apixaban (F~ 0.5), ~ 50 % of the systemically available dose is eliminated in urine and rest in feces.

2.2.8.6 What are the characteristics of drug elimination?

Apixaban is eliminated mainly in urine as unchanged drug. See section 2.2.8.5

2.2.8.7 Based on PK parameters, what is the degree of linearity in the dose-concentration relationship?

Apixaban exhibited dose-proportional PK following oral administration of 2.5 to 10 mg. Relationship between dose and C_{max}/AUC_{inf} for apixaban following single doses is presented in **Figure 7.** A similar relationship between dose and C_{max}/AUC_{inf} was observed at steady state.

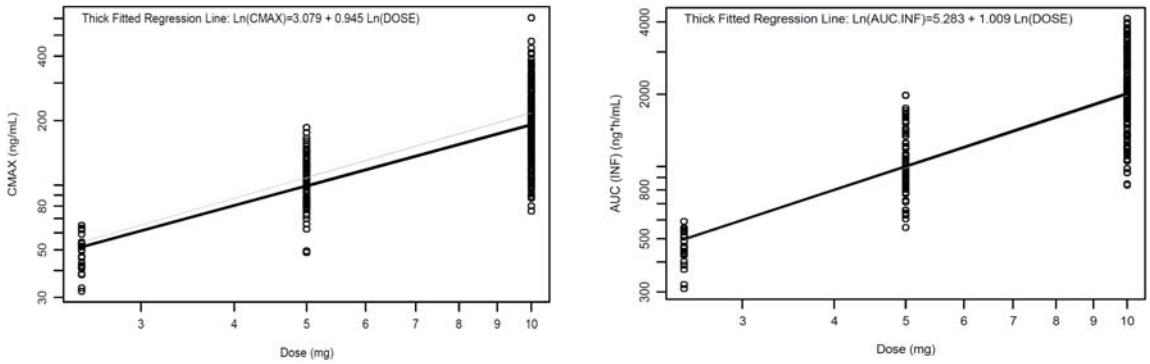


Figure 7. Dose proportional increase in apixaban C_{max} and AUC_{inf} following administration of single doses of apixaban 2.5 to 10 mg (Ref: Summary of Clinical Pharmacology, Figure 2.5.12a).

At dose higher than 10 mg, apixaban exhibited a less than dose proportional increase in C_{max}/AUC_{inf}.

2.2.8.8 How do the PK parameters change with time following chronic dosing?

Apixaban does not exhibit time dependant PK.

2.2.8.9 What is the inter- and intra-subject variability of PK parameters in healthy subjects and patients?

The between subject variability in the PK parameters for apixaban in healthy subjects is moderate. The mean estimate for between subject variability in CL/F and V/F was ~ 30%. Intrasubject variability was estimated at ~ 20%. In patients with atrial filbrilation, between subject variability increased to ~ 40%.

2.2.9 What are the PD characteristics of the drug?

Pharmacodynamic activity of apixaban was assessed using several measures (PT, aPTT, modified PT, anti-FXa activity) across the clinical pharmacology development program, albeit not consistently. At therapeutic doses (2.5 and 5 mg), apixaban did not show an effect on PT or aPTT. A close to 50 and 25% increase from baseline in PT and aPTT, respectively, was observed following administration of 50 mg apixaban.

Following administration of single and multiple doses of apixaban, a concentration dependant increase was observed in anti-FXa activity (**Figure 8**). As seen in **Figure 8** the anti-FXa activity of apixaban mirrors its plasma concentration and the relationship is linear in the dose range tested.

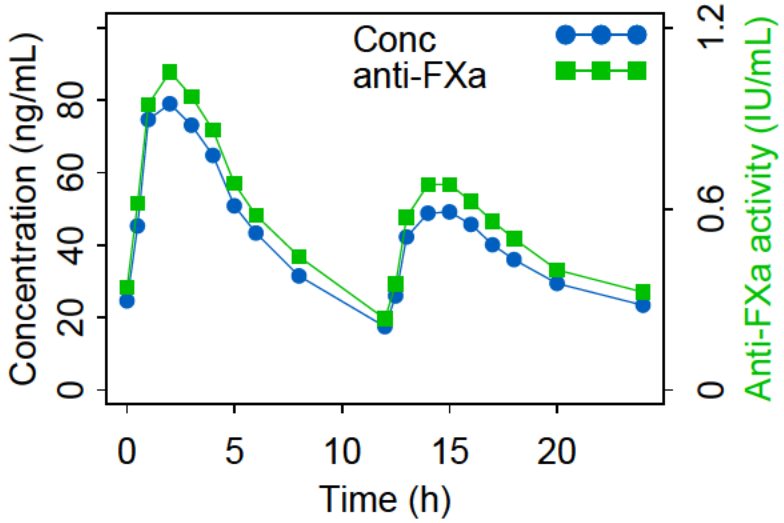


Figure 8. Concentration dependant increase in anti-FXa activity of apixaban observed at steady state following administration of 2.5 mg BID. Circles represent mean pharmacokinetic time course and squares represent mean anti-FXa activity time course (**CV185074**).

A similar, but shallow, concentration dependant increase was also observed in modified prothrombin time (**Figure 9**). As seen in **Figure 9**, at steady state following administration of apixaban 2.5 or 5 mg BID, mean mPT increased from pre-dose levels to peak levels at 3 – 6 h.

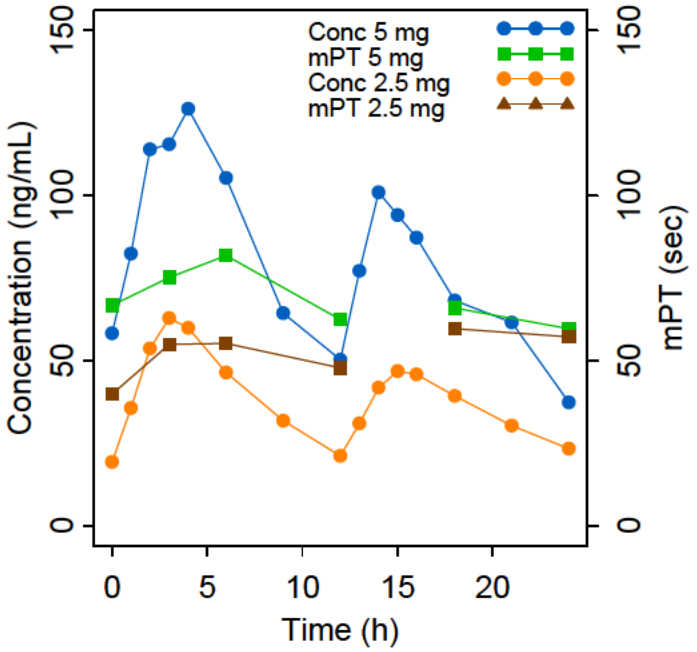


Figure 9. Concentration dependant increase in mPT observed at steady state following administration of 2.5 or 5 mg BID. Circles represent mean pharmacokinetic time course and squares represent mean mPT activity time course (**CV185002**). Samples for mPT were not collected till after 3 h post

evening dose. Hence the last two time points are not connected to the time course profile.

2.3 INTRINSIC FACTORS

2.3.1 What intrinsic factors influence exposure and/or response and what is the impact of any differences in exposure on the pharmacodynamics? Based on what is known about exposure response relationships and their variability, is dosage adjustment needed for any of the subgroups?

2.3.1.1 PK in AF patients:

Apixaban PK in AF patients and healthy subjects are described by the PPK analysis. AF patient status was included in the model as a covariate on Vc/F, but the effect (a 4% decrease relative to healthy subjects) was estimated with poor precision, suggesting that there is no substantial difference in Vc/F between healthy subjects and patients with AF. AF patient status was also a covariate on CL/F, but the effect was small (an estimated 13.9% decrease in CL/F compared to healthy subjects, which translates to an increase in steady state AUC by 16.1%). Thus dosing principles would be similar between AF subjects and studied healthy subjects from PK perspective.

2.3.1.2 Effect of Age:

A dedicated age-gender study was conducted in healthy subjects (CV185022). Elderly subjects (65-79 years) had 0.7% and 32% higher apixaban geometric mean C_{max} and $AUC_{0-\infty}$ values, respectively, than that observed in young subjects (21-40 years). Differences in apixaban PD (INR, mPT, and anti-Xa) between elderly and young subjects reflected the observed differences in apixaban plasma concentrations.

Age was a predictive covariate on CL_{NR}/F (non-renal) clearance in the AF PPK analysis. Based on the PPK analysis, a 50 year old subject would have a 13.4% decrease while an 80 year old subject would have a 15.7% increase in steady state exposures relative to the typical 65 year old subject. Given the modest differences in exposure described above between the young and elderly subjects there is no basis for dosage adjustment.

The frequency of major bleeding events appeared to be higher, regardless of treatment (apixaban and warfarin), for subjects ≥ 75 years of age relative to younger subjects. However, as per the pre-specified protocol dose modification criteria in ARISTOTLE and AVERROES studies, subjects who were at higher risk for bleeding (tow of the following 3 criteria: ≥80years of age, body weight ≤60 kg, serum creatinine (SCr) ≥1.5 mg/dL) were to receive apixaban 2.5-mg BID. Based on the subpopulation analyses for subjects who received apixaban 2.5-mg BID, dose modification for these subjects helped to maintain the desired safety and efficacy profile.

2.3.1.3 Effect of Gender:

The effect of gender was evaluated in a prospectively-designed trial that indicated there was no clinically-meaningful difference in apixaban PK between males and females (CV185022). A slightly greater exposure was observed in female subjects; apixaban mean C_{max} increased by 18% and $AUC_{0-\infty}$ increased by 15% in females compared to males.

In ARISTOTLE and AVERROES, the percentage of females randomized was 35.3% and 41.5%, respectively. Based on the PPK model, an increase of 13.8% in steady state exposure in females relative to males can be expected. Thus, the gender is not considered to result in a clinically-relevant impact on exposure and the related risk of bleeding. Sub-group analysis by gender for efficacy and safety showed similar treatment effects. Based on the subgroup analysis in the Phase 3 AF studies, no dosage adjustment is proposed on the basis of gender.

2.3.1.4 Effect of Race:

The impact of race (or ethnicity) on apixaban PK was primarily based on 3 Phase 1 studies involving Japanese, Chinese, and Caucasian subjects (CV185013, CV185046 and CV185058) and a multiple-ascending dose study (CV185002). Results from these studies indicate that the PK and PD profile observed in these healthy subjects are comparable regardless of race. For the multiple-dose comparison (CV185002, CV185046 and CV185058; evaluated for 2.5-, 5-, and 10-mg BID dose), the Chinese and Japanese subjects had approximately a 15% lower body weight than the non-Asian subjects, but the body mass index was similar across ethnic groups. Apixaban C_{max} and $AUC_{0-\infty}$ pooled across all Phase 1 studies by race (Caucasian, Black, Asian, and Other) show comparable exposure across races (**Figure 10**).

Race was also evaluated as a covariate in the PPK model. Races described as 'Black' and as 'Other' are not significant covariates in the PPK analysis. Asian race was a significant covariate on apparent total clearance resulting in a modestly lower CL/F (11.9%) for Asian subjects compared to non-Asian subjects. The small magnitude of this effect does not result in a clinically relevant impact on exposure or the related risk of bleeding in this population. There was also consistent PD response (anti-Xa vs plasma concentration) across races in phase 1 studies that included Chinese, Japanese and non-Asian subjects (**Figure 11**). Thus, it is unlikely that a clinically-significant difference in the effects of apixaban would be observed among different races in the target patient population. Therefore, no dosage adjustment is proposed on the basis of race.

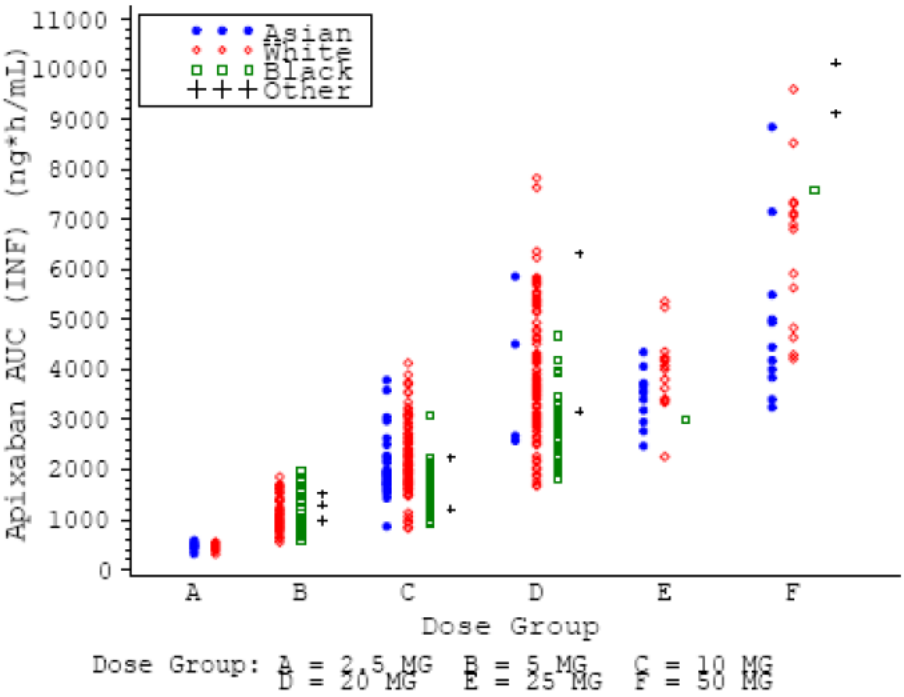
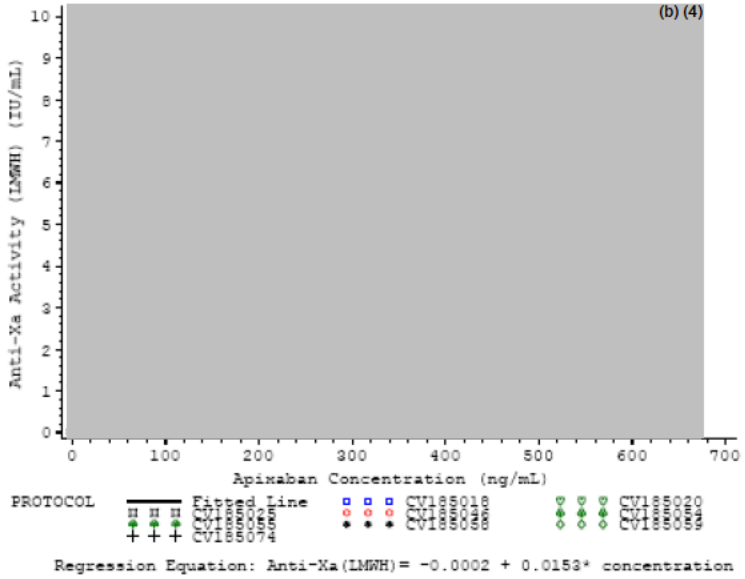


Figure 10. **Effect of Race on Apixaban $AUC_{0-\infty}$ across Phase 1 Studies.** *Source: Atrial Fibrillation Module 2.7.2: Summary of Clinical Pharmacology Report, Figures 3.2.2.3C and 3.2.2.3D, page 113*



Note: only fasted, healthy subjects with apixaban treatment alone included. Data from studies CV185046 and CV185058 represent data from Asian subjects.

Figure 11. Anti-Xa vs Apixaban Plasma Concentration in Asian and non-Asian Subjects for Apixaban Single Oral Doses of 5 and 10 mg and single IV Doses Between 0.5 to 5 mg across Phase 1 Studies. *Source: Atrial Fibrillation Module 2.7.2: Summary of Clinical Pharmacology Report, Figure 3.2.2.3E, page 114*

2.3.1.5 Effect of Body Weight:

The effect of extremes of body weight on apixaban PK was studied in a prospectively-designed study in healthy subjects (CV185059). For subjects in the low weight group (≤50 kg), apixaban C_{max} and $AUC_{0-\infty}$ were 27% and 20% higher compared to subjects in the reference weight group (65 to 85 kg). For subjects in the high weight group (≥120 kg), the apixaban Cmax and $AUC_{0-\infty}$ were 31% and 23% lower compared to subjects in the reference weight group.

In the AF PPK analysis, the effect of baseline body weight on V_c/F was less than directly proportional with a 23.3% reduction for a 50 kg subject and a 22% increase for a 90-kg subject relative to the typical 70 kg individual. Body weight was not identified as a covariate for clearance. The modest influence of weight on apixaban PPK is consistent with the results of the Phase 1 study.

The lower exposure in the high weight group (≥ 120 kg) did not result in loss of efficacy compared to warfarin. Further, a lower dose of 2.5 mg BID is proposed for low weight ((≤ 60 kg) patients who were at higher risk for bleeding (defined previously) to over come increased bleeding risk. Given the favorable safety and tolerability profile in the Phase 3 studies, no dosage adjustment is proposed on the basis of body weight alone.

2.3.1.6 Effect of Renal Function:

The effect of renal impairment on apixaban PK was studied in a prospectively-designed study in healthy and renal impaired (mild, moderate, and severe) subjects (CV185018) and the results are shown in Table 2. At the extreme of a 15 mL/min CLCR, apixaban $AUC_{0-\infty}$ was estimated to be approximately 44% higher than in subjects with normal renal function. Reductions in renal function affected exposures and C_{max} for O-desmethyl apixaban sulfate, a metabolite of apixaban, to a greater extent. However, this metabolite is not likely to impact the efficacy or safety of apixaban because of its lack of intrinsic FXa inhibitory activity, its non-reactive nature (i.e., a phenolic sulfate conjugate), and absence of unique structural alerts or interaction with cardiac ion channels. Dose adjustment in subjects with severe renal impairment does not appear to be warranted based on the modest increase in apixaban AUC (< 50%) observed in subjects with severe renal impairment. Similar finding was observed in the AF PPK analysis.

In the Phase 3 AF trials, subjects with severe to moderate renal impairment had a higher annual event rate for major bleeding than that observed for subjects with normal renal function or mild renal impairment, regardless of treatment. The majority of subjects with severe renal impairment met at least one of the other protocol dose modification criteria (ie, weight ≤60 kg and or age ≥80 years) and received lower (2.5 mg) apixaban dose. Bleeding event rates in these subjects were similar to subjects with severe renal impairment who received apixaban 5-mg BID suggesting that not all subjects with severe renal impairment require dose modification. Taken together these data indicate that a

dose adjustment is not warranted on the basis of renal function alone. Subjects on hemodialysis have not been studied for apixaban PK or PD.

Table 2. Apixaban concentration and exposures in subjects with impaired renal function*

Renal impairment	Cmax	$AUC_{0-\infty}$
Mild (CLCR=65 mL/min)	1.02	1.16
Moderate (CLCR=40 mL/min)	1.03	1.29
Severe (CLCR=25 mL/min)	1.04	1.38

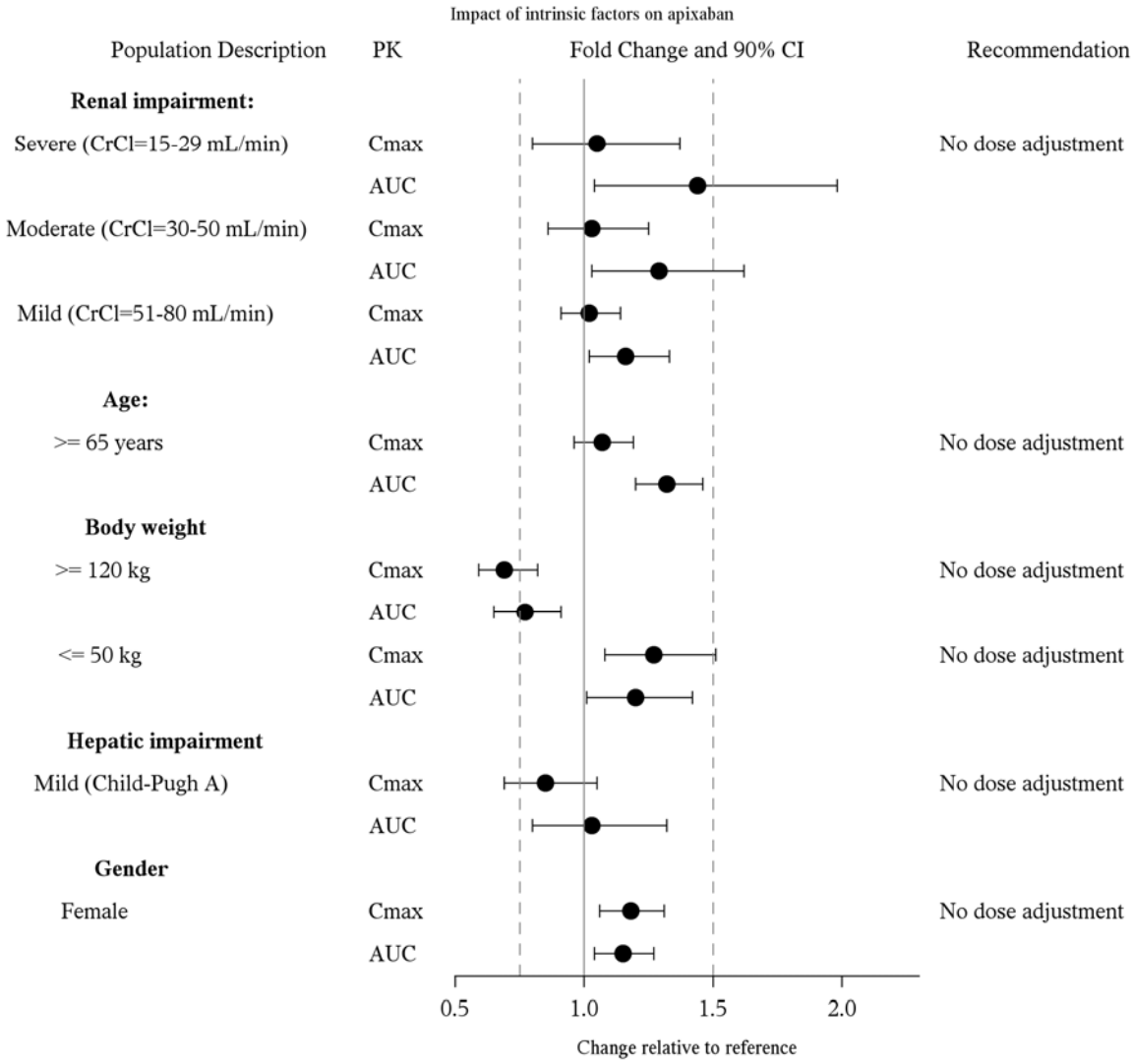
*Represented as fold change in geometric mean value with respect to subjects with normal renal function (CLCR = 100 mL/min).

2.3.1.7 Effect of Hepatic Function:

Hepatic impairment had no clinically-meaningful impact on apixaban exposure (<20% change) with respect to Cmax and $AUC_{0-\infty}$. The lack of change in apixaban apparent CL/F observed in the hepatic impairment study (CV18502525) is consistent with the multiple elimination pathways identified for apixaban. The PD of apixaban appeared to be similar between healthy subjects and subjects with mild or moderate hepatic impairment. A close relationship between apixaban plasma concentration and anti-Xa results was observed in both healthy subjects and subjects with mild or moderate hepatic impairment. Although subjects with hepatic impairment had slightly higher INR and aPTT at baseline, change from baseline appeared comparable to that observed in healthy subjects (approximately 11% to 16% change from baseline INR across all 3 groups).

The apixaban dose does not need to be adjusted in patients with mild hepatic impairment. In patients with moderate hepatic impairment, there is no clear understanding of the impact of hepatic function impairment on the coagulation cascade and its relationship to efficacy and bleeding. There is no clinical information to provide dosing recommendation for patients with moderate hepatic impairment. Subjects with severe hepatic impairment or hepatic impairment associated with clinically-relevant coagulopathy have not been studied. The use of apixaban is not recommended in severe hepatic impaired patients.

Overall, the effects of level of renal impairment, age, body weight, level of hepatic impairment and gender on the pharmacokinetics of apixaban are summarized in the forest plot below. No dose adjustment has been recommended based on most individual factor. Dose adjustment recommendation for moderate hepatic impairment can not be provided due to unknown risk of bleeding in this patient population.



2.4 EXTRINSIC FACTORS

2.4.1 Is apixaban a substrate, inhibitor or inducer of CYP enzymes and/or transporters?

Substrate:

In vitro studies have shown that apixaban is a substrate for CYP3A4 which is expressed in hepatocytes and intestinal enterocytes. The in vitro metabolism of apixaban was primarily mediated by CYP3A4/5, with relatively minor contributions by CYP1A2 and CYP2J2 to the formation of O-desmethyl apixaban; a low level of O-desmethyl apixaban formation was catalyzed by CYP2C8, CYP2C9 and CYP2C19 as well.

In vitro studies have shown that apixaban is a substrate for drug efflux transport proteins P-gp and BCRP wheras apixaban is not a substrate of the key transporters, MRP, OATP1B1, OATP1B3, OATP2B1, OAT1, and OAT3.

Inhibitor:
The potential of apixaban to inhibit CYP enxymes is minimal. Apixaban is not an inhibitor of multiple cytochromes P450 (IC_{50} values for CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2D6, and CYP3A4 are > 45 μM). There was weak inhibition of CYP2C19 with an IC_{50} between 20 and 30 μM, concentrations that greatly exceed those achieved in humans even at the highest dose tested, 50-mg QD.

In the Caco-2 cell model, apixaban at 200 μM, is not an inhibitor of P-gp.

Inducer:
Apixaban was not an inducer of CYP enxymes. At concentrations up to 20 μM, apixaban did not induce CYP1A2, CYP2B6 or CYP3A4 activity in human hepatocytes.

2.4.2 Are there other metabolic/transporter pathways that may be important?

The sulfation of O-desmethyl apixaban to form O-desmethyl apixaban sulfate, the most abundant circulating metabolite in humans, was primarily catalyzed by the sulfotransferase SULT1A1.

2.4.3 Is there an in vitro basis to suspect drug-drug interaction?

The in vitro findings related to the potential drug-drug interaction are listed below:

- Apixaban is not extensively metabolized (~20 %).
- In vitro studies have shown that apixaban is a substrate of P-gp and primarily metabolized by CYP3A4. Inhibitors or inducers of the CYP3A4 isozyme and/or P-gp may influence the exposure of apixaban. The drug-drug interaction study with strong CYP3A4 and P-gp inhibitor, ketoconazole, and other moderate CYP3A4 or P-gp inhibitors were conducted.
- Apixaban is not an inhibitor or an inducer of CYP450 isoenzymes at therapeutic levels. Exposure of drugs that are substrates of CYP450 isoenzymes is not likely to be afftected in the presence of apixaban.

2.4.4 What extrinsic factors (such as herbal products, diet, smoking and alcohol) influence exposure and or response and what is the impact of any differences in exposure on pharmacodynamics?

The effects of extrinsic factors like herbal products and smoking have not been conducted.

2.4.5 Are there any in-vivo drug-drug interaction studies that indicate the exposure alone and/or exposure response relationships are different when drugs are coadministered? If yes, is there a need for dosage adjustment?

Based on nonclinical data, the potential for other drugs to affect apixaban exposure appears to be primarily related to the inhibition or induction of CYP3A4 and 3A5

metabolism and/or P-gp mediated efflux and represent the greatest potential for drug interactions involving apixaban. Therefore, the primary focus of clinical interaction studies was to evaluate the effect of CYP3A4 and P-gp modulators on apixaban PK.

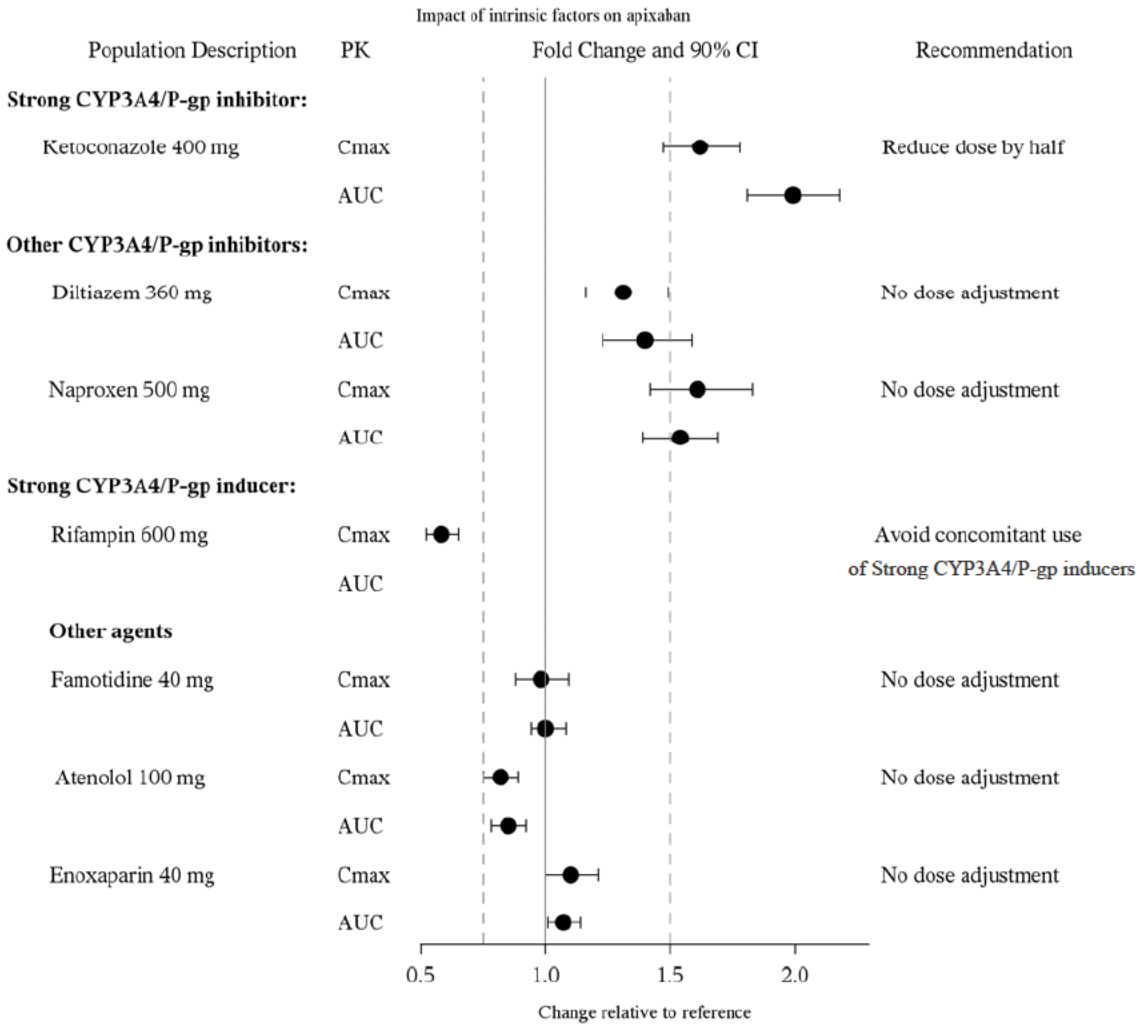
Eleven clinical drug interaction PK/PD studies were conducted including metabolism- or transporter-mediated interaction studies, anticoagulant or antiplatlet agents and commonly co-prescribed agents. A list of apixaban drug interaction studies is summarized below:

Study Description (Apixaban Dose(s) Employed in the Study)	Study Number
Metabolism- or Transporter- Mediated	
Digoxin (0.25 mg q6h loading dose, 0.25 mg QD) + Apixaban (20 mg QD) [Digoxin: anti-arrhythmic and P-gp substrate]	CV185028[17]
Naproxen (500 mg) + Apixaban (10 mg) [Naproxen: nonsteroidal anti-inflammatory agent and P-gp Inhibitor]	CV185054[24]
Ketoconazole (400 mg QD) + Apixaban (10 mg) [Ketoconazole: antifungal, strong inhibitor of CYP3A4 and P-gp]	CV185026[16]
Diltiazem (360 mg QD) + Apixaban (10 mg) [Diltiazem: common antihypertensive, moderate inhibitor of CYP3A4 and P-gp]	CV185032[20]
Rifampin (600 mg QD) + Apixaban (5 mg IV and 10 mg PO) [Rifampin: antituberculotic, strong inducer of CYP3A4 and P-gp]	CV185045[22]
Anticoagulant or Antiplatelet Agents	
Aspirin (325 mg QD) + Apixaban (5 mg BID)	CV185002B[3]
Clopidogrel (75 mg QD) + Apixaban (5 mg BID and 10 mg QD)	CV185005[4]
Aspirin (162 mg QD) and Clopidogrel (75 mg QD) + Apixaban (20 mg QD)	CV185015[9]
Naproxen (500 mg) + Apixaban (10 mg)	CV185054[24]
Enoxaparin (40 mg) + Apixaban (10 mg)	CV185055[25]
Other Commonly Co-Prescribed Agents	
Atenolol (100 mg) + Apixaban (10 mg) [Atenolol: common antihypertensive]	CV185033[21]
Famotidine (40 mg) + Apixaban (10 mg) [Famotidine: common H2-antagonist and strong organic anion transporter inhibitor]	CV185060[28]

2.4.5.1 Pharmacokinetic results:

The effect of CYP3A4 and P-gp modulators on apixaban PK and the recommendations for dose adjustment is summarized in a forest plot below. Two key recommendations for dose adjustment provided by OCP are list below:

- Avoid concomitant use of strong inducers of CYP3A4 and P-gp with apixaban.
- Dose of apixaban should be reduced by half when apixaban is to be coadministered with strong inhibitors of CYP3A4 and P-gp.



Avoid concomitant use of strong inducers of CYP3A4 and P-gp with apixaban

Co-administration of single oral dose of 5 mg apixaban to 600 mg QD rifampin resulted in 42% decrease in Cmax and a 54% increase in AUCinf of apixaban. Based on the analysis conducted by the OCP which is described previously, 25 % decrease in apixaban exposure may not result in loss of efficacy. There is no data supporting efficacy at exposure decrease greater than 25 %. OCP therefore recommends avoiding concomitant use of strong inducers of CYP3A4 and P-gp with apixaban.

Dose of apixaban should be reduced by half when strong inhibitors of CYP3A4 and P-gp are to be coadministered with apixaban

Co-administration of single dose of 10 mg apixaban to 400 mg QD ketoconazole resulted in 62% increase in Cmax and a 100% increase in AUCinf of apixaban. Due to the association of doubled apixaban exposure with ~ 70 % increased bleeding risk described previously, dose of apixaban should be reduced by half when apixaban is to be coadministered with strong inhibitors of CYP3A4 and P-gp.

2.4.5.2 Pharmacodynamic results:

As an anticoagulant, pharmacodynamic drug-drug interactions are possible following concomt tant use of apixaban and other drugs that increase the risk of bleeding (e.g. anticoagulants, heparin, and hrombolytics).

Aspirin and clopidogrel

Pharmacokinetic or pharmacodynamic interactions were not evident in healthy subjects when apixaban was coadministered with ASA 325 mg once daily. Apixaban co-administered with clopidogrel (75 mg once daily) or with the combination of clopidogrel 75 mg and ASA 162 mg once daily in Phase 1 studies did not show a relevant increase in bleeding time, further inhibition of platelet aggregation, or increase of clotting tests (PT, INR, and aPTT) compared to administration of the antiplatelet agents without apixaban.

Naproxen

Naproxen (500 mg), an inhibitor of P-gp, led to a 1.5-fold and 1.6-fold increase in mean apixaban AUC and Cmax, respectively, in healthy subjects. Corresponding increases in clotting tests were observed for apixaban. No changes were observed in the effect of naproxen on arachidonic acid-induced platelet aggregation and no clinically relevant prolongation of bleeding time was observed after concomitant administration of apixaban and naproxen.

Enoxaparin

After combined administration of enoxaparin (40-mg single dose) with apixaban (5-mg single dose), an additive effect on anti-FXa activity was observed while no PK changes were observed when co-administratered with enoxaparin. These data are consistent with the expected additive effect on factor Xa following co-administration of 2 reversible factor Xa inhibitors. Relative to apixaban administration, increases in anti-FXa activity following co-administration of apixaban + enoxaparin are modest (~40% to 50%). The observed increase in anti-Xa activity was not associated with clinically relevant bleeding events in this study. The sponsor stated that the interaction between apixaban and other parenteral anticoagulants affecting factor Xa such as heparin, LMWH other than enoxaparin, fondaparinux is likely to follow a similar additive effect that is driven by the pharmacokinetic profile of the respective agents.

2.5 GENERAL BIOPHARMACEUTICS

2.5.1 Based on the BCS principles, in what class is this drug? What solubility, permeability and dissolution data support this classification?

Apixaban is a BCS class III (high solubility, low permeability) drug.

Apixaban doses ≤ 10 mg are completely soluble in 250 mL of physiological buffer. It's solubitlity is independent of pH in the range of 1.2 to 6.8.

Permeability of apixaban across Caco-2 cell monolayers was similar to that of mannitol, a marker compound with low permeability. Apixaban is a substrate of efflux transporters P-gp and BCRP. The efflux ratio of apixaban was reduced from 27 to 3 in the presence of ketoconazole (P-gp inhibitor) in P-gp overexpressing LLC-PK cells. Similarly, directional transport of apixaban was completely inhibited by Ko134 (FTC analogue which is BCRP inhibitor) in BCRP over expressing MDCKII (MDCKII-BCRP) cells.

2.5.2 What is the relative bioavailability of the proposed to-be-marketed formulation to the pivotal clinical trial?

The final to-be marketed formulation was used in the pivotal clinical trial. Hence, bioequivalence studies were not conducted for apixaban.

2.5.3 What is the effect of food on the bioavailability of the drug from the dosage form?

Food does not significantly affect systemic exposure to apixaban. The 90% CI for AUC and Cmax were contained within the pre-determined 80 to 125% BE limits (**Figure 12**).

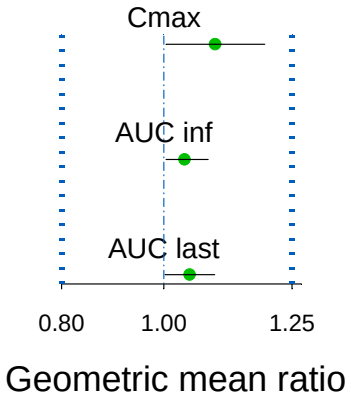


Figure 12. Food does not significantly affect systemic exposure to apixaban. The x-axis represents the geometric mean ratio, and the pre-determined BE limits are represented by the broken vertical lines.

2.6 ANALYTICAL

2.6.1 What bioanalytical method is used to assess concentrations of active moieties and is the validation complete and acceptable?

The assay validations for apixaban and its metabolites, BMS-730823 (M1) are acceptable. Concentrations of apixaban and M1 in plasma and urine were determined using validated liquid chromatography tandem mass spectrometry (LC-MS/MS) method. The lower limit of quantitation (LLOQ) for both the plasma and urine methods was 1 ng/mL and 5 ng/mL for apixaban and M1, respectively.

Summary of all analytical methods

Method No (DCN). & Matrix	Analyte	LLOQ	Inter-Precision	Intra-Precision	Accuracy
930004947 human sodium citrate plasma	Apixaban	1.0 ng/mL	≤ 9.4	≤ 3.7	± 10.2
930007599 human sodium citrate plasma	Apixaban	1.0 ng/mL	≤ 0.8	≤ 5.9	± 2.3
930021670 human serum:buffer	Apixaban	1.0 ng/mL	≤ 5.33	≤ 3.87	± 4.80
930014264 human sodium citrate plasma	Apixaban	1.0 ng/mL	≤ 4.11	≤ 5.46	± 6.00
930014264 human sodium citrate plasma	BMS-730823	5.0 ng/mL	≤ 7.60	≤ 10.30	± 9.71
930014264 amend 1 human sodium citrate plasma	Apixaban	1.0 ng/mL	≤ 2.88	≤ 2.58	± 9.00
930014264 amend 1 human sodium citrate plasma	BMS-730823	5.0 ng/mL	≤ 4.18	≤ 5.36	± 7.33
930014250 human urine	Apixaban	1.0 ng/mL	≤ 2.83	≤ 2.99	± 1.73
930014250 human urine	BMS-730823	5.0 ng/mL	≤ 3.55	≤ 4.25	± 1.07
930014250 amend 2 human urine	Apixaban	1.0 ng/mL	≤ 5.36	≤ 7.20	± 3.91
930014250 amend 2 human urine	BMS-730823	5.0 ng/mL	≤ 4.32	≤ 5.37	± 4.65

Source: Appendix 4 of the Summary of Biopharmaceutics and Associated Analytical Methods[39]
DCN = document control number

Adequate concentrations of Quality Controls were used in these assay validations.

6 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

4.0 APPENDIX

4.1 APPENDIX I

INDIVIDUAL STUDY REVIEWS

4.1.1 BIOPHARMACEUTICS STUDIES

Study CV185008 (Food effect)

Study Protocol # CV185008	**Study period** 11/2003 to 12/2003

Title

Effect of a high fat, high calorie meal on the pharmacokinetics of BMS-562247 in healthy subjects [1].

Objectives

To assess the effect of a standard FDA recommended high fat meal on systemic exposure to apixaban.

Study Design

Open label, randomized, two period, two treatment crossover study, with a minimum of five days of washout between study periods.

Study medication

Dosage Form	Tablet (P1/P2 tablet)
Dosage Strength	5 mg
Batch #.	2K64989
Administration	oral

Sampling schedule

Blood samples were collected for pharmacokinetic analysis at pre-dose, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 9, 12, 24, 36, 48, and 60 hours post-dose.

Data Analysis Methods

Summary statistics were calculated and presented for PK measures. ANOVA on log transformed parameters with fixed effects for sequence, period, and treatment, and random effect for subject within sequence. LS mean and 90% CI for the difference were constructed.

Study population

Randomized/Completed/ Discontinued Due to AE	24/21/3[⁂]
Age (range) years	33(18 – 45)
Male/Female	24/0
Race (Caucasian/Black/Asian/American Indian or Alaska native/other)	11/13/0/0/0

⁂ AEs – elevated LFTs, decreased AA induced platelet aggregation.

Results:

[1] \\Cdsesub1\evsprod\NDA202155\\0001\m5\53-clin-stud-rep\533-rep-human-pk-stud\5334-extrin-factor-pk-stud-rep\cv185008\cv185008.pdf

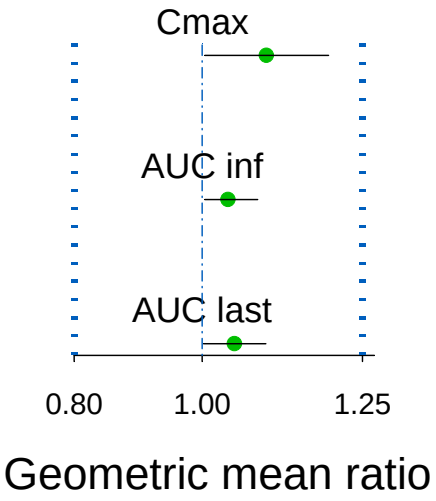


Figure Food dose not affect the bioavailability of apixaban. The broken vertical lines represent the pre-determined BE limits. The closed circles represent the geometric mean of the BE metrics and the horizontal line represents the 90%CI associated with the mean. The reference is apixaban administered in fasted state.

Assay Method

The performance of the assay method during study sample analysis is acceptable and is summarized in the table below.

Analyte	Apixaban
Method	LC/MS/MS
LOQ (ng/mL)	1.0
Range (ng/mL)	1 to 1000
QCs (ng/mL)	3, 400, 800
Accuracy/Bias (%)	< 15.0
Precision (%CV)	< 15.0

Safety Death/SAE: None

Conclusion

Food does not affect the bioavailability of apixaban.

Detailed Results: Apixaban

Parameter	N	Fasted (Reference)	N	Fed (Test)
C_{max} (ng/mL)	21	150.8 (28)	21	165.0 (18)
t_{max} (h)▲	21	3.0 (1.5, 6.0)	21	4.0 (1.0, 9.0)
$AUC_{0\text{-last}}$ (ng/mL*h)	21	1726.2 (32)	21	1811.5 (30)
$AUC_{0\text{-}\infty}$ (ng/mL*h)	21	1789.0 (31)	21	1867.8 (30)
$t_{1/2}$ (h) ▲▲	21	11.5 (4.3)	21	11.3 (2.3)

Study CV185019 (Bioequivalence)

Study Protocol # CV185019	**Study period** 08/2005 to 11/2005

Title

Bioequivalence study of apixaban tablet B and tablet C relative to tablet A in healthy subjects[2].

Objectives

To assess routes systemic exposure to apixaban following administration of two test formulations (B and C) relative to that following administration of a reference tablet formulation A..

Study Design

Open label, randomized, three period, three treatment crossover study, with a minimum of five days of washout between study periods.

Study medication

Dosage Form	Tablet A (P1/P2 tablet)	Tablet B	Tablet C (P3 protoype)
Dosage Strength	10 mg	20 mg	20 mg
Batch #.	5E06395	5G05608	5E08623
Potency	(b) (4)		
Administration	oral		

Sampling schedule

Blood samples were collected for pharmacokinetic analysis at pre-dose, 1, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 10, 12, 16, 24, 36, 48, 60, and 72 hours post-dose.

Data Analysis Methods

Summary statistics were calculated and presented for PK measures. ANOVA on log transformed parameters with fixed effects for sequence, period, and treatment, and random effect for subject within sequence. LS mean and 90% CI for the difference were constructed.

Study population

Randomized/Completed/ Discontinued Due to AE	30/30/0
Age (range) years	30(20 – 42)
Male/Female	30/0
Race (Caucasian/Black/Asian/American Indian or Alaska native/other)	12/16/2/0/0

[2] \\Cdsesub1\evsprod\NDA202155\\0001\m5\53-clin-stud-rep\531-rep-biopharm-stud\5312-compar-ba-be-stud-rep\cv185019\cv185019.pdf

Results:

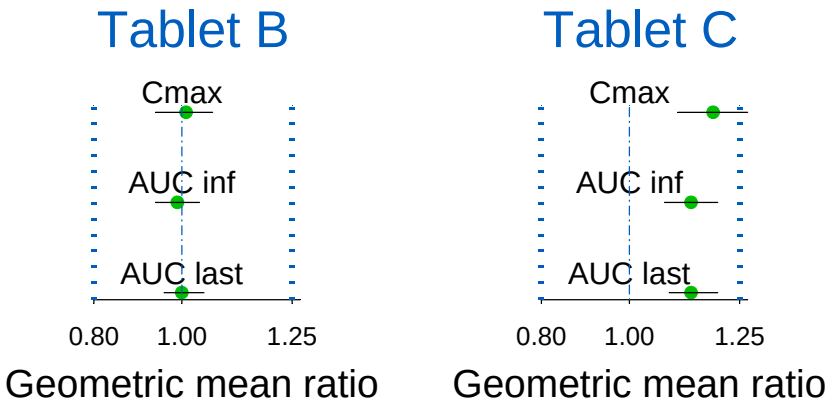


Figure Tablet B is bioequivalent to the reference formulation (Tablet A), while Tablet C is not bioequivalent to the reference formulation (Tablet A). The broken vertical lines represent the pre-determined BE limits. The closed circles represent the geometric mean of the BE metrics and the horizontal line represents the 90%CI associated with the mean.

Tablet C is bioequivalent to Tablet A after correction for differences in potency.

Reviewer's comment: Results of this study help gain an understanding of apixaban exposures attained across studies and doses. To that end, it is not crucial that the P3 prototype (Tablet C) meet BE criteria. Therefore, the pros and cons of correcting for potency will not be addressed.

Assay Method

The performance of the assay method during study sample analysis is acceptable and is summarized in the table below.

Analyte	Apixaban
Method	LC/MS/MS
LOQ (ng/mL)	1.0
Range (ng/mL)	1 to 1000
QCs (ng/mL)	3, 35, 400, 800
Accuracy/Bias (%)	± 13.7
Precision (%CV)	± 13.2

Safety Death/SAE: None

Conclusion

Systemic exposure to apixaban following administration of the two test formulations is similar to that following administration of the reference formulation (P2 tablet).

Detailed Results: Apixaban

Parameter	N	Geometric mean (%CV) Tablet A (Reference)	N	Tablet B (Test)	N	Tablet C (Test)
C_{max} (ng/mL)	30	209.4 (31)	30	210.7 (27)	30	248.7 (26)
t_{max} (h)[⋏]	30	3.5 (2.0, 5.0)	30	3.5 (2.0, 4.0)	30	3.5 (2.0,4.0)
$AUC_{0\text{-}last}$ (ng/mL*h)	30	2410 (26)	30	2419 (30)	30	2756 (29)
$AUC_{0\text{-}\infty}$ (ng/mL*h)	30	2511 (27)	30	2488 (30)	30	2863 (29)
$t_{1/2}$ (h)[⋏⋏]	30	15.2 (8.7)	30	12.6 (6.3)	30	16.2 (8.6)

⋏Median (range) ⋏⋏ Mean (SD)

Study CV185024 (Bioavailability)

Study Protocol # CV185024	**Study period** 11/2006 to 01/2007

Title

Study of bioavailability of two apixaban test formulations relative to an apixaban reference dosage form in healthy subjects[3].

Objectives

To assess systemic exposure to apixaban following administration of two test formulations (B and C) relative to that following administration of a reference tablet formulation A.

Reviewer's comment: This study provides bridging information between the phase 2 and phase 3 formulations.

Study Design

Open label, randomized, three period, three treatment crossover study, with a minimum of three days of washout between study periods.

Study medication

Dosage Form	Tablet A* (P1/P2 tablet, (b) (4)% dissolution)	Tablet B* ((b) (4)% dissolution)	Tablet C** (b) (4)% dissolution)
Dosage Strength	2.5 mg	2.5 mg	2.5 mg
Batch #.	4E83425	4K90273	6E17717
Administration	oral		

* Phase 2 formulation and (b) (4) manufacturing process.

** Phase 3 formulation and (b) (4) process.

Sampling schedule

Blood samples were collected for pharmacokinetic analysis at pre-dose, 1, 2, 3, 4, 6, 8, 12, 24, 36, 48, 60, and 72 hours post-dose.

Data Analysis Methods

Summary statistics were calculated and presented for PK measures. ANOVA on log transformed parameters with fixed effects for sequence, period, and treatment, and random effect for subject within sequence. LS mean and 90% CI for the difference were constructed.

Study population

Randomized/Completed/ Discontinued Due to AE	22/20/2*

[3] \\Cdsesub1\evsprod\NDA202155\\0001\m5\53-clin-stud-rep\531-rep-biopharm-stud\5312-compar-ba-be-stud-rep\cv185024\cv185024.pdf

Age (range) years	32(20 – 43)
Male/Female	18/4
Race (Caucasian/Black/Asian/American Indian or Alaska native/other)	11/10/0/0/1

⁂ AEs considered by the Investigator to be unrelated to the drug. One subject contributed data towards PK analysis.

Results:

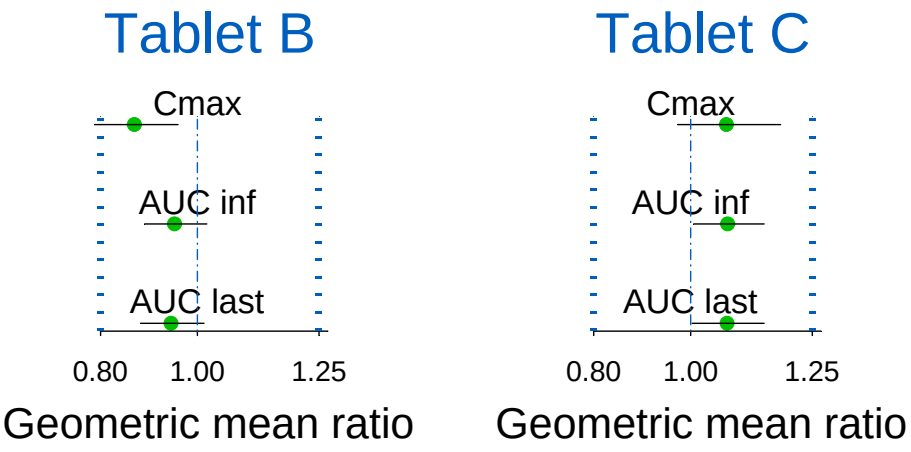


Figure Tablet C is bioequivalent to the reference formulation (Tablet A), while Tablet B is not bioequivalent to the reference formulation (Tablet A). The broken vertical lines represent the pre-determined BE limits. The closed circles represent the geometric mean of the BE metrics and the horizontal line represents the 90%CI associated with the mean.

Assay Method

The performance of the assay method during study sample analysis is acceptable and is summarized in the table below.

Analyte	Apixaban
Method	LC/MS/MS
LOQ (ng/mL)	1.0
Range (ng/mL)	1 to 1000
QCs (ng/mL)	3, 35, 400, 800
Accuracy/Bias (%)	± 3.1
Precision (%CV)	± 10.7

Safety Death/SAE: None

Conclusion

Tablet C (P3 tablet) was bioequivalent to Tablet A (P1/P2 tablet).

Detailed Results: Apixaban

Parameter	N	Geometric mean (%CV) Tablet A (Reference)	N	Tablet B (Test)	N	Tablet C (Test)
C_{max} (ng/mL)	21	101.8 (21)	20	87.8 (24)	20	108.3 (24)
t_{max} (h)[^]	21	3.0 (2.0, 6.0)	20	4.0 (3.0, 8.0)	20	4.0 (2.0, 6.0)
$AUC_{0\text{-last}}$ (ng/mL*h)	21	1054 (33)	20	992.2 (25)	20	1114.9 (26)
$AUC_{0\text{-}\infty}$ (ng/mL*h)	21	1088 (32)	20	1030.1 (25)	20	1152.9 (26)
$t_{1/2}$ (h)[^^]	21	11.8 (5.7)	20	13.7 (6.2)	20	14.2 (7.8)

[^]Median (range) [^^] Mean (SD)

Concentration time-course

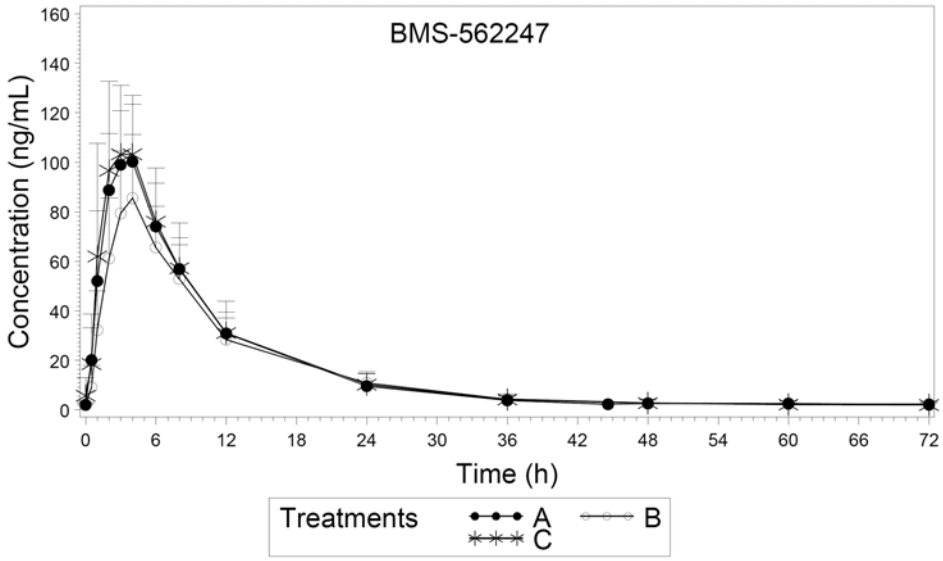


Figure Mean plasma apixaban concentration versus time profile following administration of 2x2.5 mg of test formulations (tablets B and C) and the reference formulation, tablet A, in healthy individuals. (Ref: CSR CV185024, Figure 11.2.1A)

4.1.2 IN VITRO STUDIES PERTINENT TO PK USING HUMAN BIOMATERIALS

Study 93002419 (Protein binding)

Study Report # 93002419
Title Absorption, distribution, metabolism, excretion summary.
Objectives To assess ADME characteristics of BMS-562247 in *in vitro* and pre-clinical models. *Comment: Protein binding determination was one of the objectives here, and will be the only section of the study report reviewed in this document.*
Study Design In vitro protein binding was determined by equilibrium dialysis (Dianorm dialysis system using Diachem membranes with MW cut off of 10,000, rotation at 3-5 rpm for 3 hours). Serum samples (not pooled) were obtained from four healthy men and three healthy women. The concentration range tested was 1 to 10 μM. Binding to human serum albumin and α1 - acid glycoprotein was also assessed. *Comment: The Plasma apixaban concentrations at therapeutic doses are lower than 1 μM. Protein binding in human serum was not assessed at higher concentrations.*
Results At 1 μM, the unbound fraction of apixaban in human sera was 13.2 %. There was no difference in protein binding between males and females. At 1 μM, the unbound fraction of apixaban in human albumin and human α1 - acid glycoprotein was 34 and 91%, respectively.
Conclusions Apixaban is about 87% bound to plasma proteins.

Study 930037717 (Permeability across Caco-2 cell monolayers)

Study Report # 930037717

Title Evaluation of apixaban in the Caco-2 permeability assays plus/minus co-incubation with naproxen.

Objectives To assess the transport of apixaban across Caco-2 cell monolayer, alone and in the presence of naproxen.

Study Design

Caco-2 cell monolayers were cultured and seeded according to standard procedure. Bi-directional transport of apixaban was assessed at 3 and 30 µM. To evaluate the effect of naproxen on apixaban transport, cells were co-incubated with 0.2, 1, and 6 mM of naproxen. Bi-directional transport of apixaban was also evaluated in the presence of 50 µM of ketoconazole and cyclosporine A. [^{14}C] mannitol and [^{3}H] digoxin were used as controls for monolayer integrity and P-gp expression, respectively. In addition dexamethasone, nadolol, metoprolol, verapamil and sulfasalazine (range of known Papp) were also used as controls. Samples were collected at the end of 2h post addition of the test solution/s. Apixaban was measured using an LC-MS/MS method. Radiolabeled control samples were measured using a scintillation counter. Permeability coefficient (Papp) and Papp ratio for all compounds were calculated and presented.

Comment: Single sampling time in calculation of Papp.

Results

Table 1 Apparent permeability coefficients (Pc) for apixaban with and with out cyclosporine A and ketoconazole (Ref: Study report 930037717, Table 8).

Test Condition	Percent Inhibition of Efflux, ± SD	Pc A->B (nm/sec), ± SD	Pc B->A (nm/sec), ± SD
Digoxin (5 µM)	0 ± 3	23 ± 3	205 ± 7
Digoxin (5 µM) plus Cyclosporin A (50 µM)	98 ± 1	86 ± 15	89 ± 17
Digoxin (5 µM) plus Ketoconazole (50 µM)	100 ± 0	96 ± 3	95 ± 6
Apixaban (3 µM)	0 ± 14	16 ± 1	387 ± 54
Apixaban (3 µM) plus Cyclosporin A (50 µM)	43 ± 5	67 ± 9	278 ± 25
Apixaban (3 µM) plus Ketoconazole (50 µM)	71 ± 5	70 ± 8	177 ± 21
Apixaban (30 µM)	0 ± 4	10 ± 2	292 ± 13
Apixaban (30 µM) plus Cyclosporin A (50 µM)	50 ± 6	39 ± 4	182 ± 18
Apixaban (30 µM) plus Ketoconazole (50 µM)	79 ± 14	68 ± 9	147 ± 21

Table 2 Apparent permeability coefficients (Pc) for apixaban with and with out naproxen (Ref: Study report 930037717, Table 9).

Test Condition	Percent Inhibition of Efflux, ± SD	Pc A->B (nm/sec), ± SD	Pc B->A (nm/sec), ± SD
Apixaban (3 µM)	0 ± 14	16 ± 1	387 ± 54
Apixaban (3 µM) plus Naproxen (0.2 mM)	21 ± 3	12 ± 1	307 ± 13
Apixaban (3 µM) plus Naproxen (1 mM)	29 ± 7	16 ± 3	279 ± 29
Apixaban (3 µM) plus Naproxen (6 mM)	42 ± 6	35 ± 4	251± 25
Apixaban (30 µM)	0 ± 4	10 ± 2	292 ± 13
Apixaban (30 µM) plus Naproxen (0.2 mM)	-2 ± 11	21 ± 1	310 ± 30
Apixaban (30 µM) plus Naproxen (1 mM)	3 ± 4	25 ± 2	298 ± 13
Apixaban (30 µM) plus Naproxen (6 mM)	22 ± 4	37 ± 3	257 ± 10

Conclusions

As inferred from an observed efflux ratio of 24 to 29, Apixaban is a substrate for efflux transporters, one of which is P-glycoprotein.

Study 300797734 (Permeability across LLC-PK1 cell monolayers)

Study Report # 300797734

Title Assessment of P-glycoprotein mediated transport of BMS-562247 in LLC-PK1 cell monolayers.

Objectives To assess the role of P-glycoprotein (P-gp, ABCB1) in apixaban transport.

Study Design

LLC-PK1 (human P-gp and corresponding vector transfected) cell monolayers were cultured and seeded according to standard procedure. [14C] mannitol, [3H] propranolol were used as marker compounds with low and high permeability, respectively. Lucifer yellow was used to assess monolayer integrity and [3H] digoxin transport was used to assess P-gp expression. The study was conducted in 3 parts.

In part I, bi-directional transport of [14C] apixaban was assessed at 10 μM. Samples were collected at 60, 90, and 120 minutes to assess time dependency in transport.

In part II, [14C] apixaban transport was assessed at 2.5, 5, 10, 25, 50, 100 μM in both cell lines. Samples were collected at 90 minutes post addition of the test solution.

In part III, the effect of increasing concentrations of ketoconazole (1 to 30 μM) on [14C] apixaban (5 and 50 μM) transport was assessed.

All radiolabeled samples were measured using a scintillation counter. Permeability coefficient (Papp) and Papp ratio for all compounds were calculated and presented.

Results

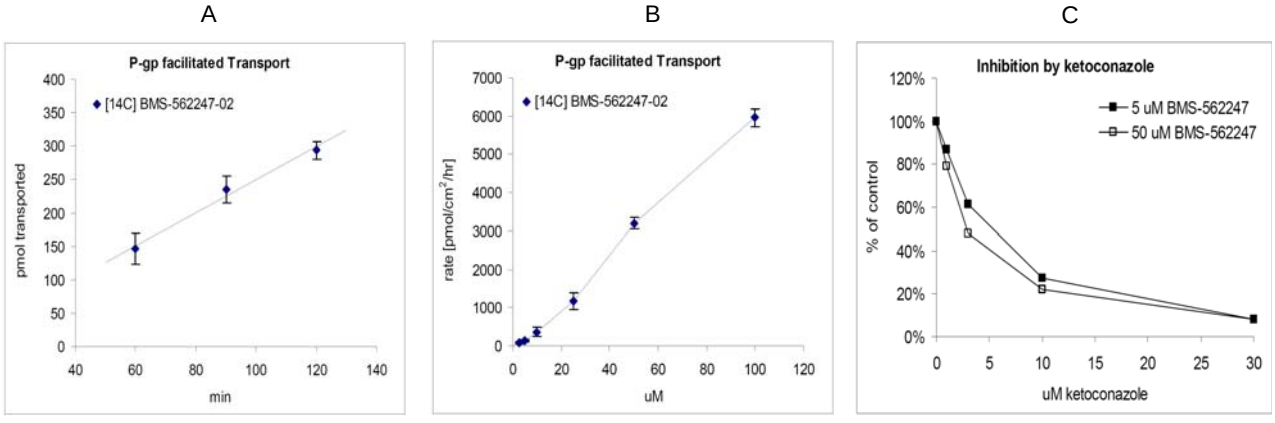


Figure 1 Apixaban transport across P-gp overexpressing LLC-PK1 cell monolayers (A) with increasing time (B) at increasing apixaban concentrations (C) in the presence of P-gp inbitor ketoconazole (Ref: Study report 300797734, Figures 1-3).

Table 1 Apparent permeability coefficients (Papp) and efflux ratios (polarization ratio) for apixaban with and with out ketoconazole (Ref: Study report 300797734, Table 12).

Nominal conc [µM]	Ketoconazole conc [µM]	Papp [cm*s] mean (n=2)		Polarization Ratio mean
		A to B	B to A	(B-A/A-B)
5	0	7.0E-07	1.9E-05	27
5	1.0	8.3E-07	2.0E-05	24
5	3.0	1.1E-06	1.8E-05	17
5	10	2.0E-06	1.7E-05	8.3
5	30	4.1E-06	1.3E-05	3.2
50	0	6.5E-07	1.9E-05	29
50	1.0	9.2E-07	2.2E-05	23
50	3.0	1.4E-06	2.0E-05	15
50	10	2.3E-06	1.7E-05	7.3
50	30	4.2E-06	1.4E-05	3.2

- Efflux ratios for apixaban in vector transfected LLC-PK1 were about 1 to 4.

Conclusions

Apixaban is a substrate P-glycoprotein substrate.

Study 930037784 (Permeability across MDCKII cell monolayers)

Study Report # 930037784
Title Bidirectional transport (Papp) and inhibition studies of BMS-562247 on MDCKII and MDCKII-BCRP monolayers.
Objectives To assess the role of breast cancer resistance protein (BCRP, ABCG2) in apixaban transport.
Study Design MDCKII-BCRP (MDCKII cells transfected with human BCRP) and MDCKII wild type cell monolayers were cultured and seeded according to standard procedure. [^{14}C] mannitol and antipyrine were used as a marker compounds with low and high permeability, respectively. [3H] prazosin was used to assess BCRP expression. Bi-directional transport of [14C] apixaban was assessed at 1, 5, 25 and100 μM. Samples were collected at 15, 30,60, and 120 minutes. Additionally, bi-directional transport of [14C] apixaban (at 5 μM) was also evaluated in the presence of ketoconazole, naproxen, diltiazem and the specific BCRP inhibitor K0134 (fumitromorgine C analogue). All radiolabeled samples were measured using a scintillation counter. Permeability coefficient (Papp) and Papp ratio for all compounds were calculated and presented.
Results • Efflux ratio for apixaban in MDCKII-BCRP cells was about 10. That in MDCKII wild type was ~ 2. • The observed directionality in transport was partially reduced by ketoconazole. • Diltiazem and naproxen did not affect apixaban transport/efflux. *Comment: Ko134 data not presented.*
Conclusions Apixaban is a BCRP substrate.

Study 930024178 (CYP inhibition in human liver microsomes)

Study Report # 930024178

Title: Evaluation of the inhibitory effects of BMS-562247 on the activity of cytochrome P450 enzymes CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 and CYP3A4 in human liver microsomes.

Objectives: To evaluate the potential of BMS-562247 to inhibit cytochrome P450 (CYP) enzymes CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 and CYP3A4 in pooled human liver microsomes (HLM).

Study Design: Apixaban was incubated with CYP probe substrates at concentrations approximately equal to their Km values in pooled HLM. Known reversible inhibitors of CYP enzymes were included as positive controls. The incubations were carried out at eight concentrations of the test compound ranging from 0 to 45 µM in a 96-well plate. HLM (0.05~0.25 mg/mL) were incubated in triplicate. Metabolites of probe substrates were analyzed using triple quadrapole LC/MS/MS. Based on the sponsor, all assay used for determination of IC50 in HLM were developed and validated. A summary of experimental conditions for the CYP enzyme assays is shown in the table below:

Enzyme	CYP reaction	Substrate (µM)	HLM Conc. (mg/mL)	Incubation time (min)	BMS-562247 Target concentration [a] (µM)
CYP1A2	Phenacetin *O*-Deethylation	45	0.15	10	0, 0.0075, 0.03, 0.15, 0.6, 3, 15, 45
CYP2A6	Coumarin, 7-hydroxylation	0.65	0.05	5	0, 0.0045, 0.018, 0.09, 0.36, 1.8, 9, 45
CYP2B6	Bupropion Hydroxylation	100	0.05	5	0, 0.0045, 0.018, 0.09, 0.36, 1.8, 9, 45
CYP2C8	Paclitaxel 6α-hydroxylation	5	0.05	5	0, 0.0045, 0.018, 0.09, 0.36, 1.8, 9, 45
CYP2C9	Diclofenac 4´-hydroxylation	10	0.15	7	0, 0.0075, 0.03, 0.15, 0.6, 3, 15, 45
CYP2C19	(*S*)-Mephenytoin 4'-hydroxylation	55	0.25	40	0, 0.0075, 0.03, 0.15, 0.6, 3, 15, 45
CYP2D6	Dextromethorphan *O*-demethylation	10	0.15	7	0, 0.0075, 0.03, 0.15, 0.6, 3, 15, 45
CYP3A4	Midazolam 1'-hydroxylation	5	0.1	5	0, 0.0045, 0.018, 0.09, 0.36, 1.8, 9, 45
CYP3A4	Testosterone 6β-hydroxylation	75	0.15	10	0, 0.0075, 0.03, 0.15, 0.6, 3, 15, 45

[a]Dimethyl sulfoxide (DMSO) was used to dissolve the test article.

Results

The IC50 results are summarized in the table below:

Enzyme	CYP Assay	IC_{50} for BMS-562247 (μM)	Positive control	
			Name	IC_{50} (μM)
CYP1A2	Phenacetin *O*-deethylation	>45	α-naphthoflavone	0.0068
CYP2A6	Coumarin 7-hydroxylation	>45	tranylcypromine	0.077
CYP2B6	Bupropion hydroxylation	>45	orphenadrine	464.7
CYP2C8	Paclitaxel 6α-hydroxylation	>45	montelukast	0.0882
CYP2C9	Diclofenac 4´-hydroxylation	>45	sulfaphenazole	0.528
CYP2C19	(*S*)-Mephenytoin 4'-hydroxylation	>20	N-3-benzylnirvanol	0.399
CYP2D6	Dextromethorphan *O*-demethylation	>45	quinidine	0.0526
CYP3A4	Midazolam 1'-hydroxylation	>45	ketoconazole	0.0302
CYP3A4	Testosterone 6β-hydroxylation	>45	ketoconazole	0.0451

- All standards and QC samples met the analytical acceptance criteria based on the sponsor.
- IC50 values for positive controls for CYP1A2, CYP2A6, CY2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 and CYP3A4 were within the range of the values set for acceptance for those nine assays.
- Apixaban showed no relevant direct inhibition for CYP enzymes studied as IC50 value were estimated to be greater than the highest concentration of BMS-562247 evaluated (IC50>45 μM), except for CYP2C19 (IC50>20 μM).

Conclusions: Apixaban showed no inhibitory effect on the activity of CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2D6 and CYP3A4 at concentration tested (IC50 values >45 μM) and a weak inhibitory effect on the activity of CYP2C19 (IC50>20 μM).

Study 930024170 (CYP induction in human hepatocytes)

Study Report # 930024170

Title: *In vitro* Evaluation of BMS-562247 as an Inducer of Cytochrome P450 Expression in Cultured Human Hepatocytes.

Objectives: To investigate the effect of BMS-562247 on the expression of cytochrome P450 enzymes in primary cultures of human hepatocytes.

Study Design: Three preparations of cultured human hepatocytes from three separate human livers were treated once daily for three consecutive days with DMSO (vehicle; 0.1% [v/v]), one of three concentrations of BMS-562247 (0.2, 2.0 or 20 μM), or one of three known human CYP inducers namely, omeprazole (100 μM), phenobarbital (750 μM) or rifampin (10 μM). After treatment, cells were harvested to prepare microsomes for the analysis of phenacetin *O*-dealkylation (marker for CYP1A2), bupropion hydroxylation (marker for CYP2B6) and testosterone 6β-hydroxylation (marker for CYP3A4/5) by HPLC/MS/MS. Additional cells from each treatment group were used to measure the levels of mRNA encoding CYP1A2, CYP2B6 or CYP3A4 and additional cultures were used to assess the cytotoxicity potential of BMS-562247 based on leakage of lactate dehydrogenase (LDH), a measure of cell membrane integrity.

Results

The fold of induction results of CYP450 enzymes are summarized in the table below:

Table 5: Effects of treating cultured human hepatocytes with BMS-562247 or prototypical inducers on the fold induction of cytochrome P450 enzymes

Treatment group	Concentration	Fold induction [a]		
		Phenacetin *O*-dealkylation § (CYP1A2)	Bupropion hydroxylation § (CYP2B6)	Testosterone 6β-hydroxylation § (CYP3A4/5)
DMSO	0.1%	1.00 ± 0.37	1.00 ± 0.30	1.00 ± 0.27
BMS-562247	0.2 μM	0.973 ± 0.003	0.892 ± 0.049	0.984 ± 0.005
BMS-562247	2.0 μM	0.934 ± 0.028 *	0.934 ± 0.044	0.907 ± 0.134
BMS-562247	20 μM	0.928 ± 0.037 *	1.12 ± 0.20	1.23 ± 0.21
Omeprazole	100 μM	37.4 ± 1.2	11.0 ± 10.9	2.50 ± 1.34
Phenobarbital	750 μM	2.03 ± 0.44	22.0 ± 22.4	7.36 ± 3.99
Rifampin	10 μM	2.19 ± 0.14	13.1 ± 6.8	8.97 ± 5.16

[a] Values are the mean ± standard deviation of three human hepatocyte preparations: H656, H658 and H660.
Fold inductions are rounded to three significant figures and standard deviation is rounded to the same degree of accuracy.
* Statistically significant according to Dunnett's test ($p>0.05$) without positive controls.
§ Significance found among treatment groups (where 0.1% DMSO is the vehicle control) according to Kruskal-Wallis One Way Analysis on Ranks ($p < 0.05$) but unable to specify the groups that statistically differ from the other groups according to Dunnett's test with positive controls.

The fold of induction results of mRNA are summarized in the table below:

Table 6: Effects of treating cultured human hepatocytes with BMS-562247 or prototypical inducers on the fold induction of cytochrome P450 mRNA levels as determined by bDNA assay (relative to GAPDH mRNA)

Treatment group	Concentration	Fold induction		
		CYP1A2 §	CYP2B6	CYP3A4
DMSO	0.1%	1.00 ± 0.63	1.00 ± 0.26	1.00 ± 0.85
BMS-562247	0.2 µM	0.825 ± 0.150	0.947 ± 0.107	1.12 ± 0.34
BMS-562247	2.0 µM	1.02 ± 0.14	1.11 ± 0.20	1.49 ± 0.41
BMS-562247	20 µM	1.16 ± 0.15	1.83 ± 0.31 †	2.77 ± 0.52 †
Omeprazole	100 µM	253 ± 193	NA	NA
Phenobarbital	750 µM	NA	16.5 ± 18.4 *	NA
Rifampin	10 µM	NA	NA	19.5 ± 8.2 *

GAPDH: Glyceraldehyde-3-phosphate dehydrogenase (a housekeeping gene).
Values are the mean ± standard deviation of three human hepatocyte preparations:H656, H658 and H660.
NA: Not applicable, treatment group not analyzed for respective CYP mRNA.
Fold Inductions are rounded to three significant figures and standard deviation is rounded to the same degree of accuracy.
§ Significance found among treatment groups (where 0.1% DMSO is the vehicle control) according to Kruskal-Wallis One Way Analysis on Ranks ($p < 0.05$) but unable to specify the groups that statistically differ from the other groups according to Dunnett's test with positive controls.
† Statistically significant compared to control (0.1% DMSO) according to Dunnett's Test ($p < 0.05$) without positive controls.
* Statistically significant compared to control (0.1% DMSO) according to Dunnett's Test ($p < 0.05$) with positive controls.

- Treatment of cultured human hepatocytes with the prototypical inducers omeprazole, phenobarbital and rifampin caused the anticipated increases in CYP enzyme activity.
- At concentrations up to 20 µM, apixaban did not cause any discernible cell toxicity or increase in CYP1A2 activity or mRNA levels.
- Apixaban caused a slight increase in the levels of mRNA encoding CYP2B6 and CYP3A4/5, but it caused no increase in microsomal CYP2B6 or CYP3A4 activity.
- Under conditions where the prototypical inducers caused the anticipated changes in CYP enzyme expression, apixaban, at concentrations up to 20 µM, caused no induction of any of the CYP activities examined.

Conclusions: Apixaban does not appear to be a significant inducer of CYP1A2, CYP2B6 or CYP3A4/5.

Study 930037129 (Metabolism of apixaban by CYP450 enzymes)

Study Report # 930037129

Title: Identification of major human P450 enzymes involved in metabolism of apixaban (BMS-562247)

Objectives: To identify the major P450 enzymes involved in metabolism of apixaban.

Study Design: [14C]Apixaban (2.5 and 25 μM) was incubated with pooled human liver microsomes (from young subjects or adults), human intestinal microsomes, human intestinal S9, human kidney micorosomes, or human cDNA-expressed P450 enzymes (CYP1A2, 2A6, 2B6, 2C8, 2C9, 2C18, 2C19, 2D6, 2E1, 2J2, 3A4, 3A5, and 3A7) to determine the catalytic turnover and the correlation between metabolite formation activities with reported CYP activities. The major P450 enzymes involved in apixaban (2.5 and 25 μM) metabolism were further investigated in HLM incubations in the presence of CYP-specific inhibitors.

[14C]Apixaban at 5 μM was incubated with HLM from 16 individual donors to evaluate the correlation between metabolite formation and enzyme activities associated with individual CYP-specific reactions. Metabolite formation was also evaluated with HLM, CYP3A4, and CYP1A2 at various concentrations of [14C]apixaban. Metabolites in incubation samples were profiled and identified by HPLC and LC/MS.

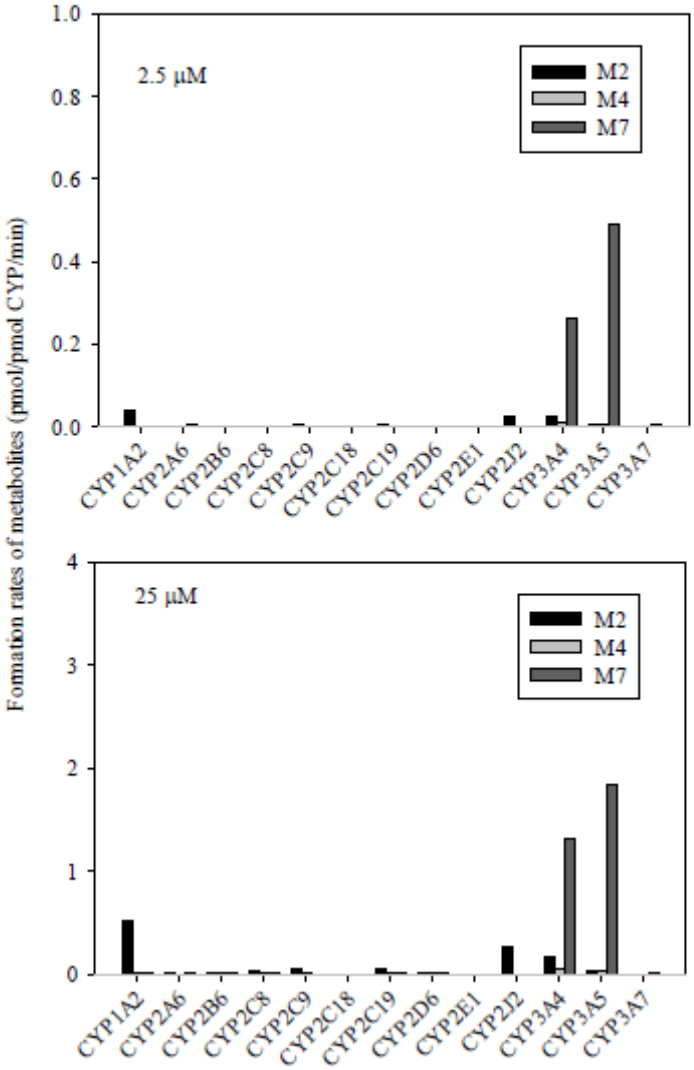
Results

Table 1: Metabolite formation activities in HLM from adult and pediatric donors and HIM at 2.5 and 25 μM [^{14}C]apixaban

	Number of donors	Formation of metabolites (pmol/min/mg protein)					
		2.5 μM			25 μM		
		M7	M4	M2	M7	M4	M2
HLM (adult)	20	3.49±0.91	0.19±0.02	0.76±0.11	33.64±12.9	2.25±0.99	8.39±2.44
HLM (1-6 years)	3	0.71±0.17	0	0.68±0.39	9.84±3.62	1.05±0.53	3.44±0.93
HLM (<1 year)	4	3.02±0.97	0.20±0.08	0.65±0.09	37.67±19.9	3.12±0.99	9.96±3.17
HIM (adult)	6	1.47±0.07	0.13±0.02	0.16±0.02	10.3±3.87	2.01±0.47	2.08±0.46

- Three metabolites (M2, M4, and M7) were formed in HLM and HIM incubations.

Formation of M2, M4, and M7 in human cDNA-expressed P450 enzymes at 2.5 and 25 µM of [^{14}C]apixaban



- The results of 2.5 µM [14C]apixaban incubations with human cDNA-expressed P450 enzymes were consistent with that of 25 µM [14C]apixaban incubations.

Table 2: Metabolite formation by human cDNA-expressed P450 enzymes with [^{14}C]apixaban (25 μM, n=3)

CYP enzyme	M7 (pmol/min/pmol CYP) Mean ± SD	M7[a] (pmol/min/mg mpe)	M4 (pmol/min/pmol CYP) Mean ± SD	M4[a] (pmol/min/mg mpe)	M2 (pmol/min/ pmol CYP) Mean ± SD	M2[a] (pmol/min/mg mpe)
1A2	0.01± 0.004	0.50±0.15	0.01±0.0098	0.45±0.36	0.52±0.18	19.19±6.64
2A6	0.01± 0.003	0.42±0.08	0.01±0.001	0.41±0.04	0	0
2B6	0.01± 0.001	0.09±0.005	0.02±0.005	0.17±0.04	0.01±0.001	0.10±0.01
2C8	0.01± 0.001	0.13±0.13	0.02±0.007	0.39±0.14	0.04±0.017	0.73±0.33
2C9	0.01± 0.002	0.33±0.14	0.01±0.001	0.82±0.0.07	0.06±0.019	3.32±1.15
2C18	0	0	0	0	0.01	1.03
2C19	0.02± 0.009	0.18±0.08	0.02±0.003	0.16±0.03	0.05±0.0.009	0.46±0.08
2D6	0.01± 0.003	0.05±0.02	0.02±0.005	0.13±0.04	0.02±0.0.004	0.13±0.03
2E1	0	0	0	0	0	0
2J2	0	0	0	0	0.27±0.06	-
3A4	1.32±0.44	100.19±33.69	0.06±0.02	4.23±1.38	0.18±0.04	13.68±3.23
3A5	1.85±0.74	1.85±0.74	0.04±0.03	0.04±0.03	0.03±0.024	0.03±0.024
3A7	0.02±0.01	-	0.01±0.00	-	0.01±0.00	-

[a]Normalized enzyme activity = activity in the expressed enzyme (pmol/min.pmol)*concentration of the enzyme in HLM (pmol P450/mg protein). Enzyme concentration in HLM used for normalization were 37, 29, 7, 19, 60, 9, 7, 76, and 1 pmol/mg microsomal protein for CYP1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 3A4, and 3A5, respectively (5). mpe=Human liver microsomal protein-equivalent.

- CYP1A2, 2J2, and 3A4 were shown to catalyze the formation of M2.
- CYP3A4 and 3A5 had higher activities to catalyze the formation of M4 and M7 than other P450 enzymes.
- Other P450 enzymes, CYP2A6, 2B6, 2C8, 2C9, 2C19, 2C18, 2D6, 2E1, and 3A7, did not significantly metabolize apixaban.

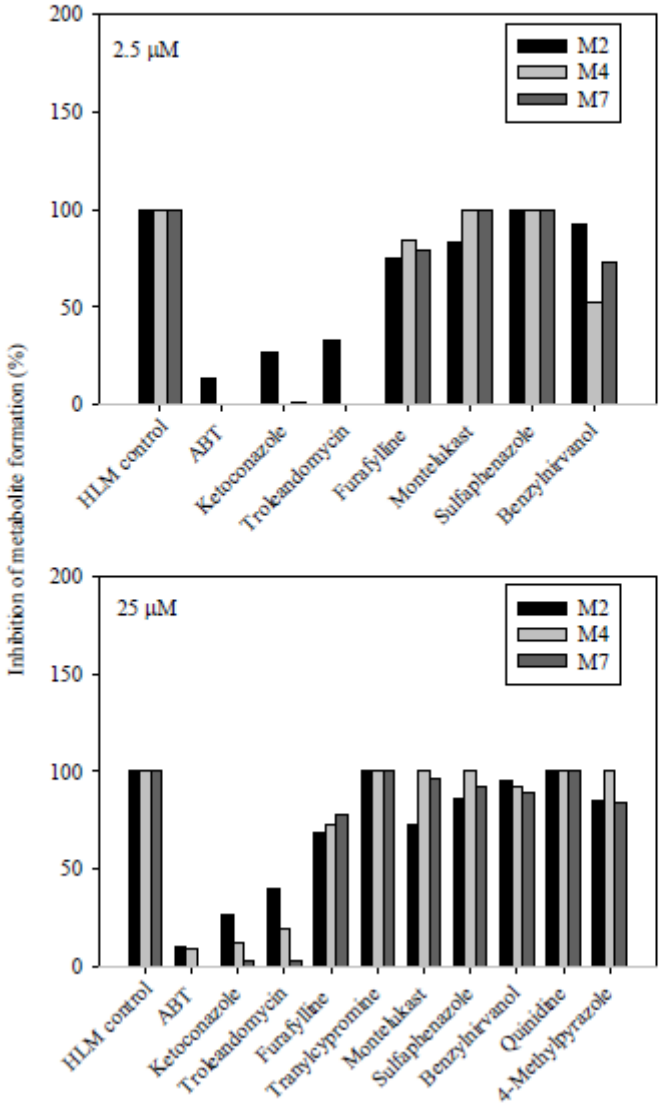
Table 3: Inhibition of metabolite formation by chemical inhibitors in HLM incubations with 2.5 and 25 μM of [^{14}C]apixaban (n=3).

Inhibitor (Concentration.)	% of inhibition for metabolite formation (mean)					
	M7		M4		M2	
	2.5 μM	25 μM	2.5 μM	25 μM	2.5 μM	25 μM
HLM control	0	0	0	0	0	0
ABT (1 mM) (All P450)	100	99.7	100	90.4	86.8	90.3
Ketoconazole (1 μM) (CYP3A4)	99.1	98.2	100	87.8	73.7	73.4
Troleandomycin (100 μM) (CYP3A4)	100	98.5	100	81	67.1	61.5
Furafylline (10 μM) (CYP1A2)	19.8	22.5	15.8	27.4	25.0	31.0
Tranylcypromine (30 μM) (CYP2A6)	ND	0	ND	0	ND	0
Montelukast (3 μM) (CYP2C8)	0	3.9	0	0	17.1	27.1
Sulfaphenazole (10 μM) (CYP2C9)	0	7.6	0	0	0	13.6

Benzylnirvanol (1 μM) (CYP2C19)	27.5	11.8	47.4	7.4	7.9	4.2
Quinidine (1 μM) (CYP2D6)	ND	0	ND	0	ND	0
4-Methylpyrazole (20 μM) (CYP2E1)	ND	16.0	ND	0	ND	15.0

% Inhibition = (activity in HLM-activity in the presence of inhibitor)/activity in HLM; ND, not determined.

Formation inhibition of M2, M4, and M7 in HLM incubations with chemical inhibitors of P450 enzymess at 2.5 and 25 μM of [^{14}C]apixaban



- 1-Aminobenzotriazole (ABT) inhibited the formation of M2, M4 and M7 by approximately 90% or over.
- Ketoconazole and troleandomycin significantly inhibited the formation of M4 and M7 (by

80 to 100%), and inhibited M2 formation by 61 to 74%;

- The CYP1A2 inhibitor, furafylline inhibited M7 formation by 20 to 23%, M4 formation by 16 to 27%, and M2 formation by 25 to 30%; The CYP2C19 inhibitor, benzylnirvanol, showed metabolic inhibition for M4 (47%) and M7 (28%) at low substrate concentration (2.5 μM).
- The inhibitors of other P450 enzymes showed no inhibition or low level inhibition.

Table 4: Correlation between the formation of M2, M4, and M7 and the predetermined activities of P450 enzymes in a panel of individual HLMs

Enzyme	Correlation coefficients (r)		
	M2 formation	M4 formation	M7 formation
CYP1A2	0.14	0.14	0.01
CYP2A6	0.24	0.34	0.38
CYP2B6	0.36	0.46	0.50 *
CYP2C8	0.65*	0.42	0.61*
CYP2C9	0.51*	0.31	0.36
CYP2C19	0.25	0.43	0.36
CYP2D6	0.12	0.26	0.39
CYP2E1	0.36	0.03	0.19
CYP3A4/5	0.76**	0.90**	0.96**
CYP4A11	0.26	0.07	0.03
FMO	0.23	0.33	0.23

t-test: *P<0.05; **P<0.01.

- The best correlations for formation of M2, M4, and M7 (r = 0.76, 0.90, and 0.96, respectively) were observed with the predetermined CYP3A4/5 activity (testosterone 6β-hydroxylation formation rate).
- A moderate correlation of M2 formation activity was observed with CYP2C8 activity (r = 0.65) and 2C9 activity.

Conclusions: CYP3A4 is the major enzyme responsible for formation of M2, M4, and M7 of apixaban in humans; CYP1A2 and 2J2 may also contribute to M2 formation.

4.1.3 PHARMACOKINETICS AND PHARMACODYNAMICS

Study CV185001 (Pharmacokinetics, FTIH)

Study Report # CV185001	**Study period** 12/2002 to 02/2003

Title

Placebo controlled ascending single dose study in healthy subjects to evaluate the safety, pharmacokinetics, and pharmacodynamcis of BMS-562247, a reversible inhibitor of factor Xa [4].

Objectives

To assess pharmacokinetics / pharmacodynamics, and tolerability of apixaban following administration of single ascending doses.

Study Design Eight healthy subjects (apixaban=6, placebo=2) were randomized to receive a single dose of 0.5, 1, 2.5, 5, 10, 25 or 50 mg of apixaban administered as a solution (0.5, 1 and 2.5 mg) or a tablet (5, 10, 25, 50 mg).

Study subjects randomized to receive the 10 mg dose returned after a 7 day washout period to participate in the food effect arm (standard FDA recommended high fat meal) of the study.

Note: A definite food effect study was conducted separately.

Study medication

Dosage Form	Powder for solution (for doses 0.5 to 2.5 mg)	Tablet (for doses 5 to 25 mg)
Dosage Strength	0.25 mg/mL	5 mg
Batch #.	2K63779	2K64989
Administration	Oral	Oral

Sample collection

Pharmacokinetics: Pre-dose, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10 12, 18, 24, 36, 48, 72, and 96 hours post-dose.

Pharmacodynamics: Pre-dose, 0.5, 1.5, 3, 6, 12, 24, and 48 hours post-dose.

Data Analysis Methods

Pharmacokinetic parameters were estimated using non-compartmental methods and presented as geometric mean (CV). For the food effect arm of the study ANOVA on log transformed parameters with fixed effects for treatment and subject was performed. LS

[4] CV185001

mean and 90% CI for the difference were constructed and reported.

The relationship between PD measures and apixaban plasma concentrations was evaluated using linear mixed effects modeling.

Study population

Randomized/Completed/ Discontinued Due to AE	57/56/1[▲]
Age (range)	20 to 43 y
Male/Female	57/0
Race (Caucasian/Black/Asian/American Indian or Alaska native/other)	30/19/1/1/6

[▲]Subject withdrew consent on day 2 of the study and was replaced. Therefore, seven individuals contributed data to the 50 mg dose group.

Results:

1. Pharmacokinetics

    a. Peak plasma apixaban concentrations were attained at about 2 and 3h following administration of apixaban solution and tablet, respectively.

    b. Apixaban appears to follow bi-exponential disposition with a distritbuiton half-life of about 3h and a terminal elimination half-life ranging from 10 to 20 h.

    Reviewer's comment: Plasma apixaban concentrations were below the LOQ at 12-24h post dose at the lower doses. The elimination $t_{1/2}$ estimated for the lower dose groups are not representative of apixaban elimination $t_{1/2}$.

    c. Pharmacokinetics of apixaban are less than dose proportional in the dose range studied.

    d. There is moderate variability (%CV~ 30) in apixaban pharmacokinetics.

    e. Food increased bioavailability of apixaban by about 45%.

2. Pharmacodynamics

    a. No increase from baseline was observed with increasing concentrations of apixaban in the conventional coagulation tests (PT/INR/aPTT). A small increase was observed at doses ≥ 25 mg.

    b. Concentration dependent increase was observed in the modified prothrombin time test.

    c. Anti FXa measurements were not evaluable.

Assay Method

Apixaban pharmacokinetics The performance of the assay method during study sample analysis is acceptable and is summarized in the table below.

Analyte	Apixaban
Method	LC/MS/MS
LOQ (ng/mL)	1.0
Range (ng/mL)	1 to 1000
QCs (ng/mL)	3, 400, 800
Accuracy/Bias	-5.4 to 11.3%
Precision	2.1 to 19.4%

Apixaban pharmacodynamics

PT, INR and aPTT were measured using standardized laboratory techniques.

Modified PT - Thromboplastin reagent used in a standard PT test was diluted in a 1:2.25 ratio with $CaCl_2$ to increase the dynamic range of the assay.

Safety

Death/SAE: None

Conclusion

Apixaban follows less than dose proportional pharmacokinetics following oral administration. Maximum tolerated dose was not defined in this study.

Apixaban does not increase PT, INR or aPTT at lower doses (< 25 mg).

Detailed Results:

Table Summary of the pharmacokinetic measures for apixaban (Ref: CSR, CV185001).

Treatment	Cmax (ng/mL) Geom. Mean (CV%)	AUC(INF) (ng•h/mL) Geom. Mean (CV%)	AUC(0-T) (ng•h/mL) Geom. Mean (CV%)	Tmax (h) Median (Min, Max)	Terminal T-HALF (h) Mean (SD)
Oral Solution					
Apixaban 0.5 mg (n=6)	9.1 (20)	61.9 (16)	52.7 (23)	1.50 (1.00, 4.00)	3.57 (1.07)
Apixaban 1 mg (n=6)	23.5 (35)	174.4 (31)	162.6 (33)	1.75 (1.00, 3.00)	4.25 (1.64)
Apixaban 2.5 mg (n =6)	52.5 (35)	437.5 (41)	421.1 (42)	1.50 (1.00, 3.00)	6.79 (1.95)
Tablet					
Apixaban 5 mg (n =6)	104.7 (25)	1016.6 (37)	976.6 (36)	3.25 (2.50, 4.00)	15.19 (8.53)
Apixaban 10 mg (n =6)	176.3 (42)	1303.6 (40)	1266.5 (38)	3.00 (2.00, 4.00)	11.06 (5.75)
Apixaban 10 mg FED (n =6)	186.6 (20)	1904.3 (32)	1812.6 (30)	3.50 (2.50, 4.00)	23.10 (18.85)
Apixaban 25 mg (n =6)	365.1 (17)	4010.0 (19)	3868.9 (22)	3.00 (2.50, 4.00)	26.80[a] (33.72)
Apixaban 50 mg (n =7)	685.2 (22)	7556.5 (25)	7096.7 (23)	2.50 (2.00, 4.00)	19.72 (15.34)

Time-course plots - Pharmacokinetics

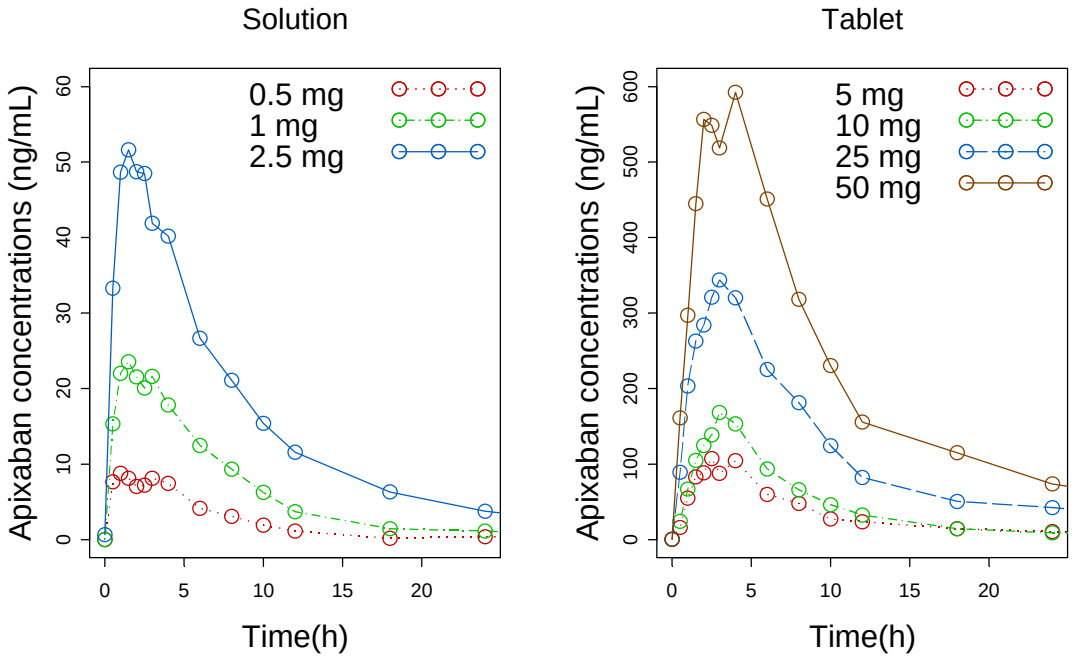


Figure Mean plasma apixaban concentration versus time course (0-24h) following

administration of apixaban solution (left panel) or apixaban tablet (right panel).

Pharmacodynamics

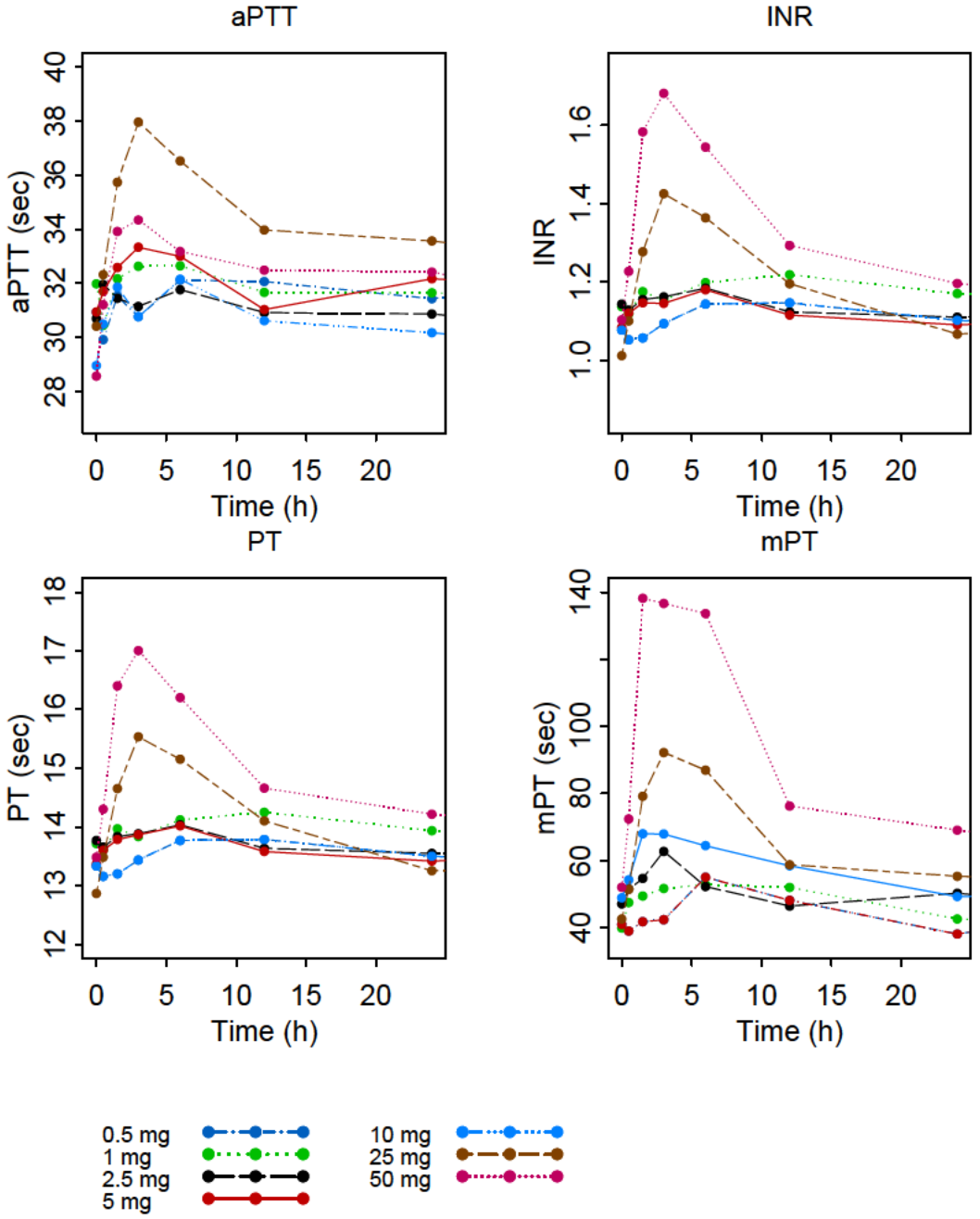


Figure Mean time course (0-24h) for aPTT, INR, PT and mPT following administration of a single dose of apixaban.

Study CV185002(a) (Pharmacokinetics, MAD)

Study Report # CV185002a	**Study period** 04/2003 to 11/2003

Title

Two Part, Placebo-Controlled, Ascending Multiple-Dose and Aspirin Interaction Study to Evaluate the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of Apixaban (BMS-562247), a Reversible Inhibitor of Factor Xa, in Healthy Subjects: Part A [5].

Objectives

To assess pharmacokinetics / pharmacodynamics, and tolerability of apixaban following administration of multiple ascending doses.

Study Design Eight healthy subjects (apixaban=6, placebo=2) were randomized to receive repeat doses of 2.5, 5, 10, or 25 mg of apixaban administered BID or 10, 25 mg apixaban administered QD for seven days.

Study medication

Dosage Form		Tablet	
Dosage Strength	2.5 mg	5 mg	20 mg
Batch #	3A68960	2K64989	3A70866
Administration		Oral	

Sample collection

Pharmacokinetics: BID regimen -Pre-dose, 1, 2, 3, 4, 6, 9, 12, 14, 15, 16, 18, 21, 24 hours post-dose on days 1 and at Pre-dose, 1, 2, 3, 4, 6, 9, 12, 14, 15, 16, 18, 21, 24, 48, and 72 hours post dose on day 7. Pre dose samples were collected on day 4.

QD regimen - Pre-dose, 1, 2, 3, 4, 6, 9, 12, 24 hours post dose on day 1 and at pre-dose, 1, 2, 3, 4, 6, 9, 12, 24, 48 and 72 hours post dose on day 7. Pre-dose samples were collected on day 4.

Pharmacodynamics: Pre-dose, 3, 6, 9, 12, 15, 18, 21, 24 hours post dose on day 1 for both BID and QD regimens. Samples were collected at pre-dose and at 3 hours post dose on day 4. An additional 48 hour sample was collected on day 7 for the QD regimen.

Data Analysis Methods

Pharmacokinetic parameters were estimated using non-compartmental methods and presented as geometric mean (CV).

Study population

[5] \\Cdsesub1\evsprod\NDA202155\\0001\m5\53-clin-stud-rep\533-rep-human-pk-stud\5331-healthy-subj-pk-init-tol-stud-rep\cv185002-parta\cv185002-part-a.pdf

Randomized/Completed/ Discontinued Due to AE	48/47/1[▲]
Age (range)	30 (20 to 41) y
Male/Female	48/0
Race (Caucasian/Black/Asian/American Indian or Alaska native/other)	29/17/1/0/1

[▲]Subject (randomized to 2.5 mg dose group) discontinued because of nausea and headache.

Results:

3. Pharmacokinetics

    a. Peak plasma apixaban concentrations were observed at about 3 to 4 hours for both BID and QD regimens.

    b. The accumulation index following BID dosing was about 1.3 to 1.9.

    c. Mean half-life following BID dosing ranged from 9 to 11 h.

    d. Total systemic exposure to apixaban increased in a less than dose proportional manner on day 1 and was greater than dose proportional on day 7, in the dose range studied. On day 1, AUC increased in the ratio of 1:1.7:4.6:8.8 with an increase in dose in the ratio of 1:2:5:10. On day 7, AUC increased in the ratio of 1:2.3:5.2:12.6.

    e. Total systemic exposure to apixaban following administration of 5 mg BID was about 20% lower than that following administration of 10 mg QD (total daily dose of 10 mg). This may be because of lower exposure to apixaban following the evening dose.

    f. There was no accumulation following QD dosing.

    g. Mean half-life following QD dosing ranged from 12 to 15 h.

4. Pharmacodynamics

    a. Consistent increase from baseline was not observed with increasing concentrations of apixaban in the conventional coagulation tests (PT/INR/aPTT).

    b. Concentration dependent increase was observed in the modified prothrombin time test. However, because samples were not collected for 3 h post second dose of the BID regimen, the impact of reduced exposure to the evening dose of apixban on its PD cannot be determined.

    c. Anti FXa measurements were not evaluable.

Assay Method

Apixaban pharmacokinetics The performance of the assay method during study sample analysis is acceptable and is summarized in the table below.

Analyte	Apixaban
Method	LC/MS/MS
LOQ (ng/mL)	1.0
Range (ng/mL)	1 to 1000
QCs (ng/mL)	3, 400, 800
Accuracy/Bias	± 2.2%
Precision	± 8.1%

Apixaban pharmacodynamics

PT, INR and aPTT were measured using standardized laboratory techniques.

Modified PT - Thromboplastin reagent used in a standard PT test was diluted in a 1:2.25 ratio with $CaCl_2$ to increase the dynamic range of the assay.

Safety

Death/SAE: None

Conclusion

Apixaban follows less than dose proportional pharmacokinetics following oral administration. Maximum tolerated dose was not defined in this study.

Apixaban does not increase PT, INR or aPTT at lower doses (< 25 mg).

Detailed Results:

Table Summary of the pharmacokinetic measures for apixaban on day 7 (Ref: CSR, CV185002a).

Apixaban Dose and Regimen	Cmax (ng/mL) Geom. Mean (CV %)	Cmin[a] (ng/mL) Geom. Mean (CV %)	AUC(TAU[b]) (ng.h/mL) Geom. Mean (CV%)	Tmax (h) Median (min, max)	AI Geom. Mean (CV.%)	T1/2 (h) Mean (S D)	Effective T1/2 (h) Mean (SD)
2.5 mg BID	62.3	21.0	462.8	3.0	1.3	8.1	5.3
(n=5)	(37)	(17)	(35)	(3.0, 9.0)	(18)	(1.8)	(2.4)
5 mg BID	128.5	49.6	1051.9	4.0	1.8	11.7	10.1
(n=6)	(10)	(20)	(9)	(2.0, 4.0)	(22)	(3.3)	(3.5)
10 mg BID	329.8	103.8	2424.9	3.0	1.5	10.9	9.6
(n=6)	(45)	(57)	(47)	(2.0, 4.0)	(33)	(2.9)	(3.8)
25 mg BID	716.6	281.1	5850.3	3.5	1.9	15.2	11.1
(n=6)	(21)	(38)	(16)	(1.0, 4.0)	(17)	(7.2)	(2.8)
10 mg QD	201.4	26.8	2015.7	3.5	1.3	14.9	12.4
(n=6)	(15)	(43)	(16)	(3.0, 4.0)	(23)	(7.2)	(5.1)
25 mg QD	428.9	55.3	4248.3	3.0	1.5	15.3	15.0
(n=6)	(20)	(33)	(19)	(2.0, 4.0)	(17)	(4.3)	(4.6)

Time-course plots - Pharmacokinetics

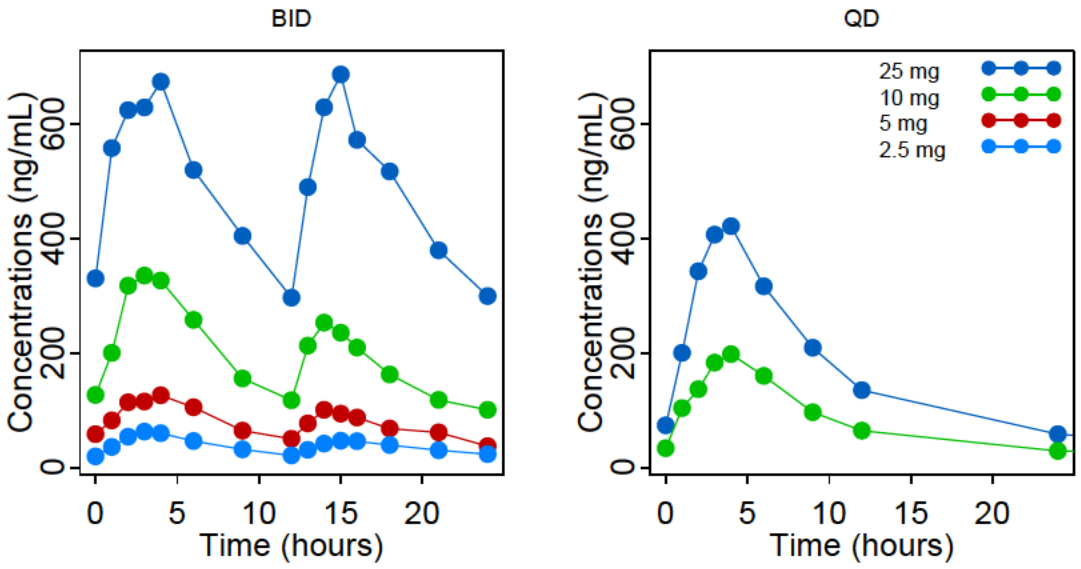


Figure Mean plasma apixaban concentration versus time course (0-24h) following administration of apixaban BID (2.5, 5, 10 or 25 mg) or QD (10 or 25 mg) on day 7.

Study CV185006 (Mass balance)

Study Protocol # CV185006	**Study period** 04/2005 to 05/2004

Title

Pharmacokinetics and metabolism of ^{14}C-labeled BMS-562247 with bile collection in healthy subjects.

Objectives

To assess routes and extent of elimination of apixaban.

Study Design

Healthy subjects were enrolled in two groups (group 1, n=6 and group 2, n=4) to receive 20 mg of ^{14}C-apixaban (108.8 μCi) administered as a solution. One hour post drug administration, bile was collected (for a period of 8h) in subjects in group 2, by suction via an oral gastro duodenal tube. At the end of seven hours post dose, subjects in group 2 were administered 20 ng/Kg cholecystokinin infusion to stimulate gall bladder contraction.

Study medication

Dosage Form	Powder for solution
Dosage Strength	20 mg/108.8 μCi
Batch #.	4B73290
Administration	oral

Sampling schedule

Blood samples were collected for pharmacokinetic analysis (total radioactivity and apixaban concentrations in plasma and whole blood) at pre-dose, 0.5, 1, 1.5, 2, 4, 8, 12, 24, 36, 48, 72, 96, 120, 144, 168, and 192 hours post-dose.

Blood samples were collected for biotransformation analysis at pre-dose, 1, 6, 12, 24, 48, and 96 hours post-dose.

Bile (group 2 only) was collected at 0-3, 3-6, and 6-8 h intervals.

Urine and feces were collected at 24 h intervals for upto 240 h or until the amount of radioactivity excreted was < 1%.

Data Analysis Methods

Summary statistics were calculated and presented for PK measures.

Study population

Randomized/Completed/ Discontinued Due to AE	11/9/1[^]
Age (range) years	26(18 – 40)

Male/Female	10/0
Race (Caucasian/Black/Asian/American Indian or Alaska native/other)	4/4/0/0/2

[^] One subject did not meet inclusion criteria and discontinued before receiving a dose, another withdrew consent on day 10.

Results:

1. About 25 % of the administered dose was eliminated in urine, 80% (20% of the dose) of which was eliminated in the first 24 h.
2. About 50 % of the administered dose was eliminated in feces.
3. Apixaban was the major component in both urine and feces.
4. About 2.5 % of the administered dose was eliminated in bile.
5. Blood to plasma ratio was 0.7 to 0.8.
6. Apixaban was the major component of total radioactivity in systemic circulation for upto 48h (98% at 1 h post dose, and ~60% at 48 h post dose). The sulfate conjugate of O-demethyl apixaban (M1) accounts for the remaining radioactivity (~2% at 1 h post dose and ~ 40% at 48h post dose).

Assay Method

The performance of the assay method during study sample analysis is acceptable and is summarized in the table below.

Analyte	Apixaban
Method	LC/MS/MS
LOQ (ng/mL)	1.0
Range (ng/mL)	1 to 1000
QCs (ng/mL)	3, 400, 800
Accuracy/Bias (plasma)	± 14.0
Precision (plasma)	± 6.0

Radioactivity in plasma, whole blood, urine and feces was measured by scintillation counting following standard techniques.

Safety Death/SAE: None

Conclusion

Apixaban appears to be eliminated by multiple pathways. About 75 to 80% of an orally administered dose is recovered within 9 days. About 25% of an administered dose is eliminated in urine, indicating that the absolute bioavailability of apixaban is atleast 25%. Apixaban is the major drug related component in systemic circulation, urine and feces. It undergoes minimal metabolism.

Detailed Results: Apixaban

Parameter	N	Geometric Mean (%CV) No bile collected	N	Bile collected
C_{max} (ng/mL)	6	480 (20)	4	453 (12)
t_{max} (h)ˆ	6	1.0 (1.0, 1.5)	4	1.25 (0.5, 2.0)
$AUC_{0\text{-}last}$ (ng/mL*h)	6	4055 (30)	4	4041 (20)
$AUC_{0\text{-}\infty}$ (ng/mL*h)	6	4100 (30)	4	4103 (20)
$t_{1/2}$ (h)ˆˆ	6	12.2 (8.48)	4	13.5 (9.9)

ˆ*Median (range)* ˆˆ *Mean ± SD*

Concentration time-course

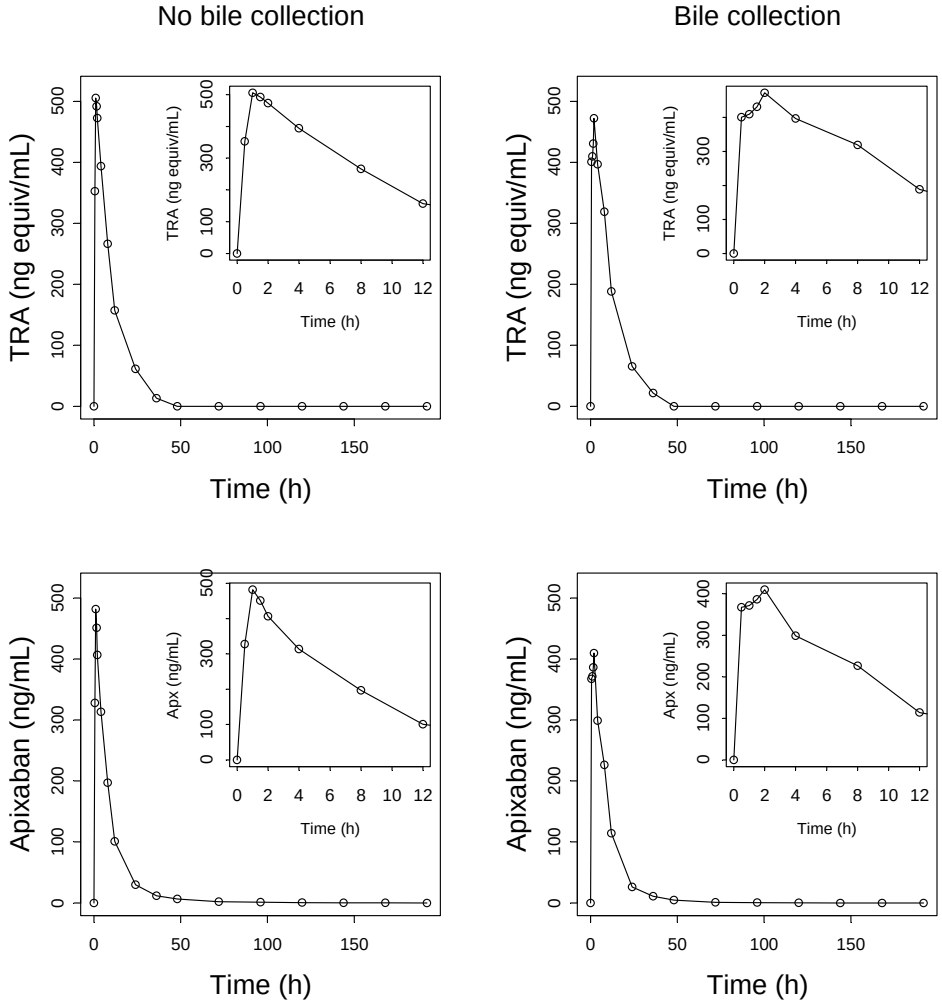


Figure Mean plasma total radioactivity (TRA)/apixaban concentration versus time profile following administration of 20 mg ^{14}C-apixaban solution in healthy individuals. Plots are presented by treatment group (No bile collected, n=6/ bile collected, n=4). A 0-12 hour post dose time profile is presented in the inset.

Study CV185007 (Regional GI absorption)

Study Protocol # CV185007	**Study period** 06/2003 to 09/2003

Title

Assessment of BMS-562247 regional gastrointestinal absorption using pharmcoscintigraphic evaluation in healthy subjects.

Objectives

To assess the extent of absorption of apixaban when delivered to specific regions in the GIT.

Study Design

Healthy subjects (n=12) were enrolled to receive apixaban solution administered orally (immediately followed by 240 mL of water), apixaban solution administered to the distal small bowel, apixaban solution administered to the ascending colon or crushed apixaban tablet delivered to the ascending colon. GI site specific delivery was done using Enterion capsules (immediately followed by 210 mL of water and 30 mL of 4MBq ^{99m}Tc-DTPA in water). The treatments were separated by a minimum of seven days of washout.

Study medication

Dosage Form	Crushed tablet	Powder for solution
Dosage Strength	2.5 mg	2.5 mg/0.8 mL (3.125 mg/mL)
Batch #	3A68960	2F52153
Administration	Ascending colon via Enterion™ capsule	Oral (using a syringe) and distal small bowel or ascending colon via Enterion™ capsule

Sampling schedule

Blood samples were collected for pharmacokinetic at pre-dose (capsule activation time for treatments B-D), 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 12, 24, 36, 48, and 60 hours post-dose (post capsule activation time for treatments B-D).

Scintigraphic images were collected prior to dosing and every 10 minutes for the first 4 hours and every 20 minutes 4 to 8 h after capsule activation. Images were collected at 12, 24, 36, 48, and 60 h thereafter or till the capsule was defecated.

Data Analysis Methods

Summary statistics were calculated and presented for PK measures.

Study population

Randomized/Completed/ Discontinued Due to AE	12/9/3[▲]
Age (range) years	28(20-37)

Male/Female	12/0
Race (Caucasian/Black/Asian/American Indian or Alaska native/other)	9/2/0/0/1

ˆ Study medication was not delivered to the site specified in two subjects and they declined to participate in a repeat treatment. One subject developed upper respiratory tract infection.

Results:

1. The mean gastric emptying time was about 2 h across all treatment groups (B – D). Mean small intestinal transit time was ~ 6 h and colon arrival time was at ~ 8.5 h post dose. Capsule recovery occurred at ~ 27 h post dose.

2. When administered as a solution to the distal small bowel, peak and total systemic exposure to apixaban (C_{max} and AUC) was ~ 40% that administered orally.

3. When administered as a solution to the ascending colon, peak and total systemic exposure to apixaban (C_{max} and AUC) was ~ 10 and ~ 16%, respectively, of that administered orally.

4. Administering apixaban as a crushed tablet to the ascending colon resulted in peak and total systemic exposure (C_{max} and AUC) of ~ 40% that of a solution administered to the ascending colon.

5. On an average peak plasma apixaban concentrations were reached in about 1 h following administration of the solution orally and to the small distal bowel, and at about 3 h when delivered to the ascending colon.

Assay Method

The performance of the assay method during study sample analysis is acceptable and is summarized in the table below.

Analyte	Apixaban
Method	LC/MS/MS
LOQ (ng/mL)	1.0
Range (ng/mL)	1 to 1000
QCs (ng/mL)	3, 400, 800
Accuracy/Bias (plasma)	± 2.6
Precision (plasma)	± 8.2

Safety Death/SAE: None

Conclusion

There is region dependant absorption of apixaban, with less absorption at distal sites of the gastrointestinal tract.

Detailed Results:

Table Summary pharmacokinetic measures for apixaban

Treatment	Apixaban Pharmacokinetic Parameters					
	Cmax (ng/mL) Geom. Mean (CV %)	AUC(0-T) (ng•h/mL) Geom. Mean (CV %)	AUC(INF) (ng•h/mL) Geom. Mean (CV %)	Mean Residence Time (h) Mean (SD)	Tmax (h) Median (Min, Max)	T1/2 (h) Mean (SD)
A (n = 11)	59.3 (41)	426.1 (85)	446.5 (82)	7.09 (2.05)	1.0 (0.5, 4.0)	6.33 (1.34)
B (n = 11)	22.9 (58)	176.7 (48)	203.3 (42)	9.02 (3.91)	1.5 (0.5, 6.0)	9.90 (6.08)
C (n = 8)	6.2 (72)	73.5 (82)	279.7 [a] (1)	11.22 (6.02)	3.0 (0.5, 5.0)	15.42 (7.81)
D (n = 8)	2.2 (35)	24.0 (72)	NA	13.62 (5.33)	10.0 (2.0, 24.0)	31.05 [a] (1.21)

A – oral solution, B – solution delivered to distal small bowel, C – solution delivered to ascending colon, D - – crushed delivered to ascending colon, a – n=2

Concentration time-course

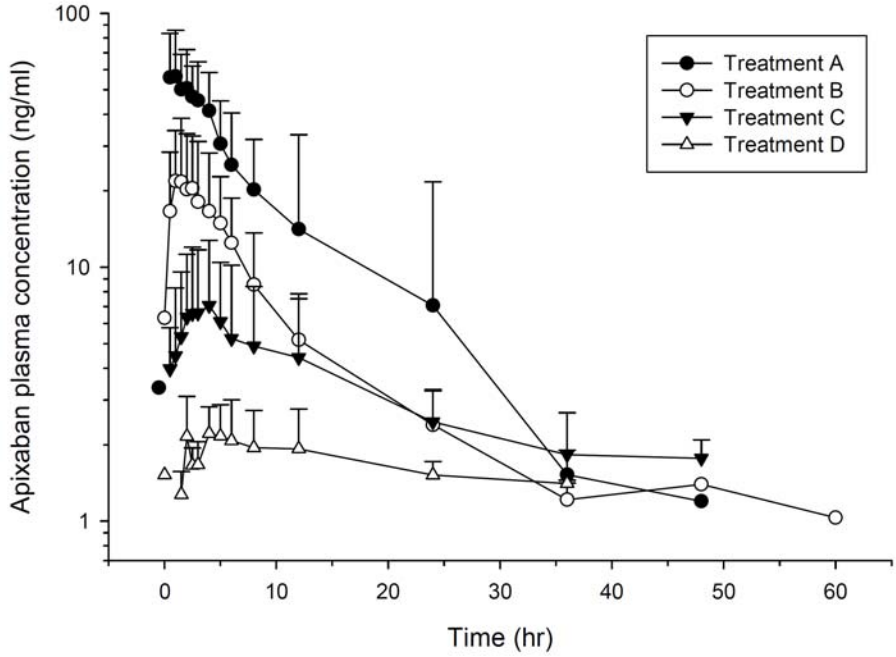


Figure Mean plasma apixaban concentration versus time profile following administration of A – oral solution, B – solution delivered to distal small bowel, C – solution delivered to ascending colon, D - – crushed delivered to ascending colon.

Study CV185020 (Pharmacokinetics, Pharmacodynamics)

Study Protocol # CV185020	**Study period** 08/2005 to 10/2005

Title

Placebo controlled ascending single dose study to evaluate the safety, pharmacokinetics, and pharmacodynamics of intravenously administered apixaban in healthy subjects [6]

Objectives

To assess pharmacokinetics / pharmacodynamics, and tolerability of apixaban following intravenous administration of single ascending doses, and to assess absolute bioavailability of apixaban.

Study Design Eight healthy subjects (apixaban=6, placebo=2) were randomized to receive a single dose of 0.5, 1.25, 2.5, 3.75, 5 mg of apixaban.

Subjects randomized to the 2.5 mg IV dose group returned after a washout period of at least seven days to receive a 5 mg *po* dose of apixaban administered as a tablet (to assess absolute bioavailability).

Note: The tablet formulation was modified and absolute bioavailability of the new formulation was assessed in another study (CV185045). Hence, detailed results are not presented here.

Study medication

Dosage Form	Solution for intravenous administration	Tablet
Dosage Strength	2.5 mg/mL	5 mg
Batch #.	5D01551	2K64989
Administration	IV	Oral

Sample collection

Pharmacokinetic: Blood samples were collected at pre-dose, 3 min, 10 min, 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 18, 24, 36, 48, 60 and 72 hours post-dose.

Urine samples were collected at 0-12h, 12-24h, 24-36h, 36-48h, 48-60h, and 60-72h intervals.

Pharmacodynamics: Blood samples were collected for mPT and INR assessments at pre - dose, 3 min, 10 min, 0.5, 1, 2, 3, 4, 6, 8, 12, 18, 24, 48, 72h post-dose. Anti-Xa activity was assessed only in the subset that received the 5 mg dose (IV and *po*) of apixaban.

[6] \\Cdsesub1\evsprod\NDA202155\\0001\m5\53-clin-stud-rep\533-rep-human-pk-stud\5331-healthy-subj-pk-init-tol-stud-rep\cv185020\cv185020.pdf

Data Analysis Methods

Pharmacokinetic parameters were estimated using non-compartmental methods and presented as geometric mean (CV).

Study population

Randomized/Completed/ Discontinued Due to AE	40/39/1[ˆ]
Age (range)	18 to 44 y
Male/Female	40/0
Race (Caucasian/Black/Asian/American Indian or Alaska native/other)	22/14/3/0/1

[ˆ]Only 5 subjects received oral apixaban.

Results:

1. Apixaban appears to follow bi-exponential disposition with a distritbuiton half-life of about 3h and a terminal elimination half-life ranging from 10 to 20 h.

2. Apixaban follows dose proportional pharmacokinetics in the dose range studied.

3. There is low variability (%CV~ 10 to 20) in apixaban pharmacokinetics.

4. About 1/3 rd of an administered dose was recovered in urine (within 72 h post dose).

5. Absolute bioavailability of apixaban is 0.66 (range 0.51 to 0.86).

   Note: The tablet formulation was modified and absolute bioavailability of the new formulation was assessed in another study (CV185045). Hence, detailed results are not presented here.

6. Peak plasma M1 concentrations were attained at about 4 to 6 h post IV administration of apixaban.

7. Systemic exposure ($AUC_{0\text{-tlast}}$) to the metabolite was about 15% that of apixaban. Metabolite concentrations were below LLOQ at 0.5 and 1.25 mg doses, and in some subjects at the higher dose groups.

8. There was no dose dependent increase in INR, while mPT increased with increasing doses of apixaban. Maximal change from baseline mPT was observed immediately following administration of an IV dose and at about 4 hours after administration of the *po* dose.

   Note: Anti FXa activity was measured/analyzed for only the 5 mg IV and po dose groups. It was considered to be exploratory in this study and therefore those data were not reviewed.

Assay Method

The performance of the assay method during study sample analysis is acceptable and is

summarized in the table below.

Analyte	Apixaban	M1 metabolite
Method	LC/MS/MS	LC/MS/MS
LOQ (ng/mL)	1.0	5.0
Range (ng/mL)	1 to 1000	5 to 1000
QCs (ng/mL)	3, 35, 400, 750	15, 80, 400, 750
Accuracy/Bias (plasma)	± 2.5%	± 7.2%
Precision (plasma)	± 2.5%	± 5.5%
Accuracy/Bias (urine)	± 8.4%	± 3.3%
Precision (urine)	± 2.7%	± 10.3%

Safety

Death/SAE: None

Conclusion

Intravenous doses upto 5 mg apixaban were well tolerated in healthy subjects. Apixaban follows dose proportional kinetics in the dose range tested. Modified prothrombin time is a better indicator of the pharmacodynamic activity of apixaban than INR.

Detailed Results:

Table Summary of pharmacokinetic measures/parameters for apixaban following intravenous administration (Ref: CSR CV185020)

Apixaban Dose (n)	AUC(INF) (ng·h/mL) Geom. Mean (C.V. %)	AUC(0-T) (ng·h/mL) Geom. Mean (C.V. %)	T-HALF (h) Mean (S.D.)	CL (L/hr) Mean (S.D.)	CLR (L/hr) Mean (S.D.)	Vss (L) Mean (S.D.)	%UR Mean (S.D.)
0.5 mg (n = 6)	145.7 (15)	135.9 (15)	3.71 (0.88)	3.47 (0.54)	1.10 (0.32)	17.09 (3.50)	29.76 (7.65)
1.25 mg (n = 6)	365.4 (23)	353.7 (23)	4.44 (0.40)	3.49 (0.71)	1.08 (0.31)	19.36 (2.33)	30.14 (6.05)
2.5 mg (n = 6)	724.2 (21)	706.4 (21)	5.61 (2.03)	3.51 (0.67)	0.61 (0.32)	21.99 (3.41)	17.40 (9.05)
3.75 mg (n = 6)	1171.0 (11)	1155.8 (11)	8.41 (2.26)	3.22 (0.31)	0.89 (0.25)	23.71 (4.27)	27.15 (5.81)
5 mg (n = 6)	1436.9 (13)	1416.5 (13)	8.03 (2.14)	3.50 (0.41)	0.97 (0.21)	25.93 (4.26)	27.48 (5.07)

Concentration time-course

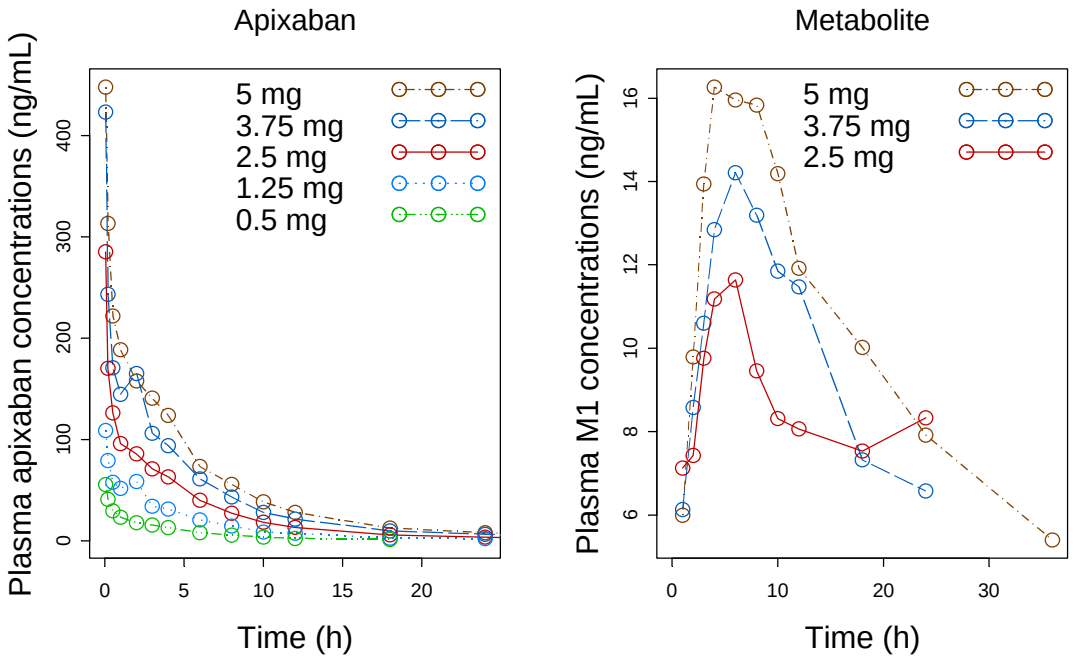


Figure Mean plasma apixaban and M1 concentration versus time profile following intravenous administration of apixaban.

Pharmacodynamic response time course

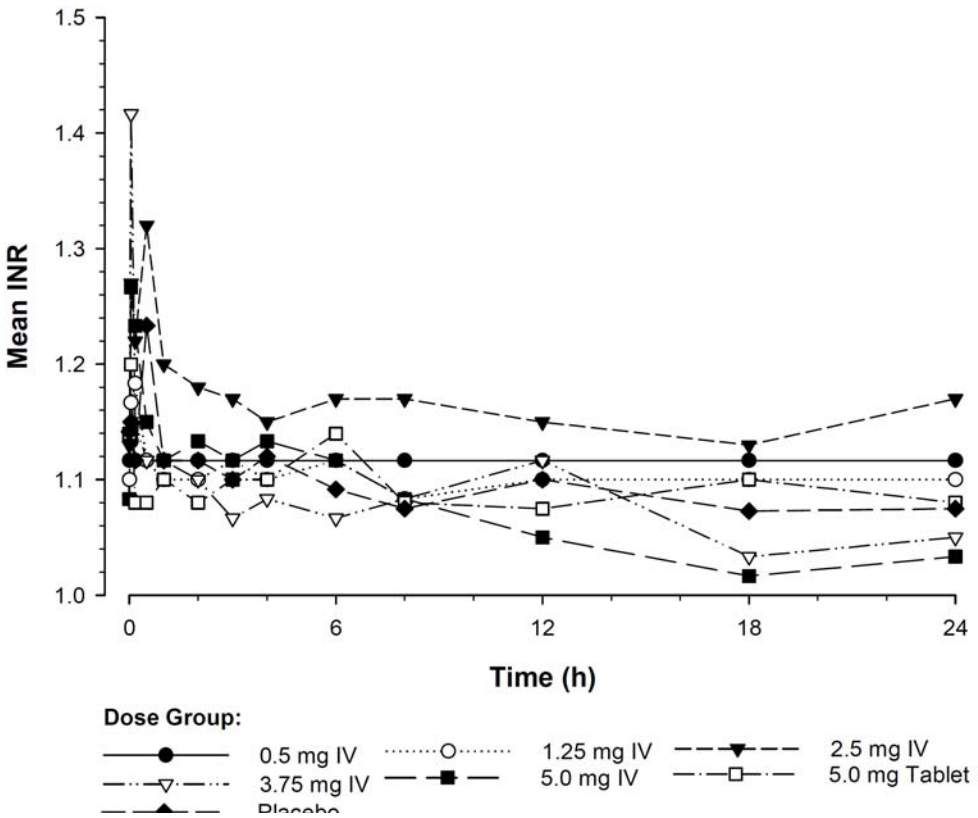


Figure Mean INR time course following single intravenous administration of 0.5, 1.25, 2.5, 3.75, 5.0 mg or 5 mg oral dose of apixaban.

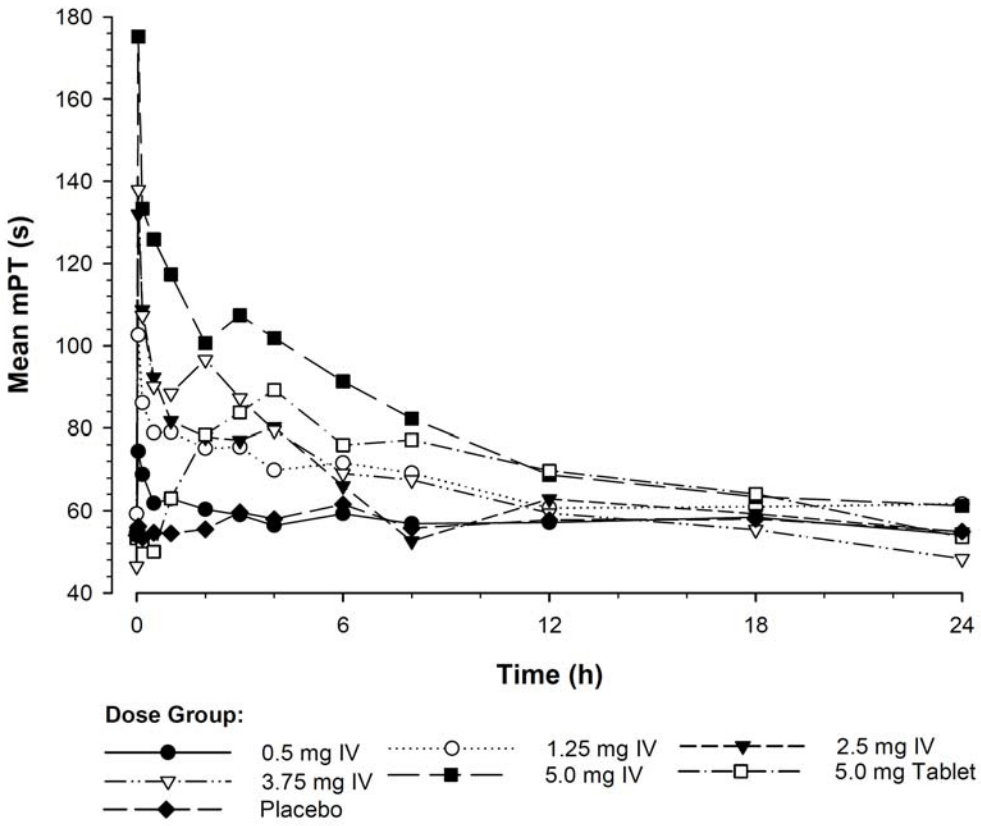


Figure Mean mPT time course following single intravenous administration of 0.5, 1.25, 2.5, 3.75, 5.0 mg or 5 mg oral dose of apixaban.

Study CV185013 (Pharmacokinetics)

Study Report # CV185013	**Study period** 12/2004 to 04/2005

Title

An assessment of BMS – 562247 single dose pharmacokinetics: an intra subject dose escalation study in healthy Japanese and Caucasian subjects [7].

Objectives

To assess and compare pharmacokinetics / pharmacodynamics, and tolerability of apixaban following administration of single ascending doses in healthy Caucasian and Japanese subjects.

Study Design Healthy Japanese (randomized to receive apixaban or placebo) and Caucasian (matched to Japanese subjects for age, body weight and smoking status) subjects were enrolled to receive four increasing doses of apixaban (2.5, 5, 10, 25, 50 mg or placebo). The treatment periods were separated by a minimum of 5 days.

Study medication

Dosage Form		Tablet	
Dosage Strength	2.5 mg	5 mg	20 mg
Batch #.	3A68960	2K64989	3A70866
Administration		Oral	

Sample collection

Pharmacokinetics: Blood samples were collected at pre-dose, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10 12, 18, 24, 36, 48, and 72 hours post-dose.

Urine samples were collected pre-dose, 0-12, 12-24, 24-36, and 36-72 hour intervals.

Pharmacodynamics: Blood samples for assessing INR, aPTT, and mPT were collected at pre-dose, 0.5, 1.5, 3, 6, 12, 24, 48, and 72 hours post-dose. Blood samples for assessing thrombin generation were collected at pre-dose, 3, 6, 12, and 24 hours post dose.

Data Analysis Methods

Pharmacokinetic parameters were estimated using non-compartmental methods and presented as geometric mean (CV). Dose proportionality was assessed using the power model ($Y=A \times Dose^b$). Non-compartmental methods were used to estimate AUEC and presented as mean (CV).

Study population

[7] \\Cdsesub1\evsprod\NDA202155\\0001\m5\53-clin-stud-rep\533-rep-human-pk-stud\5331-healthy-subj-pk-init-tol-stud-rep\cv185013\cv185013.pdf

Randomized/Completed/ Discontinued Due to AE	32/31/1[▲]
Age (range)	31 (20 to 42) y
Male/Female	32/0
Race (Caucasian/Black/Asian/American Indian or Alaska native/other)	16/0/16/0/0

[▲] Subject withdrew consent after receiving a single dose of placebo.

Results:

1. Peak plasma apixaban and M1 concentrations were observed at about 3 and 8 hours, respectively in both Japanese and Caucasian subjects.

2. Peak and total systemic exposure to apixaban increased in aless than dose proportional manner in both Japanese and Caucsian subjects.

3. Total systemic exposure (AUC) to apixaban and M1 was about 10 to 20% lower in Japanese subjects compared to Caucasian subjects.

4. Cumulative urinary recovery of apixaban was about 5% higher in Japanese subjects when compared to Caucasians. Renal elimination of apixaban is also faster in Japanese subjects as compared to Caucasians.

5. The mean change from baseline in thrombin regeneration, aPTT, INR and mPT was similar in healthy Japanese and Caucasian subjects.

Assay Method

Apixaban pharmacokinetics The performance of the assay method during study sample analysis is acceptable and is summarized in the table below.

Analyte	Apixaban	M1
Method	LC/MS/MS	LC/MS/MS
LOQ (ng/mL)	1.0	5.0
Range (ng/mL)	1 to 1000	5 to 1000
QCs (ng/mL)	3, 35, 400, 750	15, 80, 400, 750
Accuracy/Bias	± 5.4 %	± 8.4 %
Precision	± 2.6 %	± 4.2 %

Apixaban pharmacodynamics

INR and aPTT were measured using standardized laboratory techniques.

Modified PT - Thromboplastin reagent used in a standard PT test was diluted in a 1:2.25 ratio with $CaCl_2$ to increase the dynamic range of the assay.

Thrombin generation – Calibrated automated thrombin generation- Thromboscope® method was used to assess thrombin generation.

Safety

Death/SAE: None

Conclusion

The pharmacokinetics and pharmacodynamics of apixaban appear to be similar in Japanese and Caucasian subjects.

Detailed Results:

Table Summary of the pharmacokinetic measures for apixaban in healthy Japanese subjects (Ref: CSR, CV185013).

Pharmacokinetic Parameters	Apixaban Dose			
	2.5 mg (n = 12)	10 mg (n = 12)	25 mg (n = 12)	50 mg (n = 11)
Cmax (ng/mL) Geom. Mean (CV%)	52.5 (16)	175.7 (22)	368.8 (16)	485.0 (28)
AUC(INF) (ng•h/mL) Geom. Mean (CV%)	466 [a] (17)	1628 (18)	3414 (15)	4743 (34)
AUC(0-T) (ng•h/mL) Geom. Mean (CV%)	430 (16)	1607 (18)	3374 (16)	4706 (34)
Tmax (h) Median (Min, Max)	3.50 (1.5, 6.0)	3.00 (1.0, 6.0)	3.00 (2.0, 4.0)	4.00 (1.5, 6.0)
T1/2 (h) Mean (SD)	6.12 [a] (1.21)	8.11 (4.18)	8.25 (2.47)	8.47 (1.71)
CLR (L/h) Mean (SD)	1.11 (0.31)	1.15 (0.33)	1.04 (0.29)	1.05 (0.29)
%UR Mean (SD)	19.56 (6.19)	18.46 (5.60)	14.11 (3.94)	10.31 (4.94)

a → n=10

Table Summary of the pharmacokinetic measures for apixaban in healthy Caucasian subjects (Ref: CSR, CV185013).

Pharmacokinetic Parameters	Apixaban Dose			
	2.5 mg (n = 12)	10 mg (n = 12)	25 mg (n = 12)	50 mg (n = 12)
Cmax (ng/mL) Geom. Mean (CV%)	44.8 (20)	207.8 (44)	345.2 (18)	494.3 (23)
AUC(INF) (ng•h/mL) Geom. Mean (CV%)	447 (15)	1946 (15)	3819 (19)	6093 [a] (24)
AUC(0-T) (ng•h/mL) Geom. Mean (CV%)	422 (18)	1896 (15)	3747 (18)	5991 (22)
Tmax (h) Median (Min, Max)	3.50 (2.5, 4.0)	3.00 (2.5, 4.0)	3.50 (2.0, 4.0)	3.50 (2.0, 4.0)
T1/2 (h) Mean (SD)	8.87 (2.95)	13.39 (6.15)	12.70 (3.90)	16.12 [a] (7.77)
CLR (L/h) Mean (SD)	0.90 (0.21)	0.80 (0.26)	0.84 (0.10)	0.73 (0.18)
%UR Mean (SD)	15.23 (3.60)	15.59 (6.68)	12.59 (1.80)	8.81 (2.73)

a → n=10

Table Comparison of apixaban pharmacokinetic measures between Japanese and Caucasian healthy subjects (Ref: CSR CV185013).

Pharmacokinetic Variable	Dose (mg)	Geometric Means		Ratio of Geometric Means (Japanese to Caucasians)	
		Caucasians	Japanese	Point Estimate	90% Confidence Limits
Cmax (ng/mL)	2.5	44.8	52.5	1.172	(0.997, 1.379)
	10	207.8	175.7	0.846	(0.719, 0.995)
	25	345.2	368.8	1.068	(0.908, 1.257)
	50	494.3	484.2	0.980	(0.830, 1.156)
AUC(INF) (ng•h/mL)	2.5	447	463	1.036	(0.894, 1.201)
	10	1946	1628	0.836	(0.725, 0.965)
	25	3819	3414	0.894	(0.775, 1.032)
	50	6167	4795	0.778	(0.669, 0.903)
AUC(0-T) (ng•h/mL)	2.5	422	430	1.020	(0.885, 1.174)
	10	1896	1607	0.847	(0.736, 0.976)
	25	3747	3374	0.900	(0.782, 1.037)
	50	5991	4754	0.793	(0.687, 0.916)

Note: The study was not adequately powered to make a statistical inference. The sample size provides 83% confidence that the ratio of the geometric means of the PK measures are within 20% of the population mean.

Study CV185058 (Pharmacokinetics, special population)

Study Report # CV185058	**Study period** 03/2008 to 04/2008

Title

A Placebo-Controlled, Single and Multiple-Dose Study to Evaluate the Pharmacokinetics of Apixaban in Healthy Chinese Subjects [8].

Objectives

To assess pharmacokinetics and pharmacodynamics, and tolerability of apixaban following administration of single and multiple doses.

Study Design Eighteen healthy subjects (6F, 12M) were randomized to receive apixaban 10 mg BID or placebo for 10 days (morning dose on day1, followed by BID dosing days 3 to 8, morning dose alone on day 9). This was a single sequence study and the subjects were not switched over.

Study medication

Dosage Form	Tablet
Dosage Strength	5 mg
Batch #	7D29180/7B22438
Administration	Oral

Sample collection

Pharmacokinetics: Pre-dose, 0.5, 1, 2, 3, 4, 6, 9, 12, 18, 24, 36, 48, 60, and 72 hours post dose on days 1 and 9.

Urine was collected at 12 hour intervals for upto 72 hours post dose on days 1 and 9.

Pharmacodynamics: Samples were collected to assess anti-FXa activity were collected at pre-dose, 1, 2, 3, 4, 12, 24, and 48 hours post dose on days 1 and 9.

Data Analysis Methods

Pharmacokinetic parameters were estimated using non-compartmental methods and presented as geometric mean (CV).

Study population

Randomized/Completed/ Discontinued Due to AE	18/18/0
Age (range)	33 (28 to 39) y
Male/Female	12/6
Race (Caucasian/Black/Asian/American Indian or Alaska	0/0/18/0/0

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native/other)

Results:

1. Peak plasma apixaban concentrations were observed at about 2 to 4 hours following administration of single and repeat doses of apixaban 10 mg.
2. The accumulation index following BID dosing was < 2.
3. Mean half-life following BID dosing about 11 h.
4. Direct concentration dependent increase in anti-FXa activity was observed with increasing apixaban concentrations.

Assay Method

Apixaban pharmacokinetics The performance of the assay method during study sample analysis is acceptable and is summarized in the table below.

Analyte	Apixaban
Method	LC/MS/MS
LOQ (ng/mL)	1.0
Range (ng/mL)	1 to 1000
QCs (ng/mL)	3, 400, 800
Accuracy/Bias	± 2.2%
Precision	± 7.8%

Apixaban pharmacodynamics

Anti-FXa activity was assessed using the Diagnostica Stago Rotachrome heparin assay.

Safety Death/SAE: None

Conclusion

Apixaban pharmacokinetics and anti-FXa activity in healthy Chinese subjects are similar to that observed in healthy Caucasian subjects.

Detailed Results:

Table Summary of the pharmacokinetic measures for apixaban on day 9 (Ref: CSR, CV185058).

Gender (N)	Cmax (ng/mL) Geom. Mean (CV%)	Tmax (h) Median (min, max)	Cmin (ng/mL) Geom. Mean (CV%)	AUC(Tau) (ng•h /mL) Geom. Mean (CV%)	T-HALF (h) Mean (SD)	CLR (L/h) Mean (SD)	AI Geom. Mean (CV%)	DF Geom. Mean (CV%)
Male (8)	303.4 (22)	4 (2, 4)	100 (17)	2409 (17)	9.9 (2.3)	1.25 (0.27)	1.65 (20)	0.98 (26)
Female (4)	413.1 (16)	3 (3, 4)	157 (20)	3406 (17)	12.7 (8.3)	1.11 (0.24)	1.77 (11)	0.89 (13)
All (12)	336.3 (24)	3.5 (2, 4)	116 (30)	2703 (24)	10.8 (4.9)	1.20 (0.26)	1.69 (17)	0.95 (23)

Study CV185074 (PK/PD comparison with rivaroxaban)

Study Report # CV1850074	**Study period** 02/2010 to 03/2010

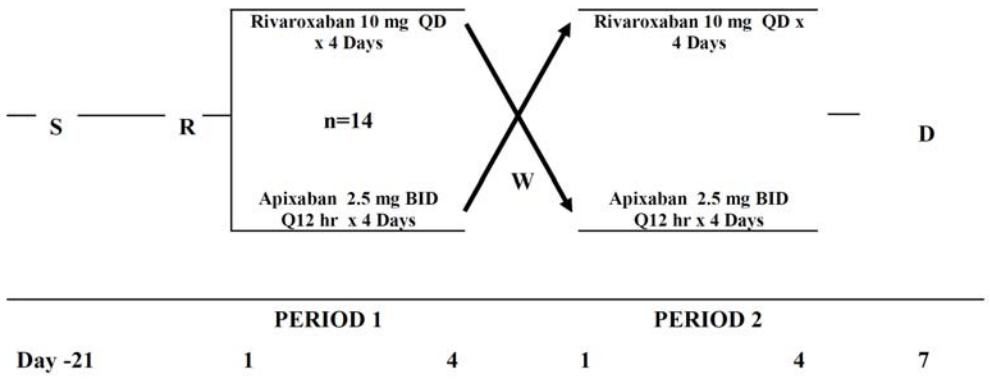
Title

Evaluation of multiple dose pharmacokinetics and pharmacodynamics of apixaban and rivaroxaban in healthy subjects[9].

Objectives

To assess pharmacokinetics / pharmacodynamics of apixaban and rivaroxaban and compare the peak to trough ratio following repeat administration.

Study Design



Study medication

Dosage Form	Apixaban	Rivaroxaban
Dosage Strength	2.5 mg	10 mg
Batch #.	8K43005	BXFBRD1
Administration	Oral	Oral

Sample collection

Pharmacokinetics and pharmacodynamics:

Rivaroxaban - Pre-dose on day 1, and pre-dose, 0.5, 1, 2, 3, 4, 5, 8, 12, 13, 14, 15, 16, 17, 18, 20, 24, 36, 48, 72 hours post-dose on day 4.

Apixaban - Pre-dose on day 1, and pre-dose, 0.5, 1, 2, 3, 4, 5, 6, 8, 12, 12.5, 13, 14, 15, 16, 17, 18, 20, 24, 36, 48, 72 hours post-dose on day 4.

[9] \\Cdsesub1\evsprod\NDA202155\\0003\m5\53-clin-stud-rep\533-rep-human-pk-stud\5331-healthy-subj-pk-init-tol-stud-rep\cv185074\cv185074.pdf

Data Analysis Methods

Pharmacokinetic parameters were estimated using non-compartmental methods and presented as geometric mean (CV). Pharmacodynamic effect at peak and trough plasma concentrations, AUEC were summarized and presented as mean (CV).

Study population

Randomized/Completed/ Discontinued Due to AE	14/14/0
Age (range)	29 (20 to 43) y
Male/Female	11/3
Race (Caucasian/Black/Asian/American Indian or Alaska native/other)	12/0/0/0/2

Results:

1. The pharmacokinetics of apixaban and rivaroxaban was consistent with earlier observations.

2. Peak to trough ratio of apixaban following BID adminsitration was ~ 5, while that for rivaroxabn following QD administration was ~ 17.

3. Anti – FXa activity for both apixaban and rivaroxaban closely followed observed plasma concentrations. Peak anti-FXa activity was observed at 2 h post drug administration for both drugs.

Assay Method

Pharmacokinetics The performance of the assay method during study sample analysis is acceptable and is summarized in the table below.

Analyte	Apixaban	Rivaroxaban
Method	LC/MS/MS	LC/MS/MS
LOQ (ng/mL)	1.0	0.5
Range (ng/mL)	1 to 1000	0.5 to 500
QCs (ng/mL)	3, 400, 800	1.5, 4, 16, 60, 375
Accuracy/Bias	± 3.7%	± 5.6%
Precision	± 6.7%	± 8.8%

Pharmacodynamics

Anti – FXa activity was measured using a chromogenic assay (STA Compact® analyzer).

Safety

Death/SAE: None

Conclusion

The degree of fluctuation (as represented by fluctuation index - FI) and the peak to trough ratio is lower following administration of apixaban 2.5 mg BID as compared to rivaroxaban administered 10 mg QD.

Detailed Results:

Table Summary of the pharmacokinetic measures for apixaban and rivaroxaban on day 4 following administration of apixaban 2.5 mg BID or rivaroxaban 10 mg QD (Ref: CSR, CV185074, Table 14.2-5).

Treatment	Cmax (ng/mL) geo.mean [N] (CV)	Cmin (ng/mL) geo.mean [N] (CV)	Tmax (h) median [N] (min-max)	AUC(TAU) (ng.h/mL) geo.mean [N] (CV)	Cmax/ Cmin ratio geo.mean [N] (CV)	FI geo.mean [N] (CV)	T-HALF (h) mean [N] (SD)
Rivaroxaban	171 [14] (46)	10.1 [14] (39)	2.00 [14] (1.00-3.00)	1094 [14] (29)	16.9 [14] (53.5)	3.51 [14] (26)	7.89 [14] (3.00)
Apixaban[a]	80.5 [14] (23)	17.1 [14] (20)	2.00 [14] (1.00-3.00)	527 [14] (22)	4.7 [14] (16.9)	1.43 [14] (12)	8.65 [14] (2.19)

Time-course plots - Pharmacokinetics

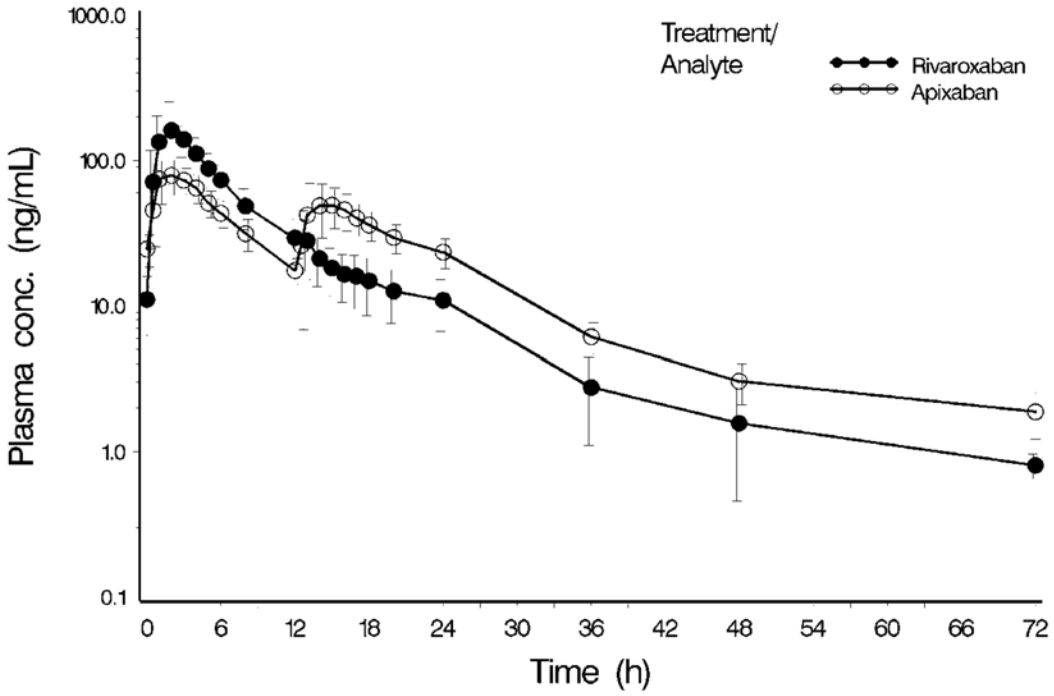


Figure Mean (SD) plasma apixaban and rivaroxaban concentration versus time course on day 4 following administration of apixaban 2.5 mg BID (open circles) or rivaroxaban 10 mg QD (closed circles) (Ref: CSR CV185074, Figure 3).

Pharmacodynamics – anti - FXa activity

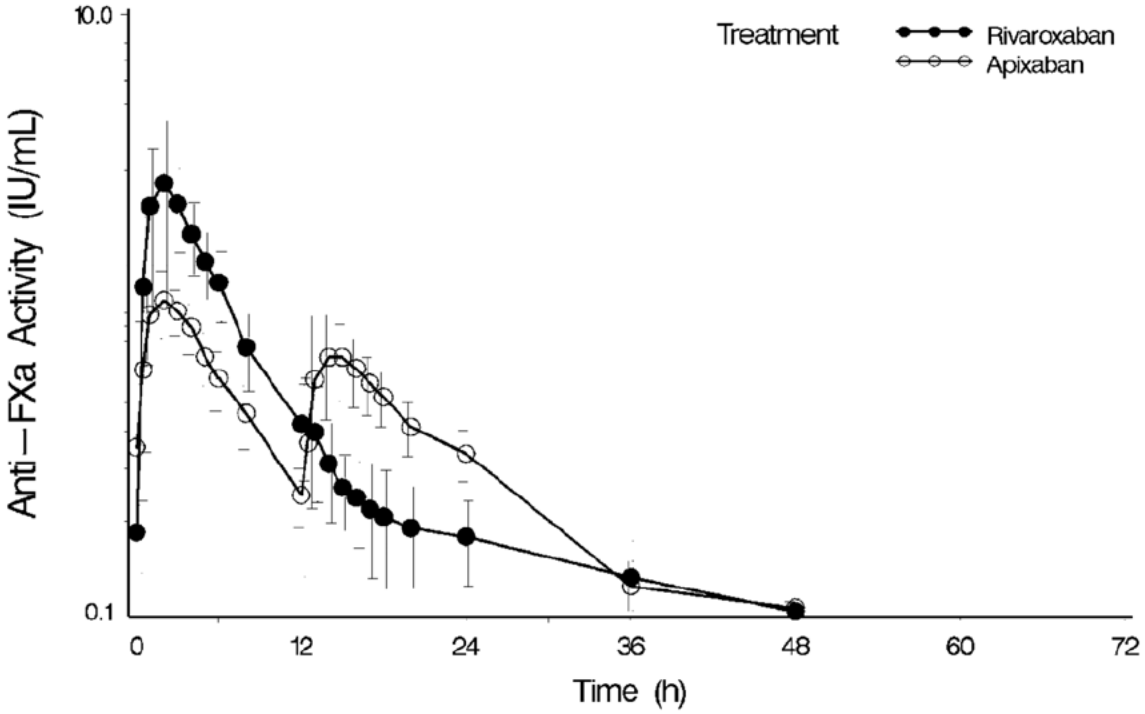


Figure Mean (SD) anti-FXa activity time course on day 4 following administration of apixaban 2.5 mg BID (open circles) or rivaroxaban 10 mg QD (closed circles) (Ref: CSR CV185074, Figure 4).

PK/PD relationship

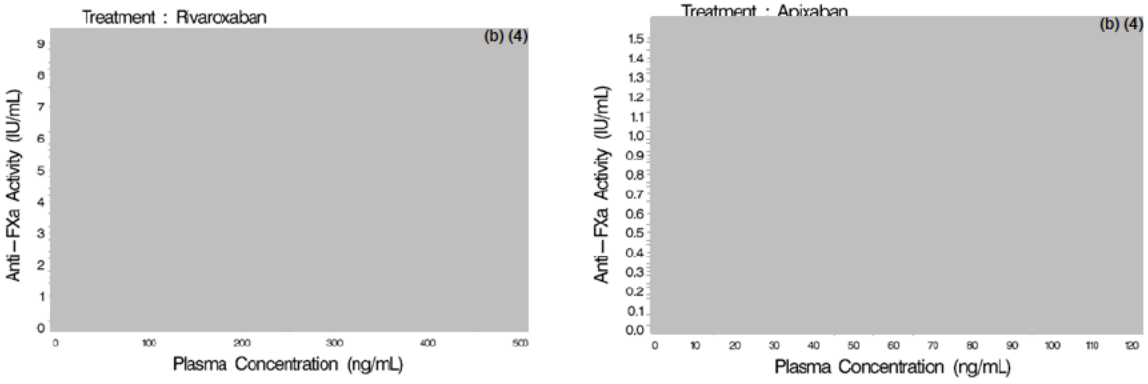


Figure Anti – FXa activity increased linearly with increasing plasma concentrations of apixaban or rivaroxaban (Ref: CSR CV185074, Figures 5 and 6).

4.1.4 EXTRINSIC FACTORS

DDI- Apixaban and Digoxin

Report # CV185028	**Study Period** 01/26/06 03/10/06	**EDR Link** \\Cdsesub1\evsprod\NDA202155\\0001\m5\53-clin-stud-rep\532-rep-stud-pk-human-biomat\5322-rep-hep-metab-interact-stud\cv185028\cv185028.pdf
Title	Effect of Apixaban on the Pharmacokinetics of Digoxin in Healthy Subjects	
Objectives	To assess the effects of apixaban on the PK of multiple-dose digoxin in healthy subjects.	

Rationale: Since apixaban is anticipated to be coadministered with digoxin in some patient populations (e.g., patients with atrial fibrillation) and digoxin is a narrow therapeutic index drug, this study is to evaluate the potential for apixaban to alter the PK of digoxin. Both digoxin and apixaban are substrates of P-gp. Digoxin also serves as an acceptable P-gp probe substrate to predict the effects of apixaban on other P-gp substrates used in the clinical setting.

Study Design Multiple-Dose Non-Randomized Open-Label Single-Sequence Single-Center 2-Period Healthy Vonuteers
Subjects underwent screening within 21 days prior to Study Day 1. Subjects were admitted to the clinical facility on the morning of Day -1. Two treatments (A followed by B) with single-sequence are detailed below.

Screening: -21days	**Washout:** None
Period 1 (A)	10 days, inpatient stay ☑Y ☐ N
Period 2 (B)	10 days, inpatient stay ☑Y ☐ N
Sequence	Single sequence: Treatment A then Treatment B

Treatments: (Fasted)
A: PO digoxin 0.25 mg tablet q6h on Day 1, digoxin 0.25 mg tablet QD on Days 2-10
B: PO apixaban 20 mg tablet QD + digoxin 0.25 mg tablet QD on Days 11-20

Study medication

Drug name	Apixaban	Digoxin
Dosage Form	Tablet	Tablet
Dosage Strength	20 mg	0.25 mg
Batch #.	3A70866 (Product batch#)	5ZP5355 (Lot #)
	3K76731 (Label batch#)	--
	562247-A020-011(Product Identification#)	--
Administration	Oral	Oral

PK Sampling (Blood)

Digoxin: 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10 12, 16 and 24 hours post-dose on Days 10 and 20.

Pre-dose on Days 1, 8-10 and 18-20 (for trough concentrations)

Apixaban: Pre-dose on Days 18-20 (for trough concentrations)

Analytical Method

The performance of the assay method during study sample analysis is acceptable and is

summarized in the table below.

Analyte	Apixaban	Digoxin
Method	LC-API/MS/MS	LC/MS/MS
Matrix	Plasma	Serum
LOQ (ng/mL)	1.00	0.1
Range (ng/mL)	1.00 to 1000	0.1 to 20
QCs (ng/mL)	3.00, 35.0, 400, 800	0.3, 10, 16
Accuracy/Bias	14.9%	3.3 %
Precision	4.34%	4.6 %

Statistical Method: Point estimates and 90% confidence intervals for the ratios of the geometric means for digoxin Cmax and AUC, with and without apixaban, were constructed.

Study Population :

Enrolled/Completed/ Discontinued Due to AE	24/22/1*
Age [Median (range)]	30 (22-45) yr
Male/Female	24/0
Race (Caucasian/Black/Asian)	10/11/3

*Subject CV185028-1-8 discontinued on Day 8 during Treatment A (digoxin only) due to elevated ALT and Subject CV185028-1-17 withdrew informed consent prior to dosing on Day 20 during Treatment B (digoxin + apixaban)

Results

- Digoxin PK was not altered with or without coadministration of apixaban. The 90% confidence intervals for the ratios of geometric means of digoxin Cmax and AUC before and after coadministration of apixaban 20 mg QD were within the equivalence interval of 80% to 125%.
- Both digoxin and apixaban had reached steady-state at the time of PK evaluation.

Summary Statistics for Digoxin Pharmacokinetics Parameters

Treatment	Digoxin PK Parameters		
	Cmax (ng/mL) Geom. Mean (CV %)	AUC(TAU) (ng·h/mL) Geom. Mean (CV %)	Tmax (h) Median (Min, Max)
A (n = 22)	1.68 (27)	16.8 (28)	1.00 (0.5, 2.0)
B (n = 22)	1.54 (25)	15.1 (28)	1.00 (1.0, 2.0)

A = digoxin 0.25 mg, PK assessment on Day 10

B = digoxin 0.25 mg + apixaban 20 mg, PK assessment on Day 20

Results of Statistical Analyses for Digoxin Cmax and AUC(TAU)

PK Variable	Treatment	Geometric Means	Ratio of Geometric Means		
			Ratio	Point Estimate	90% Confidence Limits
Cmax (ng/mL)	A	1.68	B vs A	0.92	(0.82, 1.03)
	B	1.54			
AUC(TAU) (ng·h/mL)	A	16.8	B vs A	0.90	(0.84, 0.96)
	B	15.1			

A = digoxin 0.25 mg, PK assessment on Day 10

B = digoxin 0.25 mg + apixaban 20 mg, PK assessment on Day 20

Safety

- Was there any death or serious adverse events? ☐ Yes ☒No ☐ NA

Six (6) serum chemistry MAs occurred in 4 subjects, including elevated ALT, AST, creatinine, and potassium. The elevated ALT MAs occurred in 3 subjects and were considered AEs by the Investigator

Conclusion

Multiple doses of apixaban 20 mg QD for 10 days did not affect the PK of digoxin. No dose adjustment is warranted when apixaban is co-administered with digoxin.

DDI- Apixaban and Naproxen

Report # CV185054	**Study Period** 11/13/2007 1/24/2008
Title	Evaluation of the PK and PD of naproxen and apixaban when coadministered
Objectives	To assess the effects of apixaban on the PK of naproxen and vice versa

Rationale: Naproxen was selected as a representative NSAID, widely used for the relief of pain and inflammation. Since there is high likelihood of concomitant use of NSAIDs and apixaban and both types of drugs have effects on hemstasis, it is important to examine the potential PK/PD interactions and safety of coadministration.

Study Design Single-Dose Randomized Open-Label 3-period 2-Sequence Single-Center Healthy Vonuteers

Subjects were admitted to the clinical center on Day -1 and received a single dose of apixaban (treatment A) on Day 1. After a 3-day washout, subjects were randomized to receive either a single dose of naproxen (treatment B) or an oral dose of apixaban along with an oral dose of naproxen (treatment C). Subjects were furloughed on Day 5 and returned to the clinical facility on Day 10. Subjects received the alternate treatment on Day 11 (Treatment B or C).

Screening: 21 days	**Washout:** 3-7days
Period 1 (A)	Day 1, inpatient stay ☑Y ☐ N
Period 2 (B or C)	Day 4-7, inpatient stay ☑Y ☐ N
Period 3 (B or C)	Day 11-14, inpatient stay ☑Y ☐ N
Sequence	2 sequences: Treatment B-C or C-B in period 2-3

Treatments:
A: PO apixaban 10 mg QD on Day 1
B: PO naproxen 500 mg QD on Day 4 or Day 11
C: PO apixaban 10 mg QD and naproxen 500 mg QD on Day 4 or Day 11

Study medication

Drug name	Apixaban	Naproxen
Dosage Form	Tablet	Tablet
Dosage Strength	5mg	500 mg
Batch #.	6J14405 (Product batch#)	E8465A (Lot #)
	6L21084 (Label batch#)	--
	562247-K005-027(Product Identification#)	--
Administration	Oral	Oral

PK/PD Sampling

PK samples (blood samples) were collected up to 72 hours postdose on Days 1, 4 and 11. PD tests including platelet aggregation, bleeding time, INR and anti-Xa activity assay were performed at selected time throughout the study.

Analytical Method

The performance of the assay method during study sample analysis is acceptable and is summarized in the table below.

Analyte	Apixaban	Naproxen
Method	LC-API/MS/MS	HPLC
Matrix	Plasma	Plasma
LOQ	1.00 (ng/mL)	0.1 (µg/mL)
Range	1.00 to 1000 (ng/mL)	0.1 to 100 (µg/mL)
QCs	3.00, 35.0, 400, 800 (ng/mL)	0.28, 3.70, 50.0, 76.0 (µg/mL)
Accuracy/Bias	6.25%	3.168 %
Precision (CV%)	6.58%	6.276 %

Statistical Method: Point estimates and 90% confidence intervals for the ratios of the geometric means for apixaban Cmax and AUC, with and without naproxen, were constructed using ANOVA

Study Population :

Enrolled/Completed/ Discontinued Due to AE	68/21/0
Age [Median (range)]	35(21-44) yr
Male/Female	21/0
Race (Caucasian/Black/American Indian/Alaska native)	10/10/1

PK results

- Apixaban exposures increased by about 61% and 54% for Cmax and AUC(inf) when coadminstered with naproxen. The 90% CI for geometric mean Cmax and AUC(inf) of apixaban were above the pre-specified equivalence interval of 80% to 125%.

Figure 11.2.1: Mean (±SD) Apixaban Plasma Concentration vs Time by Treatment

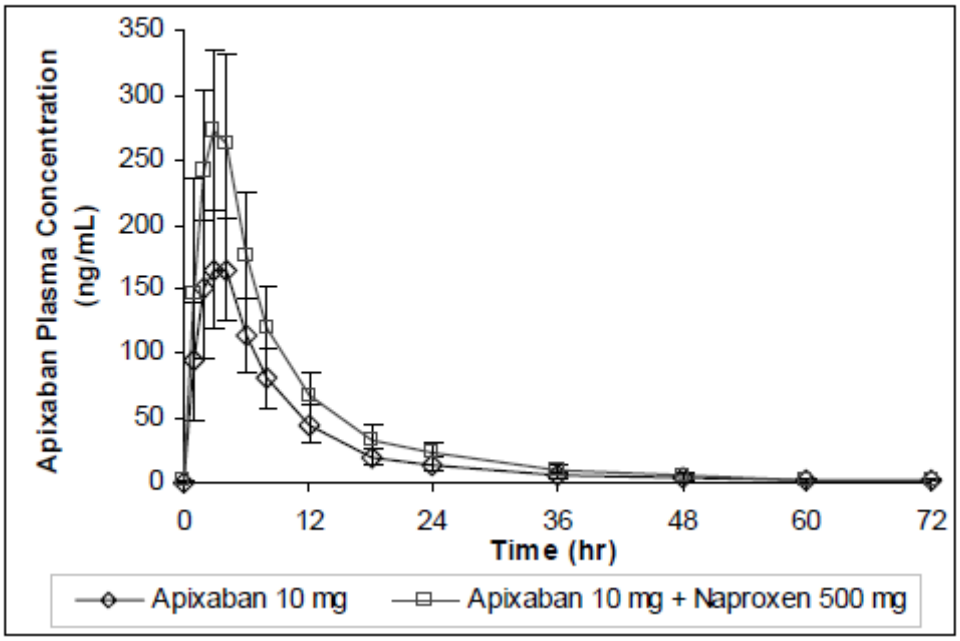


Table 11.2.1A: Summary Statistics for Apixaban Pharmacokinetic Parameters

Treatment	Apixaban Pharmacokinetic Parameters				
	Cmax (ng/mL) Geom. Mean (CV%)	AUC(INF) (ng•h/mL) Geom. Mean (CV%)	AUC(0-T) (ng•h/mL) Geom. Mean (CV%)	Tmax (h) Median (Min, Max)	T-Half (h) Mean (SD)
A (n = 21)	175 (22)	1693 (24)	1651 (25)	3 (1, 4)	13.4 (5.6)
C (n = 21)	282 (22)	2602 (24)	2556 (24)	3 (1, 4)	12.7 (4.1)

Table 11.2.1B: Results of Statistical Analyses for Apixaban Cmax, AUC(INF), and AUC(0-T)

Pharmacokinetic Variable	Treatment	Adjusted Geometric Means	Ratio of Geometric Means		
			Ratio	Point Estimate	90% CI
Cmax (ng/mL)	A	175	C vs A	1.611	(1.417, 1.831)
	C	282			
AUC(INF) (ng•h/mL)	A	1693	C vs A	1.537	(1.394, 1.694)
	C	2602			
AUC(0-T) (ng•h/mL)	A	1651	C vs A	1.549	(1.400, 1.713)
	C	2556			

- Concomitant use of apixaban 10 mg appeared to have no effect on the naproxen exposure

Figure 11.2.2: Mean (±SD) Naproxen Plasma Concentration vs Time by Treatment

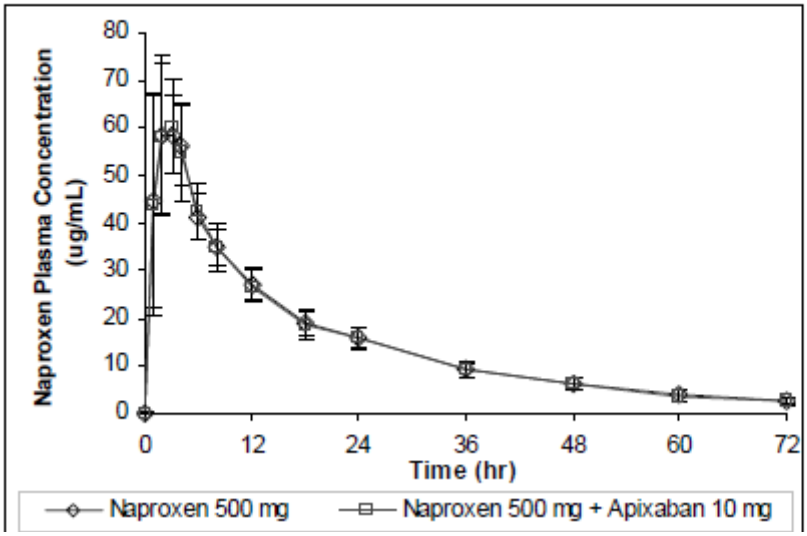


Table 11.2.2A: Summary Statistics for Naproxen Pharmacokinetic Parameters

Treatment	Naproxen Pharmacokinetic Parameters				
	Cmax (µg/mL) Geom. Mean (CV%)	AUC(INF (µg•h/mL) Geom. Mean (CV%)	AUC(0-T) (µg•h/mL) Geom. Mean (CV%)	Tmax (h) Median (Min, Max)	T-Half (h) Mean (SD)
B (n = 21)	67.4 (14)	1138 (12)	1058 (11)	2 (1, 4)	19.6 (2.8)
C (n = 21)	67.7 (15)	1126 (13)	1051 (11)	2 (1, 4)	18.7 (2.4)

Table 11.2.2B: Results of Statistical Analyses for Naproxen Cmax, AUC(INF), and AUC(0-T)

Pharmacokinetic Variable	Treatment	Adjusted Geometric Means	Ratio of Geometric Means		
			Ratio	Point Estimate	90% CI
Cmax (µg/mL)	B	67.4	C vs B	1.004	(0.940, 1.072)
	C	67.7			
AUC(INF) (µg•h/mL)	B	1138	C vs B	0.991	(0.974, 1.009)
	C	1128			
AUC(0-T) (µg•h/mL)	B	1058	C vs B	0.995	(0.977, 1.013)
	C	1052			

PD Results

- Naproxen did not appear have an effect on the PD measures such as INR and anti-Xa activity of apixaban. The increase in these PD measures following concomitant use of apixaban and naproxen appeared to be due to the increase in apixaban exposure.
- The changes in platelet aggregation and bleeding time were in agreement with the known effect of naproxen.

Table 11.3: Summary Statistics for Platelet Aggregation, Bleeding Time Change, INR and % Change from Baseline and Anti-Xa Activity

Treat-ment	Platelet Aggregation* Mean (SD)		Bleeding Time** Mean (SD)		INR** Mean (SD)		Anti-Xa Activity Mean (SD) (IU/mL)	
	Change (%)	% Change (%)	Change (min)	%Change (%)	Change	%Change (%)	0h pre-Dose	3h post-Dose
A	-0.6 (25.3)	-4 (26)	1.3 (2.4)	51 (86)	0.13 (0.05)	14 (6)	<LLQ	2.7 (0.7)
B	-64.5 (19.2)	-84 (18)	2.6 (2.6)	70 (81)	0.01 (0.03)	1 (3)	<LLQ	<LLQ
C	-65.5 (18.6)	-82 (26)	3.6 (3.0)	82 (74)	0.18 (0.06)	20 (6)	<LLQ	4.4 (1.0)

Safety

- Was there any death or serious adverse events? ☐ Yes ☒No ☐ NA

Conclusion

- Apixaban exposures increased by about 61% and 54% for Cmax and AUC(inf) when coadminstered with naproxen. Based on the exposure-response analysis, and the available strengths of apixaban, no dose adjustment is warranted when apixaban is co-administered with naproxen 500 mg QD.

DDI- Apixaban and Ketoconazole

Report # CV185026	**Study Period** 01/26/06 02/26/06	**EDR Link** \\Cdsesub1\evsprod\NDA202155\\0001\m5\53-clin-stud-rep\532-rep-stud-pk-human-biomat\5322-rep-hep-metab-interact-stud\cv185026\cv185026.pdf
Title	Effect of Ketoconazole on the Pharmacokinetics of Apixaban in Healthy Subjects	
Objectives	To determine the effect of multiple doses of ketoconazole on the single-dose pharmacokinetics of apixaban, when coadministered in healthy subjects.	

Rationale: Apixaban is P-gp substrate and metabolized by CYP3A4. Ketoconazole is a potent CYP3A4/P-gp inhibitor. Therefore, co-administration with ketoconazole might increase the exposure of apixaban. This interaction study with ketoconazole was designed to characterize the effect of the role of CYP3A4 inhibition on apixaban's PK.

Study Design Multiple-Dose Non-Randomized Open-Label Single-Sequence Single-Center 3-Period Healthy Vonuteers
Subjects underwent screening within 21 days prior to Study Day 1. Subjects were admitted to the clinical facility on Day -1. Three treatments with single-sequence are detailed below.

Screening: -21days	**Washout:** None
Sequence	Single sequence: Treatment A, B then C

Treatments: (Fasted)
A: PO apixaban 10 mg tablet on Day 1
B: PO ketoconazole 400 mg (2x200mg) tablet QD on Days 4-6
C: PO apixaban 10 mg tablet + ketoconazole 400 mg tablet on Day 7, followed by 400 mg ketoconazole alone on Day 8 and 9

Study medication

Drug name	Apixaban	Ketoconazole
Dosage Form	Tablet	Tablet
Dosage Strength	10 mg	200 mg x 2
Batch #.	5E06395 (Product batch#)	5GG163 (Lot #)
	5H01542 (Label batch#)	--
	562247-A010-013 (Product Identification#)	--
Administration	Oral	Oral

PK Sampling (Blood)

Ketoconazole: Pre-dose on Days 6-9 and 24 hours post Day 9 (last) dose. (for trough concentrations)

Apixaban: Pre-dose, 1, 2, 3, 4, 6, 8, 12, 24, 36, 48, 60 and 72 hours post-dose on Day 1 and Day 7

Analytical Method

The performance of the assay method during study sample analysis is acceptable and is summarized in the table below:

Analyte	Apixaban	Ketoconazole
Method	LC-API/MS/MS	LC/MS/MS
Matrix	Plasma	Plasma
LOQ (ng/mL)	1.00	50.0
Range (ng/mL)	1.00 to 1000	50.0 to 5000
QCs (ng/mL)	3.00, 35.0, 400, 800	150, 480, 1500, 4000
Accuracy/Bias	7.5%	5.3 %
Precision (CV%)	6.64%	4.5 %

Statistical Method: Point estimates and 90% confidence intervals for the ratios of the geometric means for apixaban Cmax and AUC, with and without ketoconazole, were constructed.

Study Population :

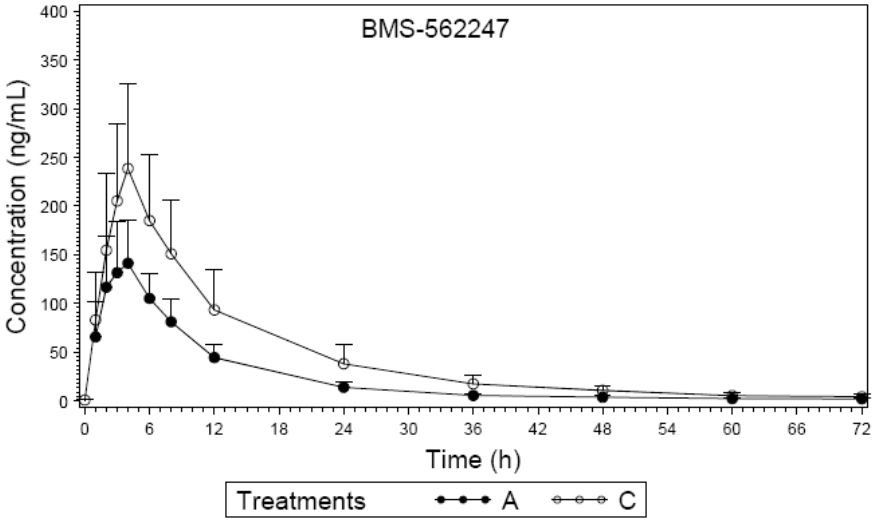
Enrolled/Completed/ Discontinued Due to AE	30/18/2*
Age [Median (range)]	29 (21-45) yr
Male/Female	20/0
Race (White/Black/Asian)	7/10/3

*Subject CV185026-1-8 was discontinued due to an AE (rash). Subject CV185026-1-9 withdrew consent (family emergency).

Results

- Apixaban Cmax and AUC were increased by 62% and 100%, respectively, in the presence of 400 mg QD ketoconazole.

Figure 11.2.1A: Mean (+SD) Apixaban Plasma Concentration vs. Time by Treatment



Summary Statistics for Apixaban Pharmacokinetic Parameters

Treatment	Apixaban Pharmacokinetic Parameters				
	Cmax (ng/mL) Geom. Mean (CV%)	AUC(0-T) (ng·h/mL) Geom. Mean (CV%)	AUC(INF) (ng·h/mL) Geom. Mean (CV%)	Tmax (h) Median (Min, Max)	T-Half (h) Mean (SD)
A (n = 18)	139.5 (32)	1490 (28)	1523 (28)	4.0 (1.0, 4.0)	11.3 (5.8)
C (n = 18)	225.3 (36)	2939 (38)	3027 (37)	4.0 (3.0, 4.0)	13.8 (6.3)

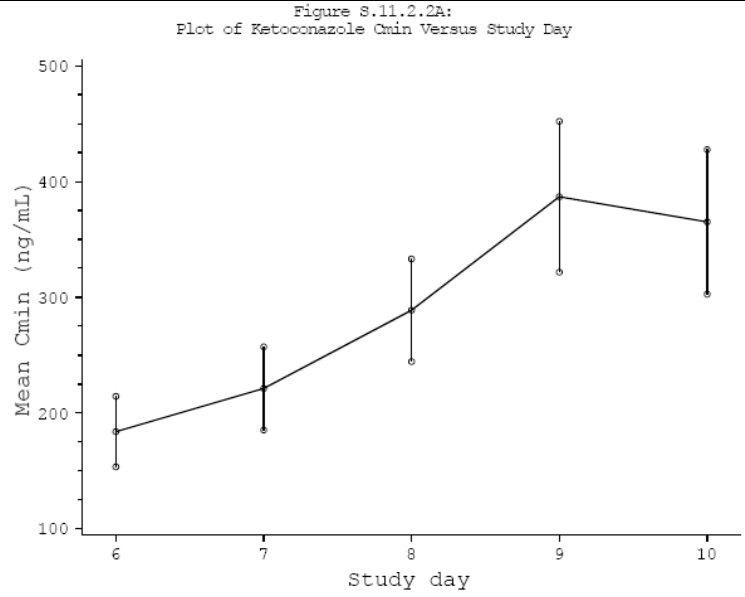
A = Apixaban single dose 10 mg

C = Apixaban single dose 10 mg + ketoconazole 400 mg QD

Table 11.2.1B: Results of Statistical Analyses for Apixaban Cmax, AUC(0-T), and AUC(INF)

Pharmacokinetic Variable	Treatment	Geometric Means	Ratio of Geometric Means		
			Ratio	Point Estimate	90% Confidence Limits
Cmax (ng/mL)	A	139.5	C vs A	1.62	(1.47, 1.78)
	C	225.3			
AUC(0-T) (ng.h/mL)	A	1490	C vs A	1.97	(1.80, 2.16)
	C	2939			
AUC(INF) (ng.h/mL)	A	1523	C vs A	1.99	(1.81, 2.18)
	C	3027			

Reviewer's comment:
Cmin of ketoconazole is increasing from Day 6 to 7 (before co-administration of apixaban) as shown in the figure below. Although the study was conducted following the Drug Interaction Draft Guidance (400mg QD for several days) and based on the terminal half-life of ketoconazole (~8hr), the steady state should have been reached, this finding might suggest otherwise. Whether the suppression of enzyme activity of CYP3A4 is maximized at this condition is unclear. Changes in apixaban exposure could be greater if the CYP3A4 activity was not completed inhibited. However, ketoconazole concentrations prior to administering the combination on Day 7 were in the 51 to 546 ng/mL range and on Day 9 ranged from 87 to 867 ng/mL. Based on the sponsor, these results were consistent with 400 mg ketoconazole plasma exposure data reported in the literature.



Safety

- Was there any death or serious adverse events? ☐ Yes ☒No ☐ NA

Conclusion

Co-administration of ketoconazole was associated with a 62% increase in Cmax and a 100% increase in AUC(INF) of apixaban. Based on the exposure-major bleeding relationship (see Pharmacometrics Review), the increase in exposure with ketoconazole is expected to result in 70 % increase in ISTH major bleeding risk. Hence we recommend reducing the dose of apixaban to 2.5 mg BID when co-administered with ketoconazole.

DDI- Apixaban and Diltiazem

Report # CV185032	**Study Period** 09/05/06 11/15/06	**EDR Link** \\Cdsesub1\evsprod\NDA202155\\0001\m5\53-clin-stud-rep\532-rep-stud-pk-human-biomat\5322-rep-hep-metab-interact-stud\cv185032\cv185032.pdf
Title	Effect of Diltiazem on the Single-dose Pharmacokinetics of Apixaban in Healthy Subjects	
Objectives	To assess the effects of diltiazem on the pharmacokinetics (PK) of single-dose apixaban in healthy subjects.	

Rationale: Apixaban is anticipated to be co-administered with diltiazem in this patient population. Also diltiazem is considered to be a moderate CYP3A4 inhibitor and apixaban is metabolized by CYP3A4. This study was therefore conducted to evaluate the potential for diltiazem to alter the pharmacokinetics (PK) of apixaban and the results of this study to contribute to recommendations for concomitant use of apixaban with other inhibitors of CYP3A4.

Study Design Multiple-Dose Non-Randomized Open-Label Single-Sequence Single-Center 3-Period Healthy Vonuteers
Subjects underwent screening within 21 days prior to Study Day 1. Subjects were admitted to the clinical facility on Day -1. Three treatments with single-sequence are detailed below.

Screening: -21days	**Washout:** None
Sequence	Single sequence: Treatment A, B then C

Treatments: (Fasted)
A: PO apixaban 10 mg tablet on Day 1
B: PO diltiazem 360 mg QD on Days 4-10
C: PO apixaban 10 mg tablet + diltiazem 360 mg on Day 11, followed by diltiazem 360 mg alone on Day 12 and 13

Study medication

Unit	Formulation	Product ID Number	Route	Label Batch Number	Product Batch Number
10 mg	Apixaban Tablet	562247-A010-013	Oral	5H01542	5E06395

The site sourced and provided the marketed product, Cardizem® LA containing 360 mg of diltiazem, from one commercial lot (Lot No. 06B094P) administered orally.

PK Sampling (Blood)

Diltiazem: Pre-dose on Days 8-11

Apixaban: Pre-dose, 1, 2, 3, 4, 6, 8, 12, 24, 36, 48, 60 and 72 hours post-dose on Day 1 and Day 11

Analytical Method

The performance of the assay method during study sample analysis is acceptable and is summarized in the table below.

Analyte	**Apixaban**	**Diltiazem**
Method	LC-API/MS/MS	LC/MS/MS

Matrix	Plasma	Plasma
LOQ (ng/mL)	1.00	0.100
Range (ng/mL)	1.00 to 1000	0.100 to 200.000
QCs (ng/mL)	3.00, 35.0, 400, 800	0.300, 5.00, 80.000, 160.000
Accuracy/Bias	6.78%	4.20 %
Precision (CV%)	6.15%	9.10 %

Statistical Method: Point estimates and 90% confidence intervals for the ratios of the geometric means for apixaban Cmax and AUC, with and without diltiazem, were constructed.

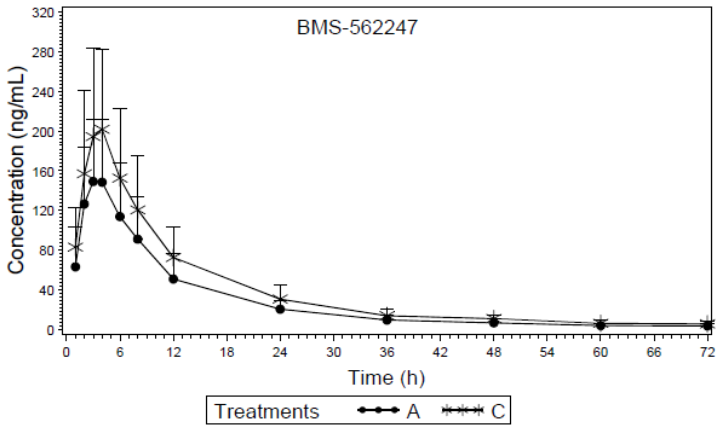
Study Population :

Enrolled/**Dosed/Completed**/ Discontinued Due to AE	99/**18/18**/0
Age [Median (range)]	29 (22-45) yr
Male/Female	13/5
Race (White/Black/Asian)	7/10/1

Results

- Apixaban Cmax increased by 31% and AUC(0-T) and AUC(INF) increased by approximately 40% when apixaban was administered with diltiazem.

Figure 11.2.1 **Mean (+SD) Apixaban Plasma Concentration vs Time by Treatment (N=18)**



Source: Supplemental Table S.11.2.1A
Treatment A: Apixaban single dose 10 mg; n=18
Treatment C: Apixaban single dose 10 mg + Diltiazem 360 QD; n=18

Apixaban Pharmacokinetic Parameters

Treatment	Cmax (ng/mL) Geom. Mean (C.V. %)	AUC(INF) (ng·h/mL) Geom. Mean (C.V. %)	AUC(0-T) (ng·h/mL) Geom. Mean (C.V. %)	Tmax (h) Median (Min, Max)	T-Half (h) Mean (S.D.)
A (n = 18)	148.1 (38)	1897[a] (38)	1779 (40)	3 (2, 8)	17.22[a] (7.37)
C (n = 18)	194.6 (41)	2606 (39)	2475 (40)	4 (2, 4)	16.30 (7.83)

A = Apixaban 10 mg
C = Apixaban 10 mg + Diltiazem 360 mg QD
[a] n = 17 for Treatment A

Results of Statistical Analyses for Apixaban Cmax, AUC(0-T), and AUC(INF)

Pharmacokinetic Variable	Treatment	Adjusted Geometric Means	Ratio of Geometric Means Ratio	Point Estimate	90% C.I.
Cmax (ng/mL)	A	148.1	C vs A	1.31	(1.158, 1.492)
	C	194.6			
AUC(0-T) (ng·h/mL)	A	1779	C vs A	1.39	(1.242, 1.559)
	C	2475			
AUC(INF) (ng·h/mL)	A	1866	C vs A	1.40	(1.230, 1.585)
	C	2606			

A = Apixaban 10 mg
C = Apixaban 10 mg + Diltiazem 360 mg QD

Diltiazem Cmin

- Cmin values did not change appreciably beyond Day 8, indicating that steady state concentrations were achieved.

Safety

- Was there any death or serious adverse events? ☐ Yes ☒No ☐ NA

The frequency of AEs was highest with diltiazem alone (23 AEs in 8 (44.4%) subjects). All AEs were of mild to moderate intensity, and all resolved without treatment. Two bleeding-related AEs are detailed below:
Subject CV185032-1-13, a 45 year-old black male, had mild subconjunctival hemorrhage of the left eye beginning on Day 11 during apixaban + diltiazem. The event resolved without treatment after 10 days and was considered possibly related to study drug.
Subject CV185032-1-12, a 22 year-old Asian female, had contusions and petechiae on both thighs on Day 14 following apixaban + diltiazem. There was no history of trauma. The AEs resolved without treatment after 12 and 5 days, respectively. Both events were mild in intensity and were considered by the Investigator to be possibly related to study drug. No bleeding related clinical laboratory abnormalities were reported for this subject.

Conclusion

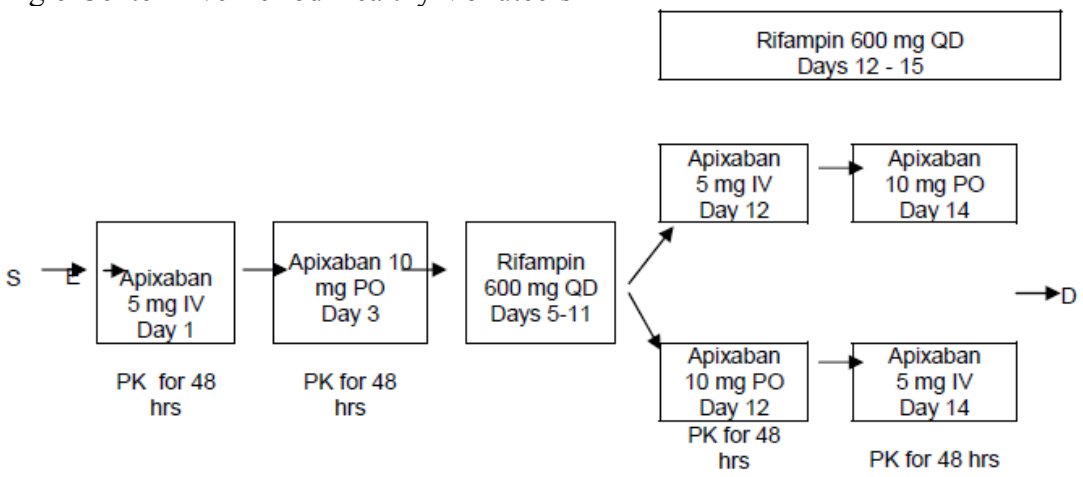
Co-administration of diltiazem resultsin a 40% increase in AUC(INF) of apixaban. Based on the exposure-response relationship and the availability of strengths, no dose adjustments are recommended when apixaban is co-administered with diltiazem.

DDI- Apixaban (IV and PO) and Rifampin

Report # CV185045	**Study Period** 08/31/06 10/30/06	**EDR Link** \\Cdsesub1\evsprod\NDA202155\\0001\m5\53-clin-stud-rep\532-rep-stud-pk-human-biomat\5322-rep-hep-metab-interact-stud\cv185045\cv185045.pdf
Title	Study to Evaluate the Effect of Rifampin on the Pharmacokinetics of Apixaban in Healthy Subjects	
Objectives	To determine the effect of rifampin on the PK of IV and PO apixaban, when coadministered in healthy subjects.	

Rationale: Apixaban is metabolized primarily by CYP3A4 and is a substrate of P-gp. Rifampin is a strong inducer of CYP3A4 and P-gp. Therefore, rifampin might decrease the exposure of apixaban when coadministered. This interaction study with rifampin was designed to characterize the effect of the role of CYP3A4 and P-gp induction on apixaban's PK.

Study Design Single-Dose Randomized Open-Label Sequencial Crossover Single-Center Five-Period Healthy Vonuteers



Subjects underwent screening within 21 days prior to Study Day 1. Subjects were admitted to the clinical facility on Day -1. Subjects were equally randomized on Day 12 to 1 of 2 treatment sequences (Treatment D then Treatment E or vice versa).

Screening: -21days	**Washout:** None
Sequence	Sequencial Crossover: Treatment A, B, C then randomized to DE or ED

Treatments: (Fasted)
A: apixaban single 5 mg IV dose alone (Day 1)
B: apixaban single 10 mg PO dose alone (Day 3)
C: rifampin 600 mg QD alone (Days 5-11)
D: apixaban single 5 mg IV dose, in the presence of rifampin 600 mg (Day12 or Day 14)
E: apixaban single 10 mg PO dose, in the presence of rifampin 600 mg (Day12 or Day 14)

Study medication

Table 5.5.2: Drug Information

Unit	Formulation	Product ID Number	Label Batch Number	Product Batch Number
2.5 mg/mL	Apixaban IV	562247-N2X5-014	5E02615	5D01551
10 mg	Apixaban Tablet	562247-A010-013	6A19027	5M02622

PK Sampling (Blood) for Apixaban:

IV:Pre-dose, 0.05, 0.25, 0.5, 1, 2, 3, 4, 8, 12, 16, 24, 36 and 48 hours post-dose on Day 1 and Day 12 or 14
PO: Pre-dose, 1, 2, 3, 4, 8, 12, 16, 24, 36 and 48 hours post-dose on Day 3 and Day 12 or 14

Analytical Method

The performance of the assay method during study sample analysis is acceptable and is summarized in the table below.

Analyte	**Apixaban**	
Method	LC-API/MS/MS	LC-API/MS/MS
Matrix	Plasma	Urine
LOQ (ng/mL)	1.00	1.00
Range (ng/mL)	1.00 to 1000	1.00 to 1000
QCs (ng/mL)	3.00, 35.0, 400, 800	3.00, 35.0, 400, 750
Accuracy/Bias	4.94%	4.03 %
Precision (CV%)	7.44%	5.12 %

Statistical Method: Means and differences between means in logarithmic scale were exponentiated to obtain point estimates and 90% confidence intervals of the ratios (with and without rifampin) of apixaban Cmax, AUC(0-T), and AUC(INF), separately for IV and PO routes of administration. Point estimate and 90% confidence intervals were also derived for the bioavailability ratios (F), with and without rifampin.

Study Population :

Enrolled/**Dosed/Completed**/ Discontinued Due to AE	53/**20/18**/1*
Age [Median (range)]	32 (21-43) yr
Male/Female	17/3
Race (White/Black)	9/11

*Subject CV185045-1-20 had treatment discontinued on Day 10 due to AEs of severe abdominal pain and moderate nausea and vomiting following administration of rifampin alone, and was discontinued from the study on Day 16.

Results

IV apixaban with or without rifampin

- Coadministration of rifampin reduced Cmax and both AUC(0-T) and AUC(INF) of intravenously administered apixaban by 13 % and 39%, respectively.
- In presence of rifampin, mean apixaban CL increased by ~1.6 fold following a single 5 mg IV dose of apixaban.
- Mean apixaban half life was reduced in the presence of rifampin.

- Following a single 5 mg IV dose of apixaban in the absence of rifampin, renal clearance (0.97 L/h) accounted for approximately 34% of total systemic clearance (2.82 L/h).

Figure 11.2.1A: Apixaban Plasma Concentration (Mean ± SD) Time Profiles After a Single IV Bolus Dose of 5 mg Apixaban in the Absence and Presence of Rifampin

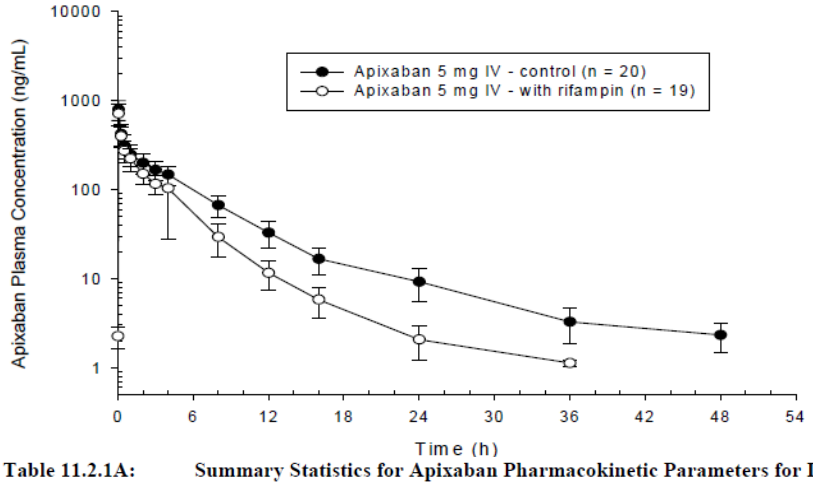


Table 11.2.1A: Summary Statistics for Apixaban Pharmacokinetic Parameters for IV Doses

Treatment	Apixaban Pharmacokinetic Parameters							
	Cmax (ng/mL) Geom. Mean (CV%)	AUC(0-T) (ng·h/mL)[a] Geom. Mean (CV%)	AUC(INF) (ng·h/mL)[a] Geom. Mean (CV%)	T-Half (h) Mean (SD)	CL (L/h) Mean (SD)	Vss (L) Mean (SD)	CLR (L/h) Mean (SD)	%UR Mean (SD)
A (n = 20)	791.3 (21)	1787 (25)	1816 (25)	9.04 (2.22)	2.82 (0.63)	20.91 (4.71)	0.97 (0.28)	34.19 (7.52)
D (n = 19)	690.8 (28)	1097 (32)	1109 (32)	4.60 (1.13)	4.66 (1.12)	18.32 (4.08)	0.81 (0.28)	17.34 (3.48)

Source: Supplemental Table S.11.2.1B

A = apixaban single 5 mg IV dose alone

D = apixaban single 5 mg IV dose, in presence of rifampin

[a] AUC was calculated using mixed log-linear method with C_0=0 (where C_0 is apixaban plasma concentration at time zero); no extrapolation from observed Cmax at 3 min was made.

Reviewer's Note: Renal clearance of apixaban appears unaltered by co-administration of rifampin suggesting rifampin doesn't affect renal excretion through P-gp in the kidneys but mainly through metabolism through CYP3A4 or intestinal or biliary excretion.

PO apixaban with or without rifampin

- In the presence of rifampin, Cmax, AUC(0-T), and AUC(INF) of orally administered apixaban were reduced by 42%, 53%, and 54%, respectively.
- Rifampin increased apixaban apparent clearance by 2.1 fold while renal clearance remained relatively consistent.
- Mean T-half values following a single 10 mg oral dose of apixaban remained unchanged in the presence and absence of rifampin.
- Dose-normalized apixaban absolute bioavailability (F) values were 49% for apixaban alone and 37% for apixaban in the presence of rifampin.
- Absolute bioavailability of apixaban was reduced by approximately 25% when apixaban was given with rifampin.

Figure 11.2.1B: Apixaban Plasma Concentration (Mean ± SD) Time Profiles After a Single Oral Dose of 10 mg Apixaban in the Absence and Presence of Rifampin

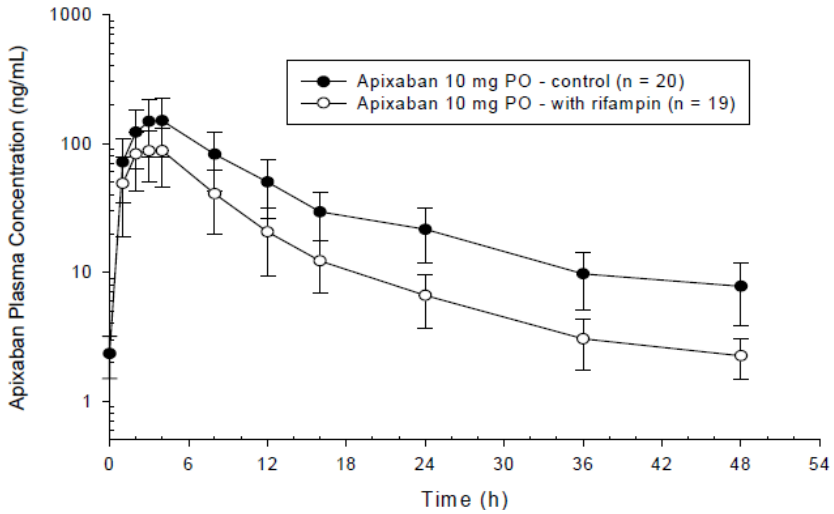


Table 11.2.1B: Summary Statistics for Apixaban Pharmacokinetic Parameters for PO Doses

Treatment	Apixaban Pharmacokinetic Parameters								
	Cmax (ng/mL) Geom. Mean (CV%)	Tmax (h) Median (Min, Max)	AUC(0-T) (ng·h/mL) Geom. Mean (CV%)	AUC(INF) (ng·h/mL) Geom. Mean (CV%)	T-Half (h) Mean (SD)	CLR (L/h) Mean (SD)	CL/F (L/h) Mean (SD)	%UR Mean (SD)	F[a] Geom. Mean (CV%)
B (n = 20)	148.6 (43)	3.00 (2.00, 4.00)	1639 (41)	1795 (40)	13.91 (3.52)	0.92 (0.31)	5.97 (2.21)	15.65 (6.33)	0.49 (24)
E (n = 19)	88.0 (44)	3.00 (1.00, 8.00)	783 (40)	866[b] (35)	14.34[b] (6.68)	0.85 (0.31)	12.60 (4.28)	6.94 (3.18)	0.39[c] (25)

Source: Supplemental Table S.11.2.1B

B = apixaban single 10 mg PO dose alone

E = apixaban single 10 mg PO dose, in presence of rifampin

[a] F is ratio of dose-adjusted AUC values for PO and IV doses (B vs A, E vs D), [b] n = 18, [c] n=19 for AUC(INF) of Treatment D and n=18 for AUC(INF) of Treatment E.

Table 11.2.1C: Statistical Analyses of Apixaban Cmax, AUC(0-T), AUC(INF), and Absolute Bioavailability (F)

Pharmacokinetic Variable	Treatment	Adjusted Geometric Means	Ratio of Geometric Means		
			Ratio	Point Estimate	90% Confidence Limits
Cmax (ng/mL)	A	791.3	D vs A	0.87	(0.77, 0.98)
	D	689.8			
	B	148.6	E vs B	0.58	(0.52, 0.65)
	E	86.7			
AUC(0-T) (ng.h/mL)	A	1787	D vs A	0.61	(0.59, 0.64)
	D	1090			
	B	1639	E vs B	0.47	(0.43, 0.50)
	E	766			
AUC(INF) (ng.h/mL)	A	1816	D vs A	0.61	(0.58, 0.63)
	D	1102			
	B	1795	E vs B	0.46	(0.42, 0.49)
	E	821			
Absolute Bioavailability (F)[a]			B vs A	0.49	(0.42, 0.59)
			E vs D	0.37	(0.31, 0.44)
			E/D vs B/A	0.75	(0.69, 0.82)

Source: Supplemental Tables S.11.2.1C, S.11.2.1D, S.11.2.1E, and S.11.2.1F

[a] Absolute bioavailability (F) is the ratio of dose-adjusted AUC(INF) values for PO and IV doses (B vs A, E vs D)

A = apixaban single 5 mg IV dose alone

B = apixaban single 10 mg PO dose alone

D = apixaban single 5 mg IV dose, in presence of rifampin

E = apixaban single 10 mg PO dose, in presence of rifampin

Safety

- Was there any death or serious adverse events? ☐ Yes ☒No ☐ NA

Conclusion

Co-administration of repeat doses of rifampin decreased the AUC(INF) of orally administered apixaban by 54%, respectively. This decrease in exposure of apixaban results in a potentially loss of efficacy. There is no adequate clinical data at this point of time to unequivocally rule out this issue. Hence, we reccomend to avoid concomitant use of strong CYP3A4 and P-gp inducers with apixaban.

DDI- Apixaban and Aspirin

Report # CV185002B	**Study Period** 04/21/03 11/10/03	**EDR Link** \\Cdsesub1\evsprod\NDA202155\\0001\m5\53-clin-stud-rep\532-rep-stud-pk-human-biomat\5322-rep-hep-metab-interact-stud\cv185002-partb\cv185002-partb.pdf
Title	Two Part, Placebo-Controlled, Ascending Multiple-Dose and Aspirin Interaction Study to Evaluate the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of BMS-562247, a Reversible Inhibitor of Factor Xa, in Healthy Subjects: Part B	
Objectives	**Primary:** To assess the safety and tolerability of multiple oral doses of apixaban when concomitantly administered with aspirin 325 mg once daily	

Rationale: Aspirin is a commonly used antiplatelet agent for prevention of thromboembolism. Apixaban, a factor Xa inhibitor, is expected to decrease the conversion of prothrombin to active thrombin, thereby diminishing thrombin-mediated activation of the coagulation process. Since apixaban is likely to be co-administered with aspirin, this study was conduted to investigate whether apixaban administration could affect the PK and PD of aspirin.

Study Design Multiple-Dose Randomized Placebo-Controlled Double-Blind Single Sequence Single-Center Two-Period Healthy Vonuteers

There was a 5-day aspirin 325 mg QD lead-in period. Upon completion of the lead-in period, 16 healthy subjects were randomized on Day 1 to receive either 5 mg of apixaban or placebo (12:4) BID in a double-blind fashion, while continuing to receive 325 mg of aspirin QD for an additional 7 days.

Screening: -21days	**Washout:** None
Sequence	Single Sequence: Treatment AB (n=12) or AC (n=4)

Treatments: (Fasted)

A: aspirin 325 mg QD (Lead in, Day -5 to Day -1)
B: apixaban 5 mg BID + aspirin 325 mg QD (Day 1 to Day 7)
C: placebo BID + aspirin 325 mg QD (Day 1 to Day 7)

Study medication

Unit	Formulation	Product ID Number	Route	Batch Number
5 mg	Apixaban Tablet	562247-A005-002	Oral	2K64989
Placebo	Tablet	000000-A000-019-0	Oral	N00036

Aspirin 325 mg tablets were sourced and provided by the Investigator, Lot Number 03A041.

PK Sampling (Blood):

Apixaban: Pre-dose, 1, 2, 3, 4, 5, 6, 8, 12, 13, 14, 15, 16, 17, 18, 20, 24, 48 and 72 hours on Day 7

ASA and SA: Pre-dose, 0.25, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 12, 16 and 24 hours post-dose on Day -1 and Day 7

Analytical Method

The performance of the assay method during study sample analysis is acceptable and is summarized in the table below.

Analyte	Apixaban	Aspirin (ASA)	(SA)
Method	LC/MS/MS	HPLC	HPLC
Matrix	Plasma	Plasma	Plasma
LOQ	1.00 (ng/mL)	0.1 (µg/mL)	0.1 (µg/mL)
Range	1.00 to 1000 (ng/mL)	0.1 to 20 (µg/mL)	0.1 to 50 (µg/mL)
QCs	3.00, 400, 800 (ng/mL)	0.3, 8.0, 16.0 (µg/mL)	0.3, 8.0, 16.0 (µg/mL)
Accuracy/Bias	4.5%	8.2 %	5.8 %
Precision (CV%)	7.0%	6.0 %	4.1 %

Statistical Method: To estimate the effect of concomitant administration of apixaban on the PK of ASA and SA, analyses of variance were performed on ln(Cmax) and ln[AUC(TAU)]. Geometric means and coefficients of variation were presented for Cmax and AUC(TAU).

Study Population :

Enrolled/**Dosed/Completed**/ Discontinued Due to AE	17/**17/16**/1*
Age [range]	24-45 yr
Male/Female	17/0
Race (White/Black)	11/6

** Subject CV185002-1-58 discontinued on Day 5 due to an AE (elevated ALT) after receiving aspirin plus placebo for 4 days.*

Results

Pharmacokinetics of ASA

- ASA geometric mean Cmax increased by 26%, with no effect on AUC(TAU) when aspirin was administered with apixaban. Similar trend was observed when aspirin was administered with placebo.
- There was no effect of coadministered apixaban on SA Cmax and AUC(TAU) when compared with aspirin alone.

Figure 11.2.2 **Mean (+SD) Plasma Concentration versus Time Profiles of ASA Following Administration of Aspirin Alone and with Apixaban**

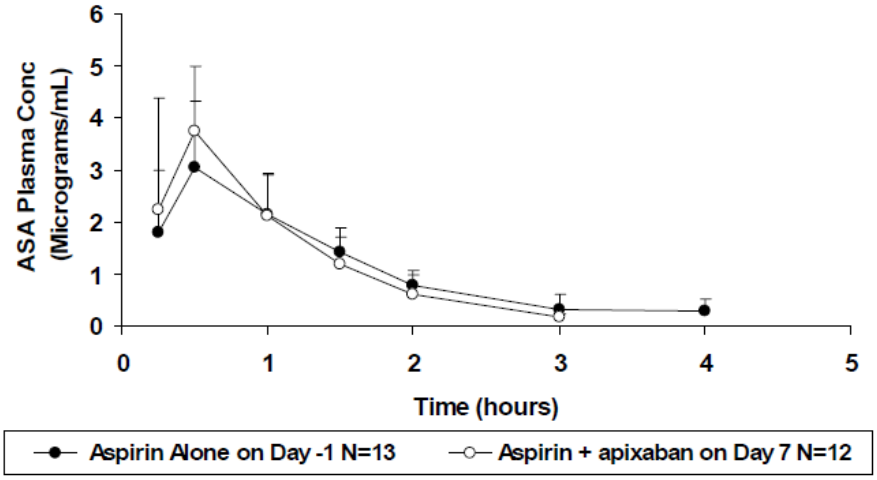


Table 11.2.2A: Summary Statistics for ASA Pharmacokinetic Parameters

Treatment[a]	Study Day[b]	Cmax (µg/mL) Geom. Mean (CV%)	AUC(TAU) (µg•h/mL) Geom. Mean (CV%)	Tmax (h) Median (Min, Max)	T1/2 (h) Mean (SD)
B	-1 (n = 13)	2.85 (40)	3.84 (21)	0.50 (0.50, 1.00)	0.70 (0.67)
	7 (n = 12)	3.65 (36)	3.77 (28)	0.50 (0.25, 1.00)	0.49 (0.13)
C	-1 (n = 4)	3.40 (78)	5.46 (45)	0.75 (0.25, 1.50)	0.78[c] (0.36)
	7 (n = 3)	4.69 (71)	4.61 (11)	1.00 (0.25, 1.00)	0.51 (0.19)

CV185002 Part B

Source: Supplemental Table S.11.2.2B

[a] B = Aspirin 325 mg + apixaban 5 mg BID; C = Aspirin 325 mg + Placebo

[b] All subjects received aspirin in the lead-in period (Days -5 to -1)

[c] n = 3

Table 11.2.2B: Results of Statistical Analyses for ASA Cmax and AUC(TAU) for Treatment B

Pharmacokinetic Variable	Adjusted Geometric Means		Ratio of Geometric Means		
	Study Day -1	Study Day 7	Ratio	Point Estimate	90% Confidence Limits
Cmax (µg/mL)	2.85	3.58	Day 7 vs. Day -1	1.258	(1.029, 1.537)
AUC(TAU) (µg•h/mL)	3.84	3.75	Day 7 vs. Day -1	0.977	(0.845, 1.129)

Pharmacokinetics of Apixaban:

- When coadministered with aspirin 325 mg, apixaban AUC(TAU) was about 45%

higher than that reported in another multiple-dose study of apixaban alone; the study design does not permit a conclusion about the effect of aspirin on apixaban PK.

Pharmacodynamics

Platelet Aggregation

- Mean Day -6 (baseline) values for arachidonic acid-induced platelet aggregation for both treatment groups (78%, aspirin plus apixaban and 79%, aspirin plus placebo) were within the normal range (60-90%) for this assay.
- Following treatment with aspirin 325 mg QD for 5 days, Day -1 mean % aggregation values in both treatment groups were reduced to 3.5% and 4.8%, respectively.
- Subsequent concomitant administration of apixaban 5 mg BID or placebo with aspirin for 7 days resulted in Day 7 mean percent aggregation values of 5.5% and 4.0% respectively, i.e., comparable to values following aspirin treatment alone.

Bleeding Time

Treatment[a]	Bleeding Time (min) Mean ± SD (Range)		
	Day -6: Pre-dose	Day 1: Predose	Day 7: 4 hr
B n=13	4.9 ± 0.8 (3.0-6.0)	6.7 ± 1.0 (5.5-9.5)	6.3 ± 1.4 (5.0-9.5)[b]
C n=4	5.6 ±0.5 (5.0-6.0)	6.3 ±1.0 (5.0-7.5)	5.2 ±0.3 (5.0-5.5)[c]

CV185002 Part B

Source: Supplemental Table 11.3.6A

[a] B = Aspirin 325 mg + apixaban 5 mg BID; C = Aspirin 325 mg + Placebo

[b] n=12

[c] n=3

- Bleeding time for both treatment groups were within the expected range at baseline.
- The mean values in both treatment groups increased but remained within the normal range following aspirin 325 mg QD treatment for 5 days.
- Subsequent concomitant administration of apixaban 5 mg BID or placebo with aspirin for 7 days did not further increase bleeding time.

mPT

- Mean Day -6 pre-dose (baseline) values for mPT for both treatment groups (53 sec for aspirin plus apixaban and 51 sec for aspirin plus placebo) were within the expected range (40-60 sec) for this assay.
- Following treatment with aspirin 325 mg QD for 5 days, mean Day -1 mPT values in both treatment groups (55 and 51 sec, respectively) were unchanged.
- Following concomitant administration of aspirin 325 mg QD plus apixaban 5 mg

BID, the mean Day 7, 6 hr post-dose mPT value (84 sec; 56% increase from baseline) was greater than the corresponding value (53 sec; 4% increase from baseline) for aspirin 325 mg QD plus placebo.

Reviewer's note: Although the mPT is higher in the coadministration of apixaban and aspirin, the clinical impact by this magnitude of change is not clear.

aPTT

- Mean Day -6 (baseline) values for aPTT for both treatment groups (31 sec, aspirin plus apixaban and 30 sec, aspirin plus placebo) were within the normal range (24.0 - 35.9 sec) for this assay.
- Following treatment with aspirin 325 mg QD for 5 days, mean Day -1 aPTT values in both treatment groups (31 and 31 sec, respectively) were unchanged.
- Following concomitant administration of aspirin 325 mg QD plus apixaban 5 mg BID or placebo for 7 days, the mean Day 7, 3 hr post-dose (near apixaban Tmax) aPTT values were 34 sec (12% increase from baseline) and 30 sec (-1% decrease from baseline), respectively.

Safety

- Was there any death or serious adverse events? ☐ Yes ☒No ☐ NA

Conclusion

Apixaban had no effect on the AUC(TAU) of acetylsalicylic acid. Although apixaban was associated with a 26% increase in acetylsalicylic acid Cmax, a similar increase was seen with placebo. Concomitant administration of apixaban 5 mg BID for 7 days did not appear to modify the near complete inhibition of arachidonic acid-induced platelet aggregation produced by aspirin 325 mg QD. The changes in mPT were consistent with the expected effects of apixaban 5 mg BID alone. No dose adjustment is recommended when apixaban is co-administered with aspirin.

DDI- Apixaban and Clopidogrel

Report # CV185005	**Study Period** 11/17/03 12/12/03	**EDR Link** \\Cdsesub1\evsprod\NDA202155\\0001\m5\53-clin-stud-rep\532-rep-stud-pk-human-biomat\5322-rep-hep-metab-interact-stud\cv185005\cv185005.pdf
Title	Double-Blind, Placebo-Controlled, Parallel Group Study to Evaluate the Safety of BMS-562247 when Co-Administered with Plavix	
Objective	**Primary:** To assess the safety and tolerability of multiple oral doses of apixaban vs. placebo when added to a daily regimen of Plavix(clopidogrel) 75 mg.	

Rationale: Clopidogrel (Plavix) is a commonly prescribed antiplatelet agent. Given the potential for clopidogrel and apixaban to be administered together and their potential to alter hemostasis, this study was conducted to understand the safety, pharmacokinetic, and pharmacodynamic profiles of these agents when coadministered.

Study Design Multiple-Dose Randomized Placebo-Controlled Double-Blind Parallel-Group Single-Center Two-Period Healthy Vonuteers
Subjects were randomized to receive one of 3 treatments detailed below. There was a 5-day clopidogrel 75 mg QD lead-in period. Upon completion of the lead-in period, subjects received 5 mg of apixaban BID, 10 mg of apixaban QD or placebo BID in a double-blind fashion, while continuing to receive 75 mg of clopidogrel QD for an additional 5 days.

Screening: -21days	**Washout:** None

Treatments: (Fasted)
A: clopidogrel 75 mg QD (Day 1 to 5), clopidogrel 75 mg QD + placebo BID (Day 6-10)
B: clopidogrel 75 mg QD (Day 1 to 5), clopidogrel 75 mg QD + apixaban 5 mg BID (Day 6-10)
C: clopidogrel 75 mg QD (Day 1 to 5), clopidogrel 75 mg QD + apixaban 10 mg QD (Day 6-10)

Study medication

Unit	Formulation	Product ID Number	Route	Batch or Lot Number	Label Batch Number
5 mg	Apixaban Tablets	562247-A005-002	Oral	2K64989	3K76734
N/A	Placebo Tablets Matching Apixaban	000000-A000-019	Oral	B5428	3K76733
75 mg	Clopidogrel (Plavix®) Tablets	N/A	Oral	3F74148	N/A

Source: Appendix 5.5.2
N/A = Not applicable

PK Sampling (Blood):

Apixaban: Pre-dose, 1, 2, 3, 4, 6, 8, 12, 16 and 24 hours post dose on Day 6 and 10

Reviewer's note: Plasma samples were also collected for PK of clopidogrel and its active metabolite; however, based on the sponsor, the performance of assay was not acceptable therefore no PK data can be reported.

Analytical Method
The performance of the assay method during study sample analysis is acceptable and is

summarized in the table below.

Analyte	Apixaban
Method	LC/MS/MS
Matrix	Plasma
LOQ	1.00 (ng/mL)
Range	1.00 to 1000 (ng/mL)
QCs	3.00, 400, 800 (ng/mL)
Accuracy/Bias	2.6%
Precision (CV%)	3.8%

Statistical Method: Summary statistics for the pharmacokinetic parameters of apixaban were tabulated by treatment (B or C) and day. Geometric means and coefficients of variation were presented for Cmax, AUC(TAU) and AI. Medians and ranges were presented for Tmax.

Study Population :

Enrolled/**Dosed/Completed**/ Discontinued Due to AE	35/**35/15**/18*
Age [range]	20-44 yr
Male/Female	29/6
Race (White)	35

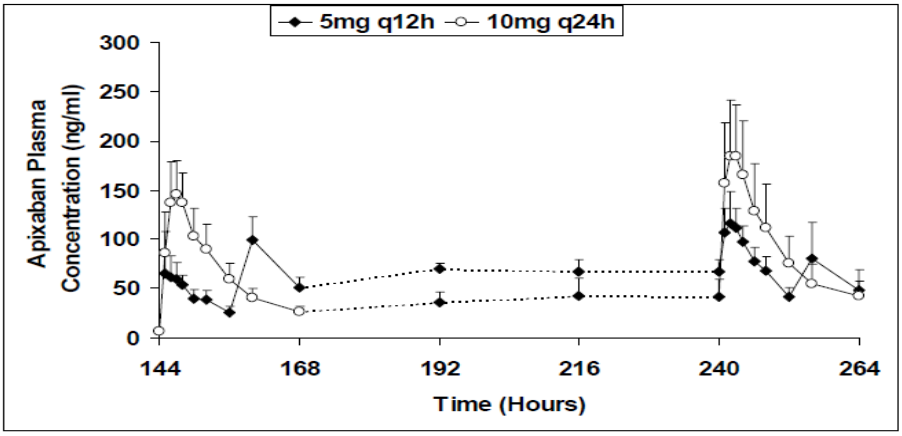
* 20 subjects discontinued prior to study completion. 13 subjects discontinued due to AEs during the lead-in period. 5 subjects discontinued due to AEs during active treatment.

Results

Pharmacokinetics of Apixaban

- The apixaban steady-state PK parameters were in agreement with values observed in other multiple ascending dose study, suggesting that clopidogrel is unlikely to affect apixaban pharmacokinetics.

Figure 11.2.3: **Mean (+SD) Apixaban Plasma Concentration vs. Time Following Apixaban 5 mg q12h or 10 mg q24h Coadministered with Clopidogrel 75 mg q24h from Day 6 to Day 10**



Source: Appendix 11.2.3A
Note: Time of clopidogrel first dose on Day 1 was counted as time zero. 144 and 240 hours in this graph correspond to time zero on Day 6 and 10, respectively.
Note: n=6 for 5 mg q12h group (Treatment B); n=8 for 10 mg q24h group (Treatment C).

Summary Statistics for Apixaban Pharmacokinetic Parameters

Treatment	Day	Cmax (ng/mL) Geom. Mean (CV%)	AUC(TAU) [a] (ng•h/mL) Geom. Mean (CV%)	Tmax (h) Median (Min, Max)	T1/2 (h) Mean (SD)	Accumulation Index (AI) [b] Geom. Mean (CV%)
B (n = 6)	6	71.5 (48)	502 (22)	2.0 (1.0, 4.0)	8.24 (3.38)	-
	10	118.0 (23)	940 (19)	2.0 (2.0, 3.0)	6.50 (0.89)	1.87 (16)
C (n = 8)	6	151.1 (22)	1598 (21)	3.0 (2.0, 4.0)	10.62 (5.69)	-
	10	192.0 (28)	2085 (33)	2.0 (1.0, 4.0)	10.39 (2.88)	1.30 (12)

[a] AUC(TAU) represents AUC(0-12) for Treatment B and AUC(0-24) for Treatment C

[b] Accumulation Index is the ratio of Study Day 10 to Study Day 6 AUC(TAU) values

B = Clopidogrel 75 mg q24h (Days 1-5) + clopidogrel 75 mg q24h with apixaban 5 mg q12h (Days 6-10)

C = Clopidogrel 75 mg q24h (Days 1-5) + clopidogrel 75 mg q24h with apixaban 10 mg q24h (Days 6-10)

NA = Not applicable

Pharmacodynamics

ADP-Induced Platelet Aggregation

- Following treatment with clopidogrel 75 mg QD, Day 6 mean % aggregation values were reduced in all treatment groups (by 50-62% from baseline).
- Concomitant administration of placebo, apixaban 5 mg BID or apixaban 10 mg QD did not have any additional effect on platelet aggregation.

Table 11.3.4.2: Summary of ADP-Induced Platelet Aggregation Values

Day	Treatment								
	A			B			C		
	n	Mean (%)	Mean Change from Baseline (%)	n	Mean (%)	Mean Change from Baseline (%)	N	Mean (%)	Mean Change from Baseline (%)
-2 [a]	12	77.75		12	79.42		11	82.18	
6	11	21.82	-57.36	12	17.50	-61.92	11	32.36	-49.82
10	7	22.43	-53.29	6	20.17	-61.50	8	33.50	-51.00

Source: Supplemental Table S.11.3.4.2A

[a] Baseline

A = clopidogrel 75 mg q24h (Days 1-5) + clopidogrel 75 mg q24h with placebo q12h (Days 6-10)

B = clopidogrel 75 mg q24h (Days 1-5) + clopidogrel 75 mg q24h with apixaban 5 mg q12h (Days 6-10)

C = clopidogrel 75 mg q24h (Days 1-5) + clopidogrel 75 mg q24h with apixaban 10 mg q24h (Days 6-10)

Bleeding Time

- Mean baseline (Day -2) values for bleeding time for all treatments were within the expected (2.3-9.5 min).
- Following treatment with clopidogrel 75 mg QD, mean Day 5 bleeding times increased above the normal range in all treatment groups (>200% increase from baseline).

- Mean bleeding times increased from Day 5 to Day 10 for all three treatment groups and the increases were somewhat larger in the two groups (B and C) receiving apixaban. However, none of these differences were statistically significant.

Summary of Bleeding Time

Day	Treatment								
	A			B			C		
	n	Mean (min)	Mean % Change from Baseline	n	Mean (min)	Mean % Change from Baseline	n	Mean (min)	Mean % Change from Baseline
-2 [a]	12	5.42		12	4.54		11	4.64	
5	12	17.79	234	12	23.50	446	11	15.32	236
10	7	18.93	283	6	23.00	383	8	22.06	434

[a] Baseline

A = Clopidogrel 75 mg q24h (Days 1-5) + clopidogrel 75 mg q24h with placebo q12h (Days 6-10)
B = Clopidogrel 75 mg q24h (Days 1-5) + clopidogrel 75 mg q24h with apixaban 5 mg q12h (Days 6-10)
C = Clopidogrel 75 mg q24h (Days 1-5) + clopidogrel 75 mg q24h with apixaban 10 mg q24h (Days 6-10)

Results of Statistical Analyses for Bleeding Time

Treatment	Means (min)		Mean Differences (Day 10 - Day 5) (min)	
	Day 5	Day 10	Point Estimate	95% Confidence Limits
A (n = 7)	12.29	18.93	6.64	(-0.72, 14.01)
B (n = 6)	12.17	23.00	10.83	(-4.80, 26.46)
C (n = 8)	12.06	22.06	10.00	(-5.63, 25.63)

A = Clopidogrel 75 mg q24h (Days 1-5) + clopidogrel 75 mg q24h with placebo q12h (Days 6-10)
B = Clopidogrel 75 mg q24h (Days 1-5) + clopidogrel 75 mg q24h with apixaban 5 mg q12h (Days 6-10)
C = Clopidogrel 75 mg q24h (Days 1-5) + clopidogrel 75 mg q24h with apixaban 10 mg q24h (Days 6-10)

Safety

- Was there any death or serious adverse events? ☐ Yes ☒No ☐ NA

Conclusion

When co-administered with clopidogrel, apixaban steady-state PK parameters were similar to those reported in a previous multiple-dose study of apixaban alone. Co-administration of apixaban did not result in additive or inhibitory effects on agonist-induced platelet aggregation. No dose adjustment is warranted when apixaban is co-administered with clopidogrel. However, this does not preclude the risk for bleeding when an antiplatelet and anticoagulant are coadministered and warrants monitoring for bleeding.

DDI- Apixaban and Aspirin+Clopidogrel

Report # CV185015	**Study Period** 11/09/05 12/15/05	**EDR Link** \\Cdsesub1\evsprod\NDA202155\\0001\m5\53-clin-stud-rep\532-rep-stud-pk-human-biomat\5322-rep-hep-metab-interact-stud\cv185015\cv185015.pdf
Title	Double-Blind, Placebo-Controlled, Two-Treatment, Parallel Group Study to Assess the Safety of Apixaban When Co-Administered with Clopidogrel and Aspirin in Healthy Subjects	
Objectives	**Primary:** To assess the safety and tolerability of apixaban when co-administered with clopidogrel and aspirin in healthy subjects.	

Rationale: Clopidogrel and aspirin are antiplatelet agents commonly used in the prevention and treatment of thromboembolism, and both are likely to be co-administered with apixaban. This study was conducted for safety assessment as well as to evaluate the effects of apixaban on the multiple-dose PK of the clopidogrel metabolite SR26334 and of aspirin metabolite salicylic acid, and the antiplatelet effects of clopidogrel and aspirin, clopidogrel and aspirin.

Study Design Multiple-Dose Randomized Placebo-Controlled Double-Blind Parallel Group Single-Center Two-Period Healthy Vonuteers
Subjects were randomized on Day 1 to receive one of the 2 treatments detailed below in a double-blind fashion.

Screening: -21days	**Washout:** None

Treatments: (Fasted)
A: 75 mg clopidogrel + 162 mg aspirin + placebo QD x 10 days
B: 75 mg clopidogrel + 162 mg aspirin + 20 mg apixaban QD x 10 days

Study medication

Unit	Formulation	Product ID Number	Route	Product Batch Number	Label Batch Number
20 mg apixaban	Tablet	562247-A020-011	Oral	3A70866	3K76731
Matching placebo for 20 mg apixaban	Tablet	000000-A000-024	Oral	B5348	3K76729

Source: CV185015 Appendix 5.5.2

Aspirin 162 mg tablet was manufactured by Bayer; lot LEM093; expiration date March 2007. Clopidogrel 75 mg tablet was manufactured by BMS/sanofi aventis; lot 5J06953; expiration date August 2008.

PK Sampling (Blood):

SR26334 (active metabolite of clopidogrel): Pre-dose on days 7-10, and 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, 24, 36 and 48 hours post Day 10 dose.
Salicylic acid (SA, metabolite of aspirin): Pre-dose on days 7-10, and 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 16 and 24 hours post Day 10 dose.

Analytical Method

The performance of the assay method during study sample analysis is acceptable and is summarized in the table below.

Analyte	SR26334	SA

Method	LC/MS/MS	LC/MS/MS
Matrix	Plasma	Plasma
LOQ	4.02 (ng/mL)	100 (ng/mL)
Range	4.02 to 4020.80 (ng/mL)	100 to 10000 (ng/mL)
QCs	12.07, 201.2, 2012, 3219.2 (ng/mL)	300, 3000, 7500 (ng/mL)
Accuracy/Bias	16 %	9.3 %
Precision (CV%)	2.6 %	5.53 %

Statistical Method: Results from analyses of variance on ln(Cmax) and ln[AUC(TAU)] were used to estimate effects of apixaban on the PK of the clopidogrel metabolite SR26334 and salicylic acid. Point estimates and 90% confidence intervals were computed for ratios of Cmax and AUC geometric means.

Study Population :

Enrolled/**Completed**/ Discontinued Due to AE	30/**22**/5*
Age [range]	18-45 yr
Male/Female	30/0
Race (White/Black/Other)	15/15/1

* Five subjects discontinued due to AEs during active treatment, 3 receiving apixaban and 2 receiving placebo.

Results

Pharmacokinetics of SR26334

- SR26334 Cmax and AUC(TAU) were slightly lower i.e., by 10% and 8%, respectively, when apixaban was co-administered with clopidogrel and aspirin as compared to clopidogrel and aspirin only.

Figure 11.2.1: **Mean (+SD) Plasma Concentration of SR26334 versus Time Profile on Day 10 during Concomitant Administration of Aspirin and Clopidogrel (A) or Apixaban Plus Aspirin and Clopidogrel (B)**

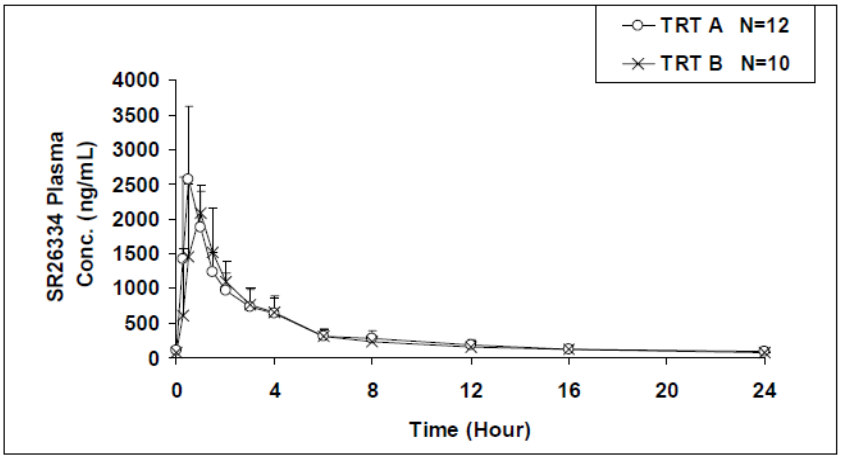


Table 11.2.1A: Summary Statistics for SR26334 Pharmacokinetic Parameters

Treatment	Cmax (ng/mL) Geom. Mean (CV %)	AUC(TAU) (ng•h/mL) Geom. Mean (CV %)	Tmax (h) Median (Min, Max)	T1/2 (h) Mean (SD)
A	2602	8344	0.50	9.33
(n = 12)	(31)	(27)	(0.25, 1.00)	(2.15)
B	2339	7679	1.00	8.53
(n = 10)	(26)	(28)	(0.50, 1.50)	(1.64)

Source: CV185015 Supplemental Table S.11.2.1B

A = 75 mg clopidogrel +162 mg aspirin + placebo, q24h for 10 days

B = 75 mg clopidogrel +162 mg aspirin + 20 mg apixaban, q24h for 10 days

Table 11.2.1B: Results of Statistical Analyses for SR26334 Cmax and AUC(TAU)

Pharmacokinetic Parameter	Geometric Means		Ratio of Geometric Means		
	Treatment	Geometric Mean	Ratio	Point Estimate	90% Confidence Limits
Cmax (ng/mL)	A	2602	B vs A	0.899	(0.731, 1.105)
	B	2339			
AUC(0-T) (ng.hr/mL)	A	8344	B vs A	0.920	(0.764, 1.108)
	B	7679			

Pharmacokinetics of SA

- Salicylic acid Cmax and AUC(TAU) were slightly lower, i.e. by 10% and 4%, respectively, when apixaban was co-administered with clopidogrel and aspirin as compared to clopidogrel and aspirin only.

Table 11.2.2A: Summary Statistics for Salicylic Acid Pharmacokinetic Parameters

Treatment	Cmax (ng/mL) Geom. Mean (C.V. %)	AUC(TAU) (ng•h/mL) Geom. Mean (C.V. %)	Tmax (h) Median (Min, Max)	T1/2 (h) Mean (S.D.)
A	12220	43265	1.00	2.88
(n = 12)	(26)	(34)	(0.25, 2.00)	(0.89)
B	10994	41366	1.25	2.18
(n = 10)	(21)	(33)	(1.00, 2.00)	(0.60)

Source: CV185015 Supplemental Table S.11.2.2B

A = 75 mg clopidogrel +162 mg aspirin + placebo, q24h for 10 days

B = 75 mg clopidogrel +162 mg aspirin + 20 mg apixaban, q24h for 10 days

Table 11.2.2B: Results of Statistical Analyses for Salicylic Acid Cmax and AUC(TAU)

Pharmaco-kinetic Parameter	Geometric Means		Ratio of Geometric Means		
	Treatment	Geometric Mean	Ratio	Point Estimate	90% Confidence Limits
Cmax (ng/mL)	A	12220	B vs A	0.900	(0.762, 1.062)
	B	10994			
AUC(0-T) (ng.hr/mL)	A	43265	B vs A	0.956	(0.757, 1.207)
	B	41366			

Source: CV185015 Supplemental Table S.11.2.2C and S.11.2.2D

A = 75 mg clopidogrel +162 mg aspirin + placebo, q24h for 10 days

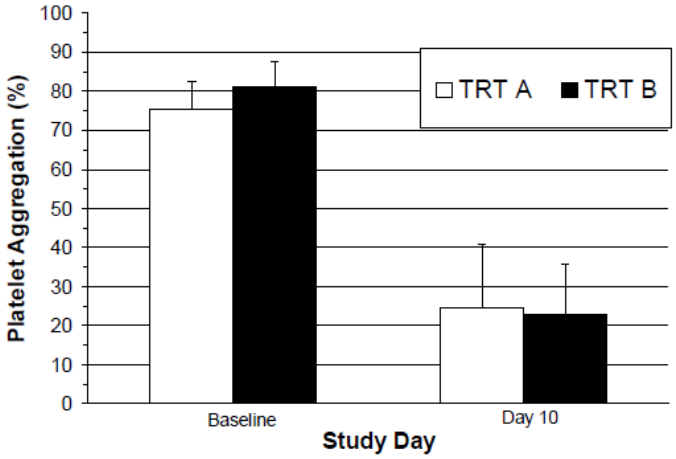
B = 75 mg clopidogrel +162 mg aspirin + 20 mg apixaban, q24h for 10 days

Pharmacodynamics

Platelet Aggregation

ADP-Induced Platelet Aggregation

Figure 11.3.1.1: Mean (+SD) ADP-Induced Platelet Aggregation

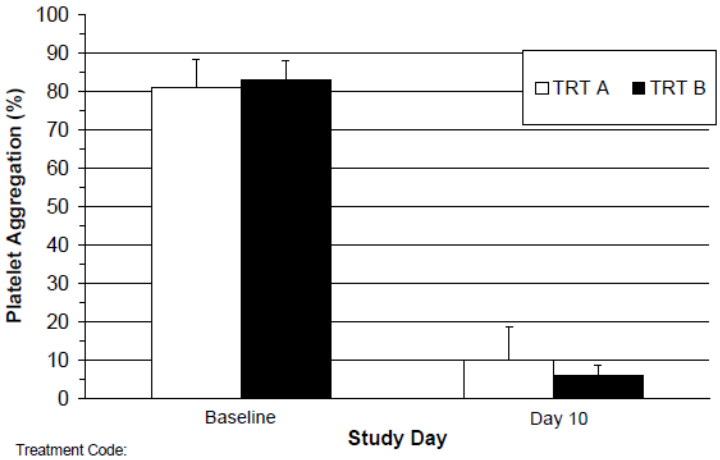


Treatment Code:
A = clopidogrel 75 mg + aspirin 162 mg + placebo, q24h for 10 days. N = 15 predose; N=12 postdose
B = clopidogrel 75 mg + aspirin 162 mg + apixaban 20 mg, q24h for 10 days. N = 15 predose; N=10 postdose

- Day 10 mean % ADP-induced aggregation values were similar (24.4% for Treatment A and 22.8% for Treatment B).
- Mean decreases from baseline were similar for the two treatment groups (49.8% for Treatment A and 59.0% for Treatment B).

Arachidonic Acid-Induced Platelet Aggregation

Figure 11.3.1.2: Mean (+SD) Arachidonic Acid-Induced Platelet Aggregation



Treatment Code:
A = clopidogrel 75 mg + aspirin 162 mg + placebo, q24h for 10 days. N = 15 predose; N=12 postdose
B = clopidogrel 75 mg + aspirin 162 mg + apixaban 20 mg, q24h for 10 days. N = 15 predose; N=10 postdose

- Day 10 mean % arachidonic acid-induced aggregation values were similar (10.1% for Treatment A and 6.0% for Treatment B) for the two treatment groups.
- Mean decreases from baseline were similar for the two treatment groups (72.2% for Treatment A and 76.6% for Treatment B).

Safety

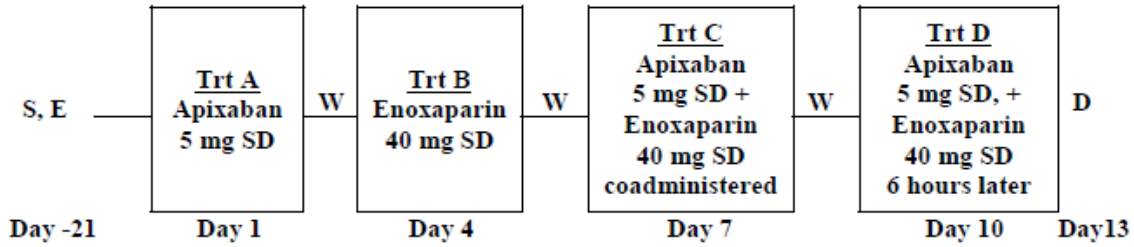
- Was there any death or serious adverse events? ☐ Yes ☒No ☐ NA

5 discontinued due to AE. 4 of 5 were bleeding related. 2 in Aspirin + Clopidogrel + Placebo and 2 in Aspirin + Clopidogrel + Apixaban so the bleeding related AEs seem to be comparable.

Conclusion

- Co-administration of apixaban 20 mg with clopidogrel 75 mg and aspirin 162 mg has no clinically relevant effects on the PK and PD of clopidogrel or aspirin.

DDI- Apixaban and Enoxaparin

Report # CV185055	**Study Period** 07/17/08 08/24/08	**EDR Link** \\Cdsesub1\evsprod\NDA202155\\0001\m5\53-clin-stud-rep\532-rep-stud-pk-human-biomat\5322-rep-hep-metab-interact-stud\cv185055\cv185055.pdf
Title	Evaluation of the Pharmacokinetic and Pharmacodynamic Drug Interactions Between Apixaban and Enoxaparin in Healthy Subjects	
Objectives	• To assess the effect of single-dose enoxaparin on the PK of apixaban, when co-administered or separated by 6 hours of dosing • To assess the anti-Factor Xa (anti-Xa) activity when enoxaparin and apixaban were coadministered or separated by 6 hours of dosing	
Rationale: Enoxaparin is a low molecular weight heparin which has antithrombotic properties. Since apixaban and enoxaparin will be used within the same populations, the purpose of this study was to examine the PK and PD of apixaban and enoxaparin when co-administered in healthy subjects.		
Study Design Single-Dose Crossover Randomized Open-Label 4-Treatment 4-Period 4-Sequence Single-Center Healthy Vonuteers Subjects were randomized on Day 1 to receive one of the 4 treatment sequences detailed below.  S = Screening; E = Enrollment; W = ≥ 3-day Washout; D = Study Discharge The full set of sequences will be: A --> B --> C --> D B --> D --> A --> C C --> A --> D --> B D --> C --> B --> A		
Screening: -21days	**Washout:** ≥ 3 days	
Treatments: (Fasted) A: Apixaban 5 mg as a single oral dose B: Enoxaparin 40 mg as a single subcutaneous dose C: Apixaban 5 mg as a single oral dose administered concomitantly with enoxaparin 40 mg as a single subcutaneous dose D: Apixaban 5 mg as a single oral dose followed 6 hours later by enoxaparin 40 mg as a single subcutaneous dose		
Study medication		

Treatment	Formulation	Route	Product ID Information	Product Batch Number	Label Batch/Lot Number
Apixaban (BMS-562247) 5 mg	Tablet	Oral	562247-K005-027	6J14405	6L21084

The clinical site obtained their on supplies of enoxaparin (LOVENOX®) 40-mg subcutaneous syringes (Sanofi Aventis; Lot # 19491, expiration April, 2011).

PK Sampling (Blood):
Apixaban: Pre-dose, 0.5, 1, 2, 3, 4, 6, 12, 24, 36, 48 and 60 hours post-dose

Analytical Method

The performance of the assay method during study sample analysis is acceptable and is summarized in the table below.

Analyte	Apixaban
Method	LC/MS/MS
Matrix	Plasma
LOQ	1.00 (ng/mL)
Range	1.00 to 1000 (ng/mL)
QCs	3.00, 400, 800 (ng/mL)
Accuracy/Bias	2.45%
Precision (CV%)	5.34%

Statistical Method: Analyses of variance were performed on apixaban ln(Cmax), ln[AUC(0-T)] and ln[AUC(INF)] values. Point estimates and 90% confidence intervals (CI) for treatment differences on the log scale were exponentiated to obtain estimates for ratios of geometric means on the original scale (Treatment C versus Treatment A, and Treatment D versus Treatment A).

Study Population :

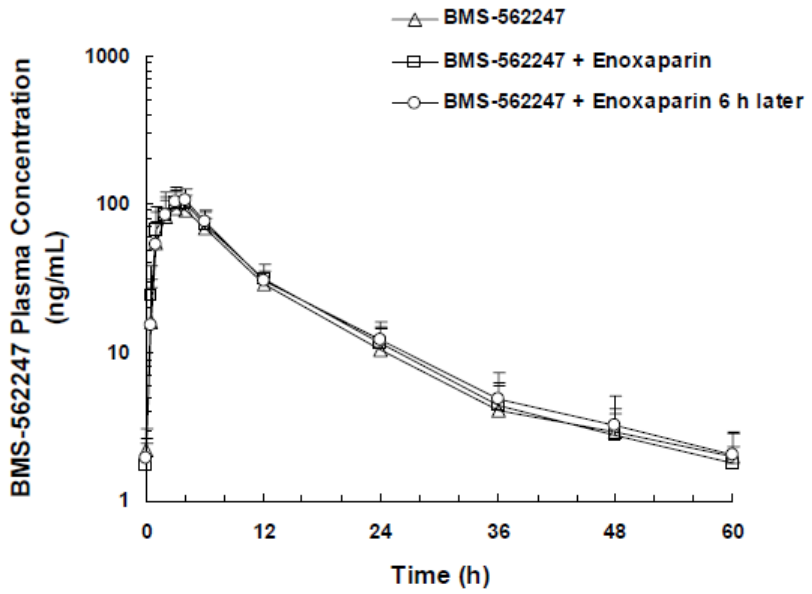
Randomized/**Completed**/ Discontinued Due to AE	20/**18**/0
Age [Mean (range)]	37 (26-45) yr
Male/Female	18/2
Race (White/Black/Asian)	9/10/1

Results

Pharmacokinetics of Apixaban

- When apixaban 5 mg was co-administered with enoxaparin 40 mg, apixaban geometric mean Cmax, AUC(INF) and AUC(0-T) were 10%, 7% and 8% higher, respectively, relative to those observed following administration of apixaban 5 mg alone.
- When apixaban 5 mg was administered 6 hours before dosing with enoxaparin 40 mg, apixaban geometric mean Cmax, AUC(INF) and AUC(0-T) were 14%, 12% and 12% higher, respectively, relative to those observed following administration of apixaban 5 mg alone.

Figure 9.2.1: Mean (+ SD) Plasma Concentration-Time Profiles for Apixaban (BMS-562247) in Study CV185055



Source: Supplemental Table S.8.2.1

Table 9.2.1A: Summary Statistics for Apixaban Pharmacokinetic Parameters

	Apixaban Pharmacokinetic Parameters				
Treatment	Cmax (ng/mL) Geom. Mean (CV %)	Tmax (h) Median (Min, Max)	AUC(INF) (ng·h/mL) Geom. Mean (CV %)	AUC(0-T) (ng·h/mL) Geom. Mean (CV %)	T-HALF (h) Mean (SD)
A (n = 20)	96 (28)	3.0 (1.0, 6.0)	1063 (22)	1030 (21)	11.5 (4.45)
C (n = 20)	106 (25)	3.0 (1.0, 4.0)	1139 (22)	1108 (22)	11.3 (4.24)
D (n = 19)	110 (19)	3.0 (2.0, 6.0)	1196 (17)	1160 (17)	12.9 (5.71)

Source: Supplemental Table S.8.2.4

Treatment: A = Apixaban 5 mg
C = Apixaban 5 mg + Enoxaparin 40 mg co-administered
D = Apixaban 5 mg + Enoxaparin 40 mg 6 hours later

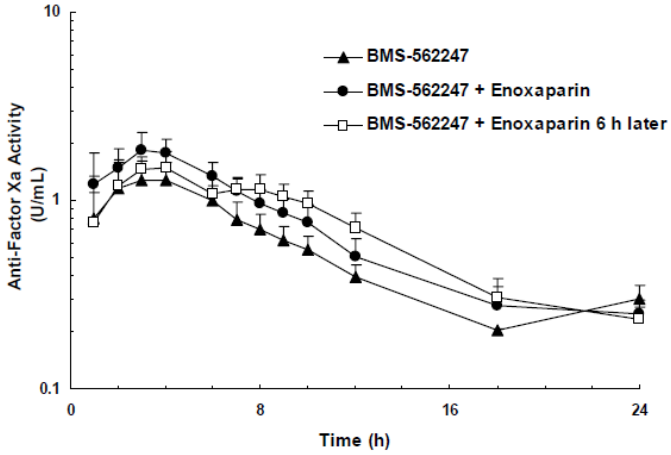
Pharmacodynamics

Apixaban Anti-Factor Xa Activity

- When apixaban 5 mg was co-administered with enoxaparin 40 mg, the geometric means for anti-Xa Cmax and AUC(0-T) increased by 42% and 52%, respectively, relative to those observed following administration of apixaban 5 mg alone.
- When apixaban 5 mg was administered 6 hours prior to enoxaparin 40 mg, the geometric means for anti-Xa Cmax and AUC(0-T) increased by 15% and 58%, respectively, relative to

those observed following administration of apixaban 5 mg alone.

Figure 10.2.1: **Mean (+ SD) Plasma Anti-Factor Xa Activity-Time Profiles for Apixaban in Study CV185055**



Source: Supplemental Table S.8.3.1

Table 10.2.1B: Results of Apixaban Statistical Analyses for Anti-Xa Activity Cmax and AUC(0-T)

Anti-Xa Activity Variable	Treatment	Adjusted Geometric Means	Ratio of Geometric Means		
			Ratio	Point Estimate	90% CI
Cmax (U/mL)	A	1.36	C vs A	1.416	(1.272, 1.577)
	C	1.92			
	D	1.56	D vs A	1.147	(1.031, 1.277)
AUC(0-T) (U·h/mL)	A	10.18	C vs A	1.520	(1.412, 1.635)
	C	15.46			
	D	16.03	D vs A	1.575	(1.436, 1.727)

Source: Supplemental Tables S.8.3.1A and S.8.3.2A

Treatment: A = Apixaban 5 mg
C = Apixaban 5 mg + Enoxaparin 40 mg co-administered
D = Apixaban 5 mg + Enoxaparin 40 mg 6 hours later

Table 10.2.1A: Summary Statistics for Anti-Xa Activity Parameters in All Treatments

Treatment	Anti-Xa Activity Parameters			
	Cmax (U/mL)	Tmax (h)	AUC(0-T) (U·h/mL)	T-HALF (h)
	Geom. Mean (CV %)	Median (Min, Max)	Geom. Mean (CV %)	Mean (SD)
A (n = 20)	1.36 (24)	3.0 (1.0, 4.0)	10.18 (23)	5.0 (1.97)
B (n = 19)	0.42 (41)	4.0 (3.0, 9.0)	2.04 (45)	6.1[a] (2.75)
C (n = 20)	1.92 (22)	3.00 (1.0, 4.0)	15.28 (25)	5.1 (1.75)
D (n = 19)	1.56 (19)	4.0 (2.0, 8.0)	15.98 (16)	5.8 (1.46)

Source: Supplemental Table S.8.3.4

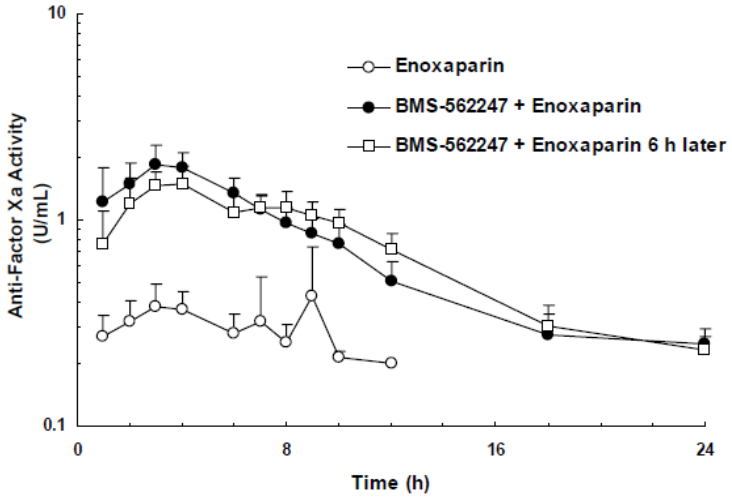
[a] n = 9

Treatment: A = Apixaban 5 mg
B = Enoxaparin 40 mg
C = Apixaban 5 mg + Enoxaparin 40 mg co-administered
D = Apixaban 5 mg + Enoxaparin 40 mg 6 hours later

Enoxaparin Anti-Factor Xa Activity

- When enoxaparin 40 mg was co-administered with apixaban 5 mg, the geometric means for anti-Xa Cmax and AUC(0-T) of increased by more than 4- and 7-fold, respectively, relative to those observed following administration of enoxaparin 40 mg alone.

Figure 10.2.2.1: **Mean (+ SD) Plasma Anti-Xa Activity-Time Profiles for Enoxaparin in Study CV185055**



Source: Supplemental Table S.8.3.1

Table 10.2.2.1: **Results of Enoxaparin Statistical Analyses for Anti-Xa Activity Cmax and AUC(0-T)**

Anti-Xa Activity Variable	Treatment	Adjusted Geometric Means	Ratio of Geometric Means		
			Ratio	Point Estimate	90% CI
Cmax (U/mL)	B	0.43	C vs B	4.510	(3.810, 5.338)
	C	1.92			
AUC(0-T) (U·h/mL)	B	2.07	C vs B	7.455	(6.013, 9.243)
	C	15.46			

Source : Supplemental Tables S.8.3.1A and S.8.3.2A

Treatment: B = Enoxaparin 40 mg

C = Apixaban 5 mg + Enoxaparin 40 mg co-administered

Safety

- Was there any death or serious adverse events? ☐ Yes ☒No ☐ NA

Conclusion

Co-administration of enoxaparin did not affect the PK of apixaban.There was an additive effect on anti-Xa activity in the presence of both apixaban and enoxaparin when compared to the effect with either agent alone. This was expected based on the mechanism of action of the 2 agents.

DDI- Apixaban and Atenolol

Report # CV185033	**Study Period** 06/01/07 06/26/07	**EDR Link** \\Cdsesub1\evsprod\NDA202155\\0001\m5\53-clin-stud-rep\532-rep-stud-pk-human-biomat\5322-rep-hep-metab-interact-stud\cv185033\cv185033.pdf
Title	Drug Interaction Study of Apixaban and Atenolol in Healthy Subjects	
Objectives	To assess the effect of atenolol 100 mg on the PK of apixaban and the effect of apixaban 10 mg on the PK of atenolol in healthy subjects.	

Rationale: Since apixaban is expected to be coadministered with beta-blockers in some patient populations, this study was to assess the potential for PK interactions between these two agents.

Study Design Single-Dose Randomized Open-Label Cross-Over Single-Center 3-Period Healthy Vonuteers On Day 1 of Period 1, subjects were randomized to one of 6 treatment sequences to receive each of the 3 treatments detailed below.

Screening: -21days	**Washout:** 4 days
Period 1/2/3	4/4/4 days, inpatient stay ☑Y ☐ N
Sequence	Six sequences: ABC, ACB, BAC, BCA, CAB, CBA

Treatments: (Fasted)
A: PO Apixaban 10 mg (2 x 5 mg) single dose
B: PO Atenolol 100 mg single dose
C: PO Apixaban 10 mg + Atenolol 100 mg

Study medication

Drug name	Apixaban	Atenolol
Dosage Form	Tablet	Tablet
Dosage Strength	5 mg	100 mg
Batch #.	6J14405 (Product batch#)	clinical site sourced
	6L21084 (Label batch#)	--
	562247-K005-027 (Product Identification#)	--
Administration	Oral	Oral

PK Sampling (Blood)

Atenolol: Pre-dose, 1, 2, 3, 4, 6, 8, 10, 12, 24, 36 and 48 hours post-dose

Apixaban: Pre-dose, 1, 2, 3, 4, 6, 8, 12, 24, 36, 48, 60 and 72 hours post-dose

Analytical Method

The performance of the assay method during study sample analysis is acceptable and is summarized in the table below.

Analyte	**Apixaban**	**Atenolol**
Method	LC-API/MS/MS	LC/MS/MS
Matrix	Plasma	Plasma
LOQ (ng/mL)	1.00	1.000
Range (ng/mL)	1.00 to 1000	1.000 to 1001.150
QCs (ng/mL)	3.00, 35.0, 400, 800	3.000, 40.250, 402.350, 804.750
Accuracy/Bias	5.08 %	8.44 %
Precision	9.38 %	6.32 %

Statistical Method: The 90% confidence intervals for the ratios of the geometric means for apixaban Cmax and AUCinf with and without atenolol and for atenolol Cmax and AUCinf with and without apixaban were constructed. The equivalence interval was set to be from 70% to 143%.

Reviewer's comments: Utilizing the equivalence criteria of 70 % to 143 % for concluding whether there is PK change is not appropriate.

Study Population :

Enrolled/Completed/ Discontinued Due to AE	44/14/1*
Age [Median (range)]	18-44 yr
Male/Female	13/2
Race (Caucasian/Black)	8/7

*Subject CV185033-1-11 discontinued due to moderate cellulitis on Day 4 of Period 2. The Investigator considered the event unrelated to study drug.

Results

Apixaban Pharmacokinetics

Figure 11.2.1: Mean (+SD) Apixaban Plasma Concentration vs Time by Treatment

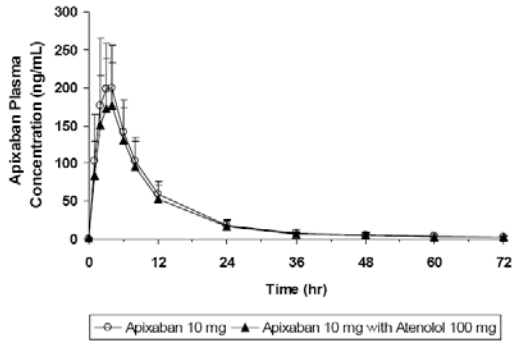


Table 11.2.1A: Summary Statistics for Apixaban Pharmacokinetic Parameters

	Apixaban Pharmacokinetic Parameters				
	Cmax (ng/mL)	AUC(0-T) (ng•h/mL)	AUC(0-INF) (ng•h/mL)	Tmax (h)	T-HALF (h)
Treatment	Geom. Mean (CV%)	Geom. Mean (CV%)	Geom. Mean (CV%)	Median (Min, Max)	Mean (SD)
A (n = 15)	216 (33)	2103 (31)	2157 (31)	3 (1,4)	13.9 (6.1)
C (n = 14)	180 (32)	1838 (33)	1878 (33)	4 (2,4)	11.7 (3.8)

Source: Supplemental Table S.11.2.1B
A = apixaban 10 mg
C = apixaban 10 mg + atenolol 100 mg

Statistical Analysis of Apixaban Pharmacokinetic Parameters

Pharmacokinetic Variable	Treatment	Adjusted Geometric Mean	Ratio of Geometric Means		
			Ratio	Point Estimate	90% CI
Cmax (ng/mL)	A	214	C vs A	0.82	(0.75, 0.89)
	C	176			
AUC(0-T) (ng•h/mL)	A	2086	C vs A	0.85	(0.79, 0.92)
	C	1777			
AUC(INF) (ng•h/mL)	A	2140	C vs A	0.85	(0.78, 0.92)
	C	1815			

A = apixaban 10 mg
C = apixaban 10 mg + atenolol 100 mg

1. Median Tmax of apixaban was not significantly changed with or without coadministration of atenolol.
2. Apixaban Cmax, AUC(0-T), and AUC(INF) values decreased by 18%, 15% and 15%, respectively, when apixaban was coadministered with atenolol. The magnitude of pharmacokinetic changes was within the sponsor's pre-specified equivalence criteria.

Reviewer's comments: Although this study is not intended to compare bioequivalence between two treatments, applying the equivalence criteria of 70 % to 143 % and conclude no PK changes based on this criteria is not adequate. While the point estimates were less than 20% decrease, the upper bound of 90 % confidence intervals for all three parameters were all below 1. Based on the pharmacometric analyses, decreases in exposure upto 25% does not negatively impact the efficacy.

Atenolol Pharmacokinetics

Figure 11.2.2: Mean (+SD) Atenolol Plasma Concentration vs Time by Treatment

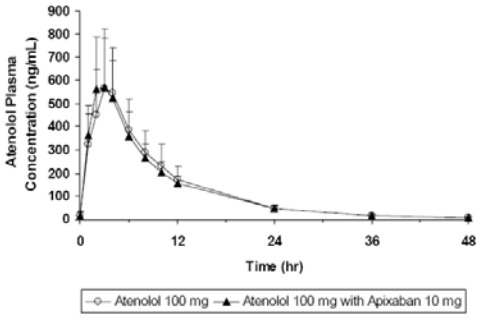


Table 11.2.2A: Summary Statistics for Atenolol Pharmacokinetic Parameters

Treatment	Atenolol Pharmacokinetic Parameters				
	Cmax (ng/mL)	AUC(0-T) (ng•h/mL)	AUC(INF) (ng•h/mL)	Tmax (h)	T-HALF (h)
	Geom. Mean (CV%)	Geom. Mean (CV%)	Geom. Mean (CV%)	Median (Min, Max)	Mean (SD)
B (n = 14)	603 (39)	5500 (29)	5596 (29)	3 (1,6)	8.33 (1.64)
C (n = 15)	598 (33)	5528 (22)	5649 (22)	2 (2,4)	8.57 (1.89)

Source: Supplemental Table S.11.2.2B
B = atenolol 100 mg
C = apixaban 10 mg + atenolol 100 mg

Statistical Anlysis of Atenolol Pharmacokinetic Parameters

Pharmacokinetic Variable	Treatment	Adjusted Geometric Means	Ratio of Geometric Means		
			Ratio	Point Estimate	90%CI
Cmax (ng/mL)	B	597	C vs B	0.98	(0.84, 1.13)
	C	584			
AUC(0-T) (ng•h/mL)	B	5482	C vs B	1.00	(0.90, 1.11)
	C	5479			
AUC(INF) (ng•h/mL)	B	5582	C vs B	1.00	(0.91, 1.11)
	C	5602			

B = atenolol 100 mg
C = apixaban 10 mg + atenolol 100 mg

1. Atenolol PK was not altered with or without coadministration of apixaban. The 90% confidence intervals for the ratios of geometric means of atenolol Cmax and AUC before and after coadministration of apixaban 10 mg were within the pre-specified equivalence interval of (b) (4) (also with 80% to 125%).

Safety: Was there any death or serious adverse events? ☐ Yes ☒No ☐ NA

Conclusion

- Co-administration of apixaban 10 mg had no effect on the pharmacokinetics of atenolol.
- Apixaban Cmax and AUCinf decreased by 18% and 15%, respectively, when co-administered with atenolol. No dose adjustment is warranted as the decrease in exposure is less than 25% (lower bound of n"No dose adjustment" derived based on pharmacometrics review).

DDI- Apixaban and Famotidine

Report # CV185060	**Study Period** 09/02/08 09/25/08	**EDR Link** \\Cdsesub1\evsprod\NDA202155\\0001\m5\53-clin-stud-rep\532-rep-stud-pk-human-biomat\5322-rep-hep-metab-interact-stud\cv185060\cv185060.pdf
Title	Effect of Famotidine on Apixaban Pharmacokinetics in Healthy Subjects	
Objectives	To assess the effect of famotidine 40 mg on the single-dose pharmacokinetics of apixaban in healthy subjects.	

Rationale: Since apixaban is expected to be co-administered with H2 antagonists and other pH modifiers in targeted patient populations, this study was to understand if the PK of apixaban are affected by the drugs that alter gastric pH.

Study Design Single-Dose Randomized Open-Label Cross-Over Single-Center 2-Period Healthy Vonuteers On Day 1 of Period 1, subjects were randomized to one of 2 treatments detailed below.

Screening: -21days	**Washout:** 4 days
Period 1/2	3/3 days, inpatient stay ☑Y ☐ N
Sequence	AB, BA

Treatments: (Fasted)
A: PO Apixaban 10 mg (2 x 5 mg) single dose
B: PO Apixaban 10 mg (2 x 5 mg) 3 hours after PO Famotidine 40 mg

Study medication

Drug name	Apixaban	Famotdine
Dosage Form	Tablet	Tablet
Dosage Strength	5 mg	40 mg
Batch #.	7A32833 (Product batch#)	clinical site sourced
	8F37006 (Label batch#)	--
	562247-K005-029 (Product Identification#)	--
Administration	Oral	Oral

PK Sampling (Blood)

Apixaban: Pre-dose, 0.5, 1, 2, 3, 4, 6, 12, 24, 36, 48 and 60 hours post-dose

Analytical Method

The performance of the assay method during study sample analysis is acceptable and is summarized in the table below.

Table 9.1: Summary of Assay and Performance for Apixaban in Plasma

Analyte	LLOQ (ng/mL)	ULOQ (ng/mL)	Between-Run %CV[a]	Within-Run %CV[a]	Mean % Deviation from Nominal Concentration
Apixaban	1.00	1000	≤ 5.95	≤ 11.9	± 9.55

Source: Appendix 8
[a] Maximum value from analytical QC samples
LLOQ = lower limit of quantitation; ULOQ = upper limit of quantitation; CV = coefficient of variation

Statistical Method: The 90% confidence intervals for the ratios of the geometric means for

apixaban Cmax and AUCinf with and without famotidine were constructed. The equivalence interval was set to be from 80% to 125%.

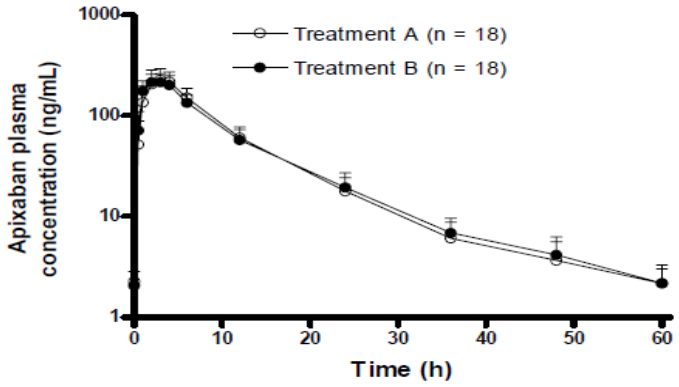
Study Population :

Enrolled/Completed/ Discontinued Due to AE	18/18
Age [Mean (range)]	34 (20-44) yr
Male/Female	14/4
Race (Caucasian)	18

Results

Apixaban Pharmacokinetics

- Administration of famotidine (40 mg, single oral dose 3 hours before administration of apixaban) does not affect the pharmacokinetics of apixaban.



Treatments: A = Apixaban 10 mg
B = Apixaban 10 mg + famotidine 40 mg

Table 5 : Summary Statistics for Apixaban Pharmacokinetic Parameters

Treatment	Apixaban Pharmacokinetic Parameters				
	Cmax (ng/mL)	Tmax (hours)	AUC(INF) (ng·h/mL)	AUC(0-T) (ng·h/mL)	T-Half (h)
	Geometric Mean (%CV)	Median (Min, Max)	Geometric Mean (%CV)	Geometric Mean (%CV)	Mean (SD)
A (n = 18)	230 (28)	3.00 (1.00, 5.98)	2222 (25)	2193 (26)	9.2 (4.42)
B (n = 18)	225 (20)	2.01 (1.00, 4.02)	2237 (20)	2198 (20)	11.0 (4.61)

A = Apixaban 10 mg
B = Apixaban 10 mg + famotidine 40 mg
CV = coefficient of variation; SD = standard deviation

Safety: Was there any death or serious adverse events? ☐ Yes ☒No ☐ NA

Conclusion

Concomitant administration of famotidine had no effect on the bioavailability of apixaban, hence no dose adjustment is warranted.

4.1.5 INTRINSIC FACTORS

Age and Gender Effect

Report # CV185022	**Study Period** 05/04/05-11/27/05
Title	Effects of Age and Gender on the Single-Dose Pharmacokinetics of BMS-562247 in Healthy Subjects

EDR Link \\Cdsesub1\evsprod\NDA202155\\0001\m5\53-clin-stud-rep\533-rep-human-pk-stud\5333-intrin-factor-pk-stud-rep\cv185022\cv185022.pdf

Study Design

Single-Dose	Non-Randomized	Open-Label	Parallel	Multi-Center	
No. of Groups	**4**	☑ Young males (18-40 yrs)	☑Young females (18-40 yrs)	☑Old females (18-40 yrs)	☑ Old females (>65 yrs)
No. of Subject /Completed	**79/79**	20	20	20	19
Age, Mean(range)		31(21-40)	34(21-40)	71(65-79)	69(65-76)
Body Weight, kg, Mean(range)		76.8 (60.0-97.0)	65.3 (53.7-86.0)	78.9 (55.0-114)	70.2 (54.0-89.0)
Dose	20 mg	20 mg	20 mg	20 mg	20 mg
Sampling Times: PK, PD, plasma: Pre-dose and 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 18, 24, 36, 48, 72 and 96 hours post dose.					

Each subject received a single oral dose of a 20 mg apixaban tablet.

Table 5.5.2: Drug Information

Unit	Formulation	Product ID Number	Route	Product Batch Number	Label Batch Number
20 mg	apixaban tablet	562247-A020-011	Oral	3A70866	3K76731

- The selected dose is acceptable ☑ Yes ☐ No
- Dosing is long enough to obtain steady state ☐ Yes ☐ No☑ Not Applicable
- Sample size was determined based on statistical analysis ☑ Yes ☐ No
- The overall study design acceptable: ☑ Yes ☐ No

Analytical Method (Study Samples Analysis)

- Study samples were analyzed within the established stability period: ☑ Yes ☐ No
- Quality control samples range is acceptable ☑ Yes ☐ No
- Internal standard was used ☑ Yes ☐ No
- Method was validated prior to use ☑ Yes ☐ No
- Chromatograms were provided ☑ Yes ☐ No
- Overall performance is acceptable ☑ Yes ☐ No

LC/MS/MS methods were utilized for determination of apixaban in plasma and urine. Assay performances are provided below:

Analyte	**Apixaban**	
Method	LC-API/MS/MS	LC-API /MS/MS
Matrix	Plasma	Urine
LOQ (ng/mL)	1.00	1.00
Range (ng/mL)	1.00 to 1000	1.00 to 1000
QCs (ng/mL)	3.00, 35.0, 400, 800	3.00, 35.0, 400, 750
Accuracy/Bias	16.2%	12.4 %
Precision (CV%)	9.49%	3.65 %

Pharmacokinetics

Figure 11.2.1A: Mean Apixaban Plasma Concentration vs Time Profiles by Age and Gender Group

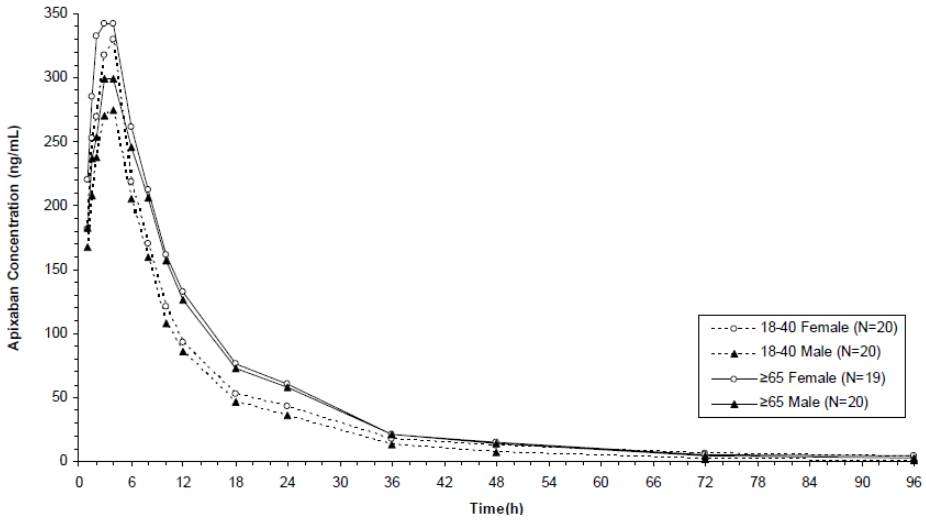


Table 11.2.1A: Summary Statistics for Apixaban Pharmacokinetic Parameters by Age Group

Pharmacokinetic Variable	**Age Group**	
	Young (18-40 Years) (n = 40)	**Elderly (≥ 65 Years) (n = 39)**
Cmax (ng/mL) Geom. Mean (CV%)	315.4 (34)	336.9 (27)
AUC(INF) (ng·h/mL) Geom. Mean (CV %)	3424[a] (32)	4536 (23)
AUC(0-T) (ng·h/mL) Geom. Mean (CV%)	3360 (32)	4451 (23)
Tmax (h) Median (Min, Max)	3.00 (1.0, 4.0)	3.00 (1.0, 4.0)
T1/2(h) Mean (SD)	11.98[a] (5.15)	15.45 (7.39)
CLR (L/h) Mean (SD)	0.63 (0.33)	0.45 (0.13)
%UR Mean (SD)	10.43 (5.40)	10.18 (3.37)

Source: Supplemental Table S.11.2.1B

[a] n = 39

Table 11.2.1B: Summary Statistics for Apixaban Pharmacokinetic Parameters by Gender Group

Pharmacokinetic Variable	Gender Group	
	Female (n = 39)	Male (n = 40)
Cmax (ng/mL) Geom. Mean (CV%)	353.4 (31)	301.0 (26)
AUC(INF) (ng·h/mL) Geom. Mean (CV%)	4235[a] (28)	3680 (30)
AUC(0-T) (ng·h/mL) Geom. Mean (CV%)	4116 (29)	3626 (30)
Tmax (h) Median (Min, Max)	3.00 (1.0, 4.0)	3.00 (1.0, 4.0)
T1/2(h) Mean (SD)	14.89[a] (7.06)	12.60 (5.92)
CLR (L/h) Mean (SD)	0.46 (0.18)	0.62 (0.31)
%UR Mean (SD)	9.50 (3.37)	11.09 (5.28)

Source: Supplemental Table S.11.2.1B

[a] n = 38

Table 11.2.1C: Results of Statistical Analyses for Apixaban Cmax and AUC(INF) by Age and Gender

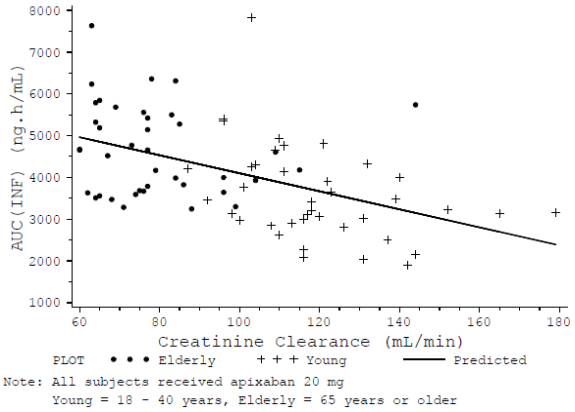
Age/ Gender	Pharmacokinetic Variable	Adjusted Geometric Means		Ratio of Geometric Means		
		Group[+]	Mean	Ratio	Point Estimate	90% Confidence Limits
Age	Cmax (ng/mL)	Young	315.4	Elderly/Young	1.07	(0.96, 1.19)
		Elderly	337.6			
	AUC(INF) (ng.h/mL)	Young	3433	Elderly/Young	1.32	(1.20, 1.46)
		Elderly	4541			
Gender	Cmax (ng/mL)	Male	301.0	Female/Male	1.18	(1.06, 1.31)
		Female	353.7			
	AUC(INF) (ng.h/mL)	Male	3680	Female/Male	1.15	(1.04, 1.27)
		Female	4235			

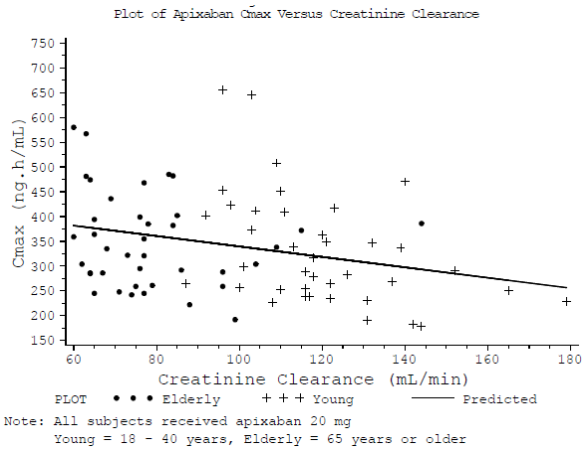
- The geometric mean AUC(INF) for elderly subjects is 32% higher.
- Female subjects have higher geometric mean Cmax and AUC(INF), 18% and 15% respectively, compared to male subjects.
- The effects of age and gender were independent of each other. For both Cmax and AUC(INF), age by gender interaction was insignificant (p-value: 0.94 for Cmax and 0.40 for AUC(INF)).

Reviewer's note: The slightly higher exposure in females might just be the effect of body weight asin this study, females are ~10 kg lower than males in both age groups.

Relationship between PK and creatinine clearance

Figure 11.2.1D **Linear Regression of AUC(INF) of Apixaban vs. Creatinine Clearance in Elderly and Young Subjects**



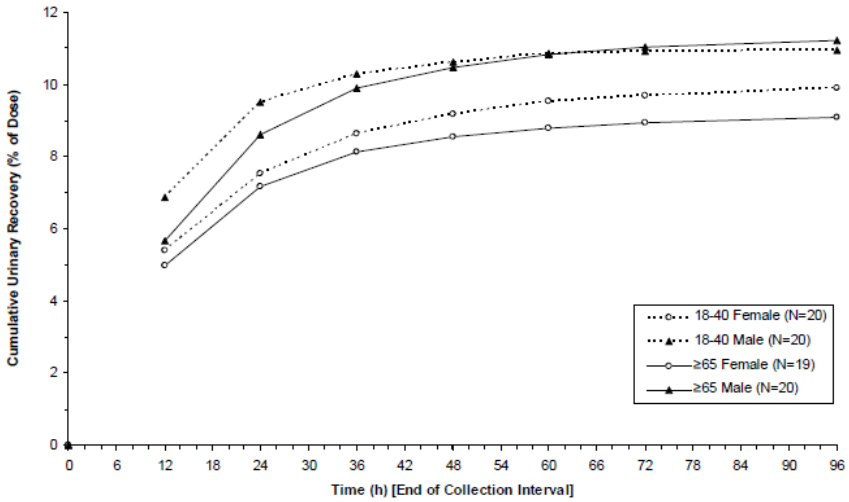


- Both apixaban AUC(INF) and Cmax showed linearly decreasing trends versus creatinine clearance.
- There appears to be a trend in mean renal clearance across groups where CLR was greatest in young males (0.72 L/h) and lowest in elderly females (0.38 L/h).
- The sponsor stated that differences in creatinine clearance may play a role in the differences observed between groups.

Reviewer's note: As the range of creatinine clearance reported here are within relatively normal range (>60 mL/min to 180 mL/min), not much can be concluded and applied based on this result. In addition, based on the renal impairment study, mild impairment doesn't cause significant exposure change while at the extreme renal function at CLcr 15 mL/min, the magnitude of PK change is ~ 40%. The utility of the renal function in dose adjustment require further evaluations.

Renal clearance

Figure 11.2.2: **Mean Apixaban Cumulative Urinary Recovery vs. Time Profiles by Age and Gender Group**



- Mean %UR and CLR were numerically greater in male subjects, particularly in young male subjects.

Pharmacodynamics

mPT and Anti-Xa

Figure 11.3.2B Scatter Plot of Individual mPT Versus Apixaban Plasma Concentration

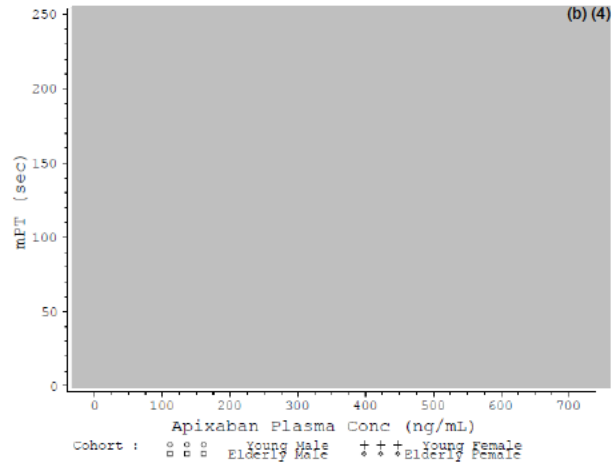
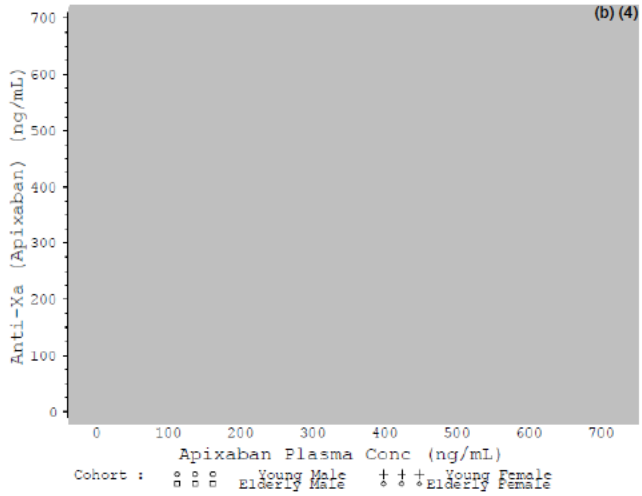


Figure 11.3.3.1B Scatter Plot of Individual Anti-Xa (Apixaban) Versus Apixaban Plasma Concentration



- Linear relationships between apixaban concentrations and INR, mPT and anti-Xa were observed.
- However, the variability in INR, mPT is higher than that of anti-Xa.

Safety

Was there any death or serious adverse events? ☐ Yes ☑ No ☐ NA

Conclusions

Is there is a need to adjust the dose based on age or gender? ☐ Yes ☑ No
Dose adjustment based solely on age or gender is not necessary; however, combination of additional risk factors might lead to dose adjustment.

- There was no effect of age on the Cmax of apixaban. AUC(INF) was 32% higher in elderly subjects.
- The 90% CI for apixaban Cmax and AUC(INF) by gender were outside the 80% to 125% no effect criteria. Apixaban Cmax and AUC(INF) of apixaban were 18 and 15% higher in females, respectively.
- Modest differences in the profiles of INR, mPT, and anti-Xa activity for age and gender groups appeared to be related to observed differences in apixaban PK.

Comments

Age and renal function are confounding. Effect of either one of them cannot be clearly distinguished.

Renal Impairment

Report # CV185018	**Study Period** 09/14/05-09/05/08
Title	The Safety, Pharmacokinetics, and Pharmacodynamics of BMS-562247 (Apixaban) in Subjects with Normal Renal Function or Mild, Moderate, or Severe Renal Impairment

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Study Design

Single-Dose	Non-Randomized	Open-Label		Parallel		Multi-Center (7)
No. of Groups	**4**	☑Normal	☑Mild	☑Moderate	☑Sever	☐ESRD
No. of Subject /Completed	**32/32**	8	10	7	7	
Males/Females	**18/14**	3/5	4/6	6/1	5/2	
Age, Mean(range)		59(56-62)	61(35-76)	68(51-85)	65(53-74)	
Body Weight, kg, Mean(range)		83.3 (66.2-92.8)	79.3 (60.0-112.4)	74.5 (58.9-103.7)	84.1 (59.0-132.3)	
Dose	10 mg	10 mg	10 mg	10 mg	10 mg	
Sampling Times: PK, plasma: Pre-dose and 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, 18, 24, 36, 48, 72 and 96 hours post dose.						
Enrollment and pre-classification of subjects into renal function groups was based upon the estimated CLcr value determined using Cockcroft-Gault formula at the time of screening. The 24-hr CLcr value obtained on Day 1 was used for final classification and statistical analysis.						

Table 1: Drug Information

Unit	Route	Product ID Number	Label Batch Number	Product Batch Number
Apixaban 2.5 mg coated tablet	Oral	562247-A2X5-010	6D20372	6D20372
Apixaban 5 mg coated tablets	Oral	562247-A005-002	3K76734	2K64989
Omnipaque® 300mg/mL solution	IV	10292979, 10416644, 320353F, 10628180, 10545796	NA	NA
Omnipaque® 180 mg/mL solution	IV	10257660	NA	NA

Two strengths of the drugs were used in the study.

- Classification of renal function is consistent with the FDA Guidance Recommendations:

☑ Yes ☐ No (Old Guidance 1998, classification shown below)

Group	Description	Creatinine Clearance (CLcr)
A	Normal renal function	> 80 mL/min
B	Mild renal function impairment	> 50 and ≤ 80 mL/min
C	Moderate renal function impairment	≥ 30 and ≤ 50 mL/min
D	Severe renal function impairment	< 30 mL/min

- Renal function was determined via ☑ G-C formula ☐ MDRD formula
- Renal function was determined at: ☑ Screening ☑Baseline
- The control group is adequate ☑ Yes ☐ No
- The groups are matched by☑ Age ☑ Sex ☑ Body Weight ☐ Smoking Status ☐ Race
- The selected dose is acceptable ☑ Yes ☐ No
- Protein Binding: not evaluated in this study
- Dosing is long enough to obtain steady state ☐ Yes ☐ No☑ Not Applicable
- Sample size was determined based on statistical analysis ☑ Yes ☐ No
- The overall study design acceptable: ☑ Yes ☐ No

Analytical Method (Study Samples Analysis)

- Study samples were analyzed within the established stability period: (With one exception for subject CV185018-3-15) ☑ Yes ☐ No
- Quality control samples range is acceptable ☑ Yes ☐ No
- Internal standard was used ☑ Yes ☐ No
- Method was validated prior to use ☑ Yes ☐ No
- Chromatograms were provided ☑ Yes ☐ No
- Overall performance is acceptable ☑ Yes ☐ No

LC/MS/MS methods were utilized for determination of apixaban, its metabolite, BMS-730823 (M1) and iohexol. Assay performances are provided below:

Table 9.1A: Summary of Assay and Performance for Apixaban (BMS-562247) and BMS-730823 in Plasma and Urine

Analyte	Matrix	LLOQ (ng/mL)	ULOQ (ng/mL)	Between-run %CV[a]	Within-run %CV[a]	Mean % Deviation from Nominal Concentration[a]
BMS-562247	Plasma	1.00	1000	≤ 6.29	≤ 5.03	± 5.02
BMS-730823	Plasma	5.00	250	≤ 6.37	≤ 7.55	± 3.21
BMS-562247	Urine	1.00	1000	≤ 11.2	≤ 26.6	± 5.19
BMS-730823	Urine	5.00	250	≤ 15.1	≤ 30.7	± 3.07

Table 9.1B: Summary of Assay and Performance for Iohexol in Plasma

Analyte	LLOQ (µg/mL)	ULOQ (µg /mL)	Between-run %CV[a]	Within-run %CV[a]	Mean % Deviation from Nominal Concentration[a]
Iohexol	1.00	500	≤ 1.9	≤ 13.9	± 5.5

Classification of renal function

Four methods for CLcr estimation were used and comparison is shown below:

Table 5.3.2: Summary of Baseline (Day 1) Renal Function Assessments

Renal Function Group	24-hr CLcr (mL/min) Mean (SD) Range	Cockcroft-Gault Estimated CLcr (mL/min) Mean (SD) Range	MDRD Estimated CLcr (mL/min) Mean (SD) Range	Iohexol Clearance (mL/min) Mean (SD) Range
Normal (n= 8)	106.7 (14.3)	98.9 (11.2)	80.7 (5.6)	112.5 (17.6)
	88.2 - 126.7	80.2 - 112.4	72.3 - 89.3	94 - 143.7
Mild (n=10)	58.8 (8.1)	53.7 (9.8)	49.3 (12.8)	50.2 (10.4)
	50.6 - 76	40.0 - 62.9	29.4 - 70.2	40.6 - 69
Moderate (n= 7)	38.0 (6.4)	41.1 (11)	44.7 (19.3)	42.5 (22.7)
	31.3 - 46.4	23.8 - 56.5	18.1 - 74	14 - 81
Severe (n=7)	24.5 (4.1)	23.7 (5.0)	19.2 (6.7)	19.1[a] (4.5)
	15.7 - 28.0	15.1 - 28.8	11.8 - 31.4	13.8 - 24.2

Figure 5.3.2A: Scatter Plot of Cockcroft-Gault Estimated CLcr versus 24-hr CLcr

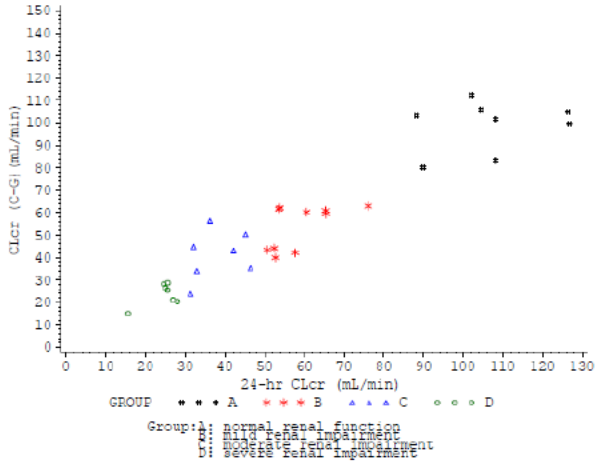
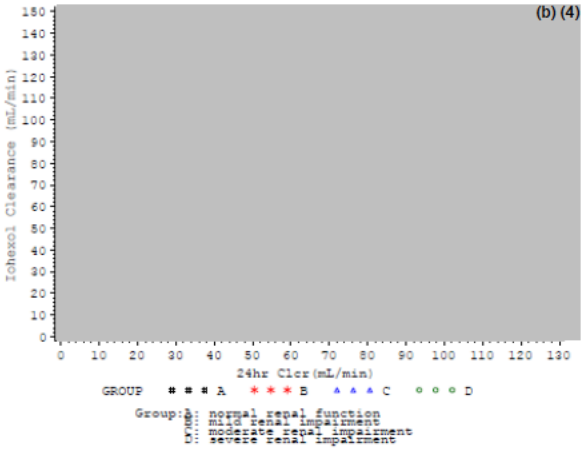


Figure 5.3.2C: Scatter Plot of Iohexol Total Body Clearance versus 24-hr Creatinine Clearance



- Cockcroft-Gault formula was used for pre-classification of subjects into renal function groups and the 24-hr CLcr value obtained on Day 1 was used for final classification and statistical analysis.
- These methods are generally comparable with Iohexol clearance correlated best with 24-hr CLcr and MDRD tend to under estimate at higher CLcr range.

Pharmacokinetics

1. Is there a relationship between creatinine clearance and AUC? ☒ Yes ☐ No, if yes explain
2. Is there a relationship between creatinine clearance and C_{max}? ☐ Yes ☒ No, if yes explain

Figure 9.2C: Scatter Plot of Apixaban Cmax versus 24-hr CLcr

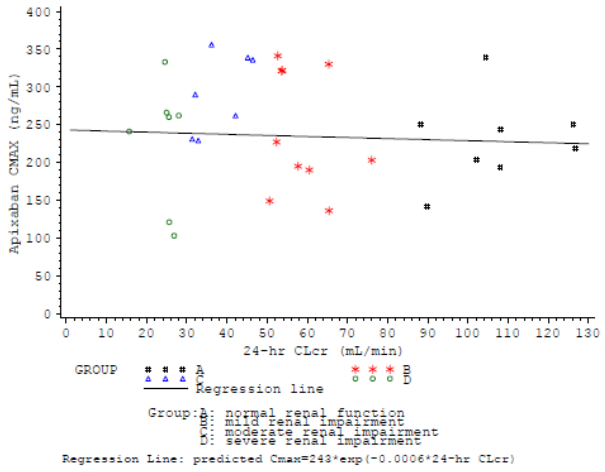
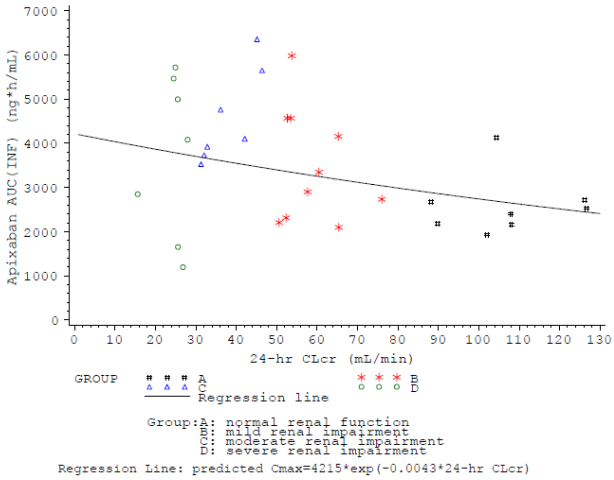


Figure 9.2D: Scatter Plot of Apixaban AUC(INF) versus 24-hr CLcr



- Apixaban Cmax was not influenced by renal function.
- Apixaban AUC increased with decreased renal function.

Figure 9.2A: Mean (+SD) Plasma Concentration-Time Profiles for Apixaban by Renal Function Group (Linear Scale)

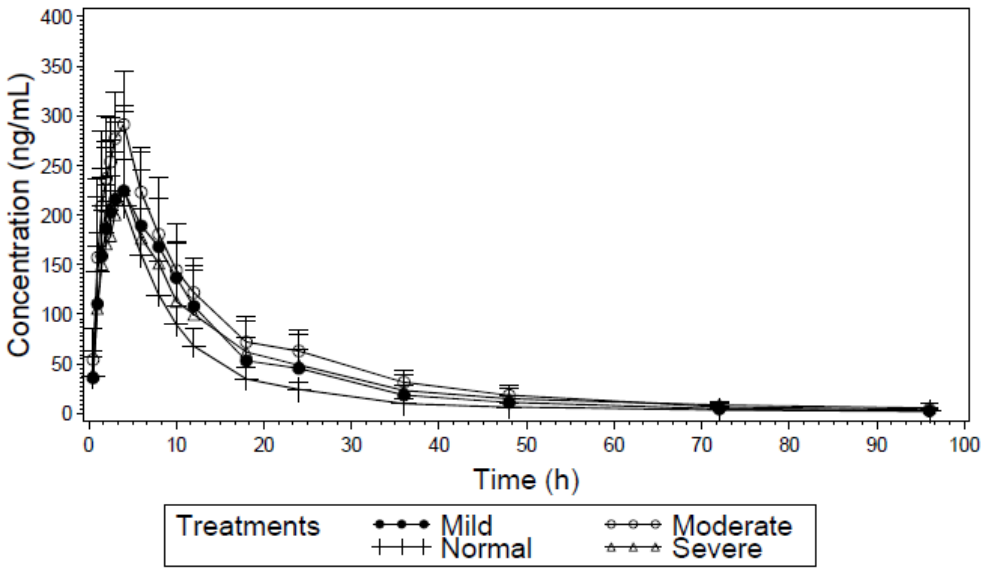


Table 9.2A: Summary Statistics for Apixaban Pharmacokinetic Parameters by Renal Function Group

Renal Function Group	Apixaban Pharmacokinetic Parameters							
	Cmax (ng/mL)	Tmax (h)	AUC (INF) (ng·h/mL)	AUC (0-T) (ng·h/mL)	T-HALF (h)	CLT/F (mL/min)	CLR (mL/min)	%UR (%)
Normal (n = 8)	224 (25)	2.75 (2 - 4)	2528 (26)	2469 (27)	15.1 (7.6)	65.9 (20)	6.83 (33)	10.42 (2.66)
Mild (n = 10)	229 (33)	4 (1 - 6)	3288 (37)	3226 (38)	14.6 (7.3)	50.7 (34)	3.81 (53)	9.36 (6.23)
Moderate (n = 7)	288 (18)	4 (3.1 - 4)	4479 (23)	4387 (23)	17.6 (6.0)	37.2 (21)	1.94 (89)	7.18 (6.53)
Severe (n = 7)	210 (37)	4 (3 - 4)	3221 (49)	3115 (49)	17.3 (7.4)	51.7 (69)	1.94 (45)	4.65 (3.34)

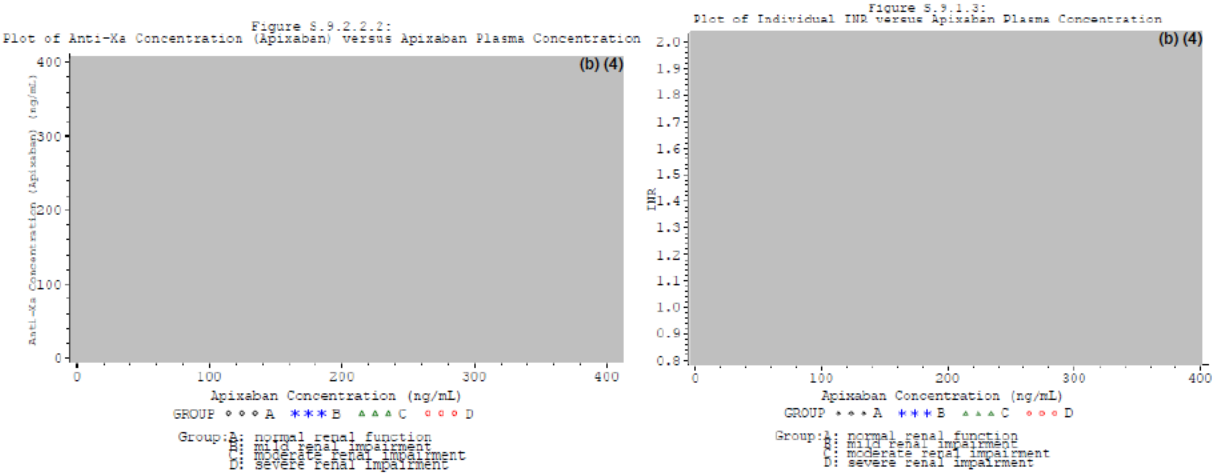
Note: Results are presented as geometric mean (%CV) except for Tmax which is presented as median (min-max) and T-HALF and %UR which are presented as mean (SD).

Table 9.2.C: Results of Statistical Analysis of Apixaban Cmax, AUC(INF) and AUC(0-T) Based on the Regression Model

Pharmacokinetic Variable	24-hour CLcr (mL/min)	Predicted Geometric Mean	Ratio of Predicted Geometric Means		
			Comparison	GMR	90% CI
Cmax (ng/mL)	100	230			
	65	234	65 vs. 100	1.020	(0.914, 1.138)
	40	238	40 vs. 100	1.034	(0.857, 1.249)
	25	240	25 vs. 100	1.043	(0.824, 1.320)
	15	241	15 vs. 100	1.049	(0.803, 1.370)
AUC(INF) (ng·h/mL)	100	2749			
	65	3193	65 vs. 100	1.161	(1.017, 1.325)
	40	3552	40 vs. 100	1.292	(1.030, 1.621)
	25	3788	25 vs. 100	1.378	(1.038, 1.829)
	15	3953	15 vs. 100	1.438	(1.043, 1.982)
AUC(0-T) (ng·h/mL)	100	2690			
	65	3118	65 vs. 100	1.159	(1.015, 1.325)
	40	3466	40 vs. 100	1.289	(1.025, 1.619)
	25	3693	25 vs. 100	1.373	(1.032, 1.827)
	15	3852	15 vs. 100	1.432	(1.036, 1.979)

- When compared with subjects with normal renal function, apixaban AUC increased approximately 16 %, 29 %, 37 % and 43 % in subjects with CLcr of 65 mL/min, 40 mL/min, 25 mL/min and 15 mL/min, respectively.

Pharmacodynamics



- Good correlation was observed between apixaban concentrations and anti-Xa concentrations.
- A correlation between apixaban concentrations and INR was also observed with a shallow relationship.

Metabolite (M1, BMS-730823)

Figure 9.3A: Mean (+SD) Plasma Concentration-Time Profiles for BMS-730823 by Renal Function Group (linear scale)

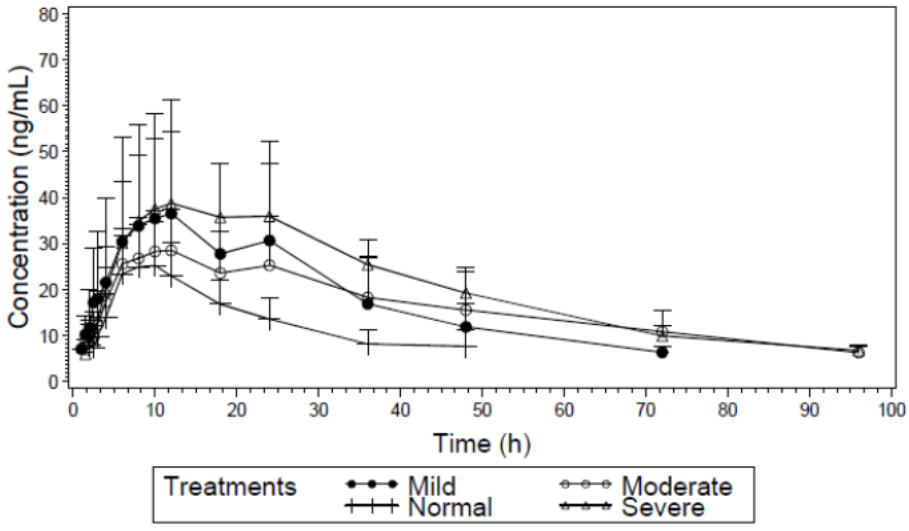


Table 9.3A: Summary Statistics for BMS-730823 Pharmacokinetic Parameters by Renal Function Group

Renal Function Group	BMS-730823 Pharmacokinetic Parameters							
	Cmax (ng/mL)	Tmax (h)	AUC(INF) (ng·h/mL)	AUC(0-T) (ng·h/mL)	T-HALF (h)	CLR (mL/min)	%UR (%)	MR*
Normal (n = 8)	25.3 (35)	10 (8 - 12)	686 (38)	521 (37)	16.1 (5.7)	2.71 (47)	0.73 (0.45)	0.24 (28)
Mild (n = 10)	32.1 (64)	11 (8 - 24)	1284 (52)	992 (64)	21.9 (7.9)	2.07 (76)	1.26 (1.06)	0.34 (63)
Moderate (n = 7)	29.3 (31)	10 (6 - 12)	1374 (48)	1093 (58)	24.5 (7.2)	0.49 (107)	0.42 (0.34)	0.27 (49)
Severe (n = 7)	38.0 (36)	12 (8 - 24)	2076 (23)	1750 (28)	28.4 (4.3)	0.48 (77)	0.76 (0.66)	0.56 (46)

Note: *MR=Metabolic Ratio of Metabolite: Parent

Results are presented as geometric mean (CV%) except for Tmax which is presented as median (min-max) and T-HALF and %UR which are presented as mean (SD).

Table 9.3C: Results of Statistical Analysis of BMS-730823 Cmax, AUC(INF) and AUC(0-T) Based on the Regression Model

Pharmacokinetic Variable	24-hour CLcr (mL/min)	Predicted Geometric Mean	Ratio of Predicted Geometric Means		
			Comparison	GMR	90% CI
Cmax (ng/mL)	100	25.5			
	65	29.9	65 vs. 100	1.171	(1.014, 1.351)
	40	33.4	40 vs. 100	1.310	(1.024, 1.676)
	25	35.8	25 vs. 100	1.402	(1.031, 1.907)
	15	37.4	15 vs. 100	1.466	(1.035, 2.078)
AUC(INF) (ng·h/mL)	100	763			
	65	1150	65 vs. 100	1.506	(1.314, 1.725)
	40	1540	40 vs. 100	2.017	(1.597, 2.547)
	25	1835	25 vs. 100	2.404	(1.796, 3.218)
	15	2063	15 vs. 100	2.702	(1.942, 3.761)
AUC(0-T) (ng·h/mL)	100	569			
	65	899	65 vs. 100	1.580	(1.345, 1.858)
	40	1247	40 vs. 100	2.192	(1.662, 2.891)
	25	1518	25 vs. 100	2.667	(1.868, 3.770)
	15	1730	15 vs. 100	3.039	(2.053, 4.500)

- T-half of M1 appeared to increase with severity of renal impairment from 16 hr (normal) to 28 hr (severe).
- Cmax of M1 increased up to 47 % while AUC increased up to ~3 fold at CLcr of 15 mL/min. However, as M1 is inactive and the level of M1 observed in this study is lower than that observed in the toxicological study in animals, the PK changes is not expected to have clinically meaningful impact.

Safety

Was there any death or serious adverse events? ☐ Yes ☑ No ☐ NA

Conclusions

Is there is a need to adjust the dose in patients with renal impairment? ☐ Yes ☑ No
Dose adjustment based solely on renal function may not be warranted; however, combination of additional risk factors might lead to dose adjustment.

- Apixaban exposure gradually increased with an increased degree of renal impairment, and was modestly higher (<50%) in subjects at the extreme end (CLcr = 15 mL/min) of the severe renal impairment group.
- The increases in BMS-730823 Cmax and AUC were more pronounced, up to ~3-fold for mean AUC, with declining renal function. As M1 is inactive and the level of M1 observed in this study is lower than that observed in the toxicological study in animals, the PK changes is not expected to have clinically meaningful impact.
- A single 10 mg oral dose of apixaban was safe and well tolerated in this study.
- Renal impairment did not appear to affect the direct relationship between apixaban plasma concentration and anti-Xa activity or INR.
- Changes in anti-Xa activity were closely related to the increase in apixaban plasma concentration observed with the increasing severity of the renal impairment and those changes were less variable than changes observed for INR.
- The assessment of renal function measured by Cockcroft-Gault, the Modified Diet in Renal Disease and iohexol total body clearance was in general agreement with that determined by 24-hr CLcr and the same trends observed between 24-hr CLcr and apixaban exposure were also observed with these alternative assessments of renal function.

Reviewer Comments

There are several issues for this study: 1) The study started in 2005 but ended in 2008. It is very unusual for a small study to complete in such long time frame. It would be expected to have much greater variability in the study conduct when it lasted for too long. 2) The study completed 32 subjects but was conducted in 7 clinical sites (93 screen failure). It is again not common for a small study to be conducted in many sites. This factor alone is not a major problem but could easily increase variability in the study conduct as controlling the consistency of study conduct in different sites is always a challenge. 3) Two strengths of the drug were used in this study by either 2 x 5 mg tablets or 4 x 2.5 mg tablets. No rationale was provided for using 2 strengths. 4) There were mislabeled and missing samples. In one subject, 2 pre-dose samples were received and one 10 hr post dose sample was missing. The sponsor stated that one of the pre-dose samples is likely the 10 hr sample based on the plasma concentration but this cannot be confirmed. In another subject, pre-dose apixaban concentration is > 20 % higher than the Cmax. Although both data were excluded, these raise a flag that the reliability of the study result might be questionable.

Hepatic Impairment

Report # CV185025	**Study Period** 12/04/06-12/02/07
Title	Single-Dose Safety and Pharmacokinetics of Apixaban in Subjects with Hepatic Impairment Compared to Healthy Subjects

EDR Link \\Cdsesub1\evsprod\NDA202155\\0001\m5\53-clin-stud-rep\533-rep-human-pk-stud\5333-intrin-factor-pk-stud-rep\cv185025\cv185025.pdf

Study Design

Single-Dose	Non-Randomized		Open-Label	Parallel		Multi-Center (3)
No. of Groups	**3**	☑Normal	☑Mild	☑Moderate	☐ Severe	Total
No. of Subject /Completed	**32**	16	8	8		73
Males/Females	**18/14**	9/7	4/4	5/3		
Age, Mean(range)		48(36-60)	52(44-64)	50(44-59)		
Dose	5 mg	5 mg	5 mg	5 mg		

Drug information:

Table 5.5.2A: Apixaban Information

Unit	Route	Product ID Number	Label Batch Number	Product Batch Number
BMS-562247 2.5 mg coated tablet	Oral	562247-K2X5-025	6F13211	6E17717

- Sampling Times:
  - PK, plasma: 0, 1, 2, 2.5, 3, 3.5, 4, 6, 8, 12, 16, 24, 30, 36, 48, 60, 72 and 96 hours post dose.
  - PD, plasma: 0, 3, 3.5, 6, 12, 24, 48, 72 and 96 hours post dose.
  - Protein Binding: ☑All ☐Limited (in all subjects)
    Sampling Times: 3 hrs post dosing
    Method: equilibrium dialysis
- Classification of hepatic function is consistent with the FDA Guidance Recommendations: ☑ Yes ☐ No
- Hepatic function was determined via Child-Pugh classification ☑ Yes ☐ No
- Hepatic function was determined at: ☑ Screening ☑Baseline
- The control group is adequate ☑ Yes ☐ No
- The groups are matched by☑ Age ☑ Sex ☑ Body Weight ☑ Smoking Status ☐ Race
- The selected dose is acceptable ☑ Yes ☐ No
- Dosing is long enough to obtain steady state ☐ Yes ☐ No☑ Not Applicable
- Sample size was determined based on statistical analysis ☑ Yes ☐ No
- The overall study design acceptable: ☑ Yes ☐ No

Analytical Method (Study Samples Analysis)

- Study samples were analyzed within the established stability period: ☑ Yes ☐ No
- Quality control samples range is acceptable ☑ Yes ☐ No
- Internal standard was used ☑ Yes ☐ No
- Method was validated prior to use ☑ Yes ☐ No
- Chromatograms were provided ☑ Yes ☐ No
- Overall performance is acceptable ☑ Yes ☐ No

Table 11.1A: Summary of Assay and Performance for Apixaban in Human Plasma

Analyte	LLQ (ng/mL)	ULQ (ng/mL)	Between-run %CV	Within-run %CV	Mean % Deviation from Nominal Concentration
Apixaban	1.00	1000	≤ 12.5 (≤ 156 with outlier included)[a]	≤ 15.2 (≤ 116 with outlier included)[a]	± 3.52 (± 51.2 with outlier included)[a]

Source: Appendix 5.10.3A

[a] Calculated value fails to meet method acceptance criteria due to possible sample preparation or analysis error. Value is excluded from statistics. Statistics in parenthesis are calculated including the values outside of method criteria.

Table 11.1B: Summary of Assay and Performance for Apixaban and M1 in Human Urine

Analyte	LLQ (ng/mL)	ULQ (ng/mL)	Between-run %CV	Within-run %CV	Mean % Deviation from Nominal Concentration
Apixaban	1.00	1000	≤ 4.52	≤ 2.44	± 6.89
M1	5.00	1000	≤ 6.28	≤ 11.2	± 6.00

Pharmacokinetics

Figure 1: Mean Apixaban Plasma Concentration vs Time by Treatment

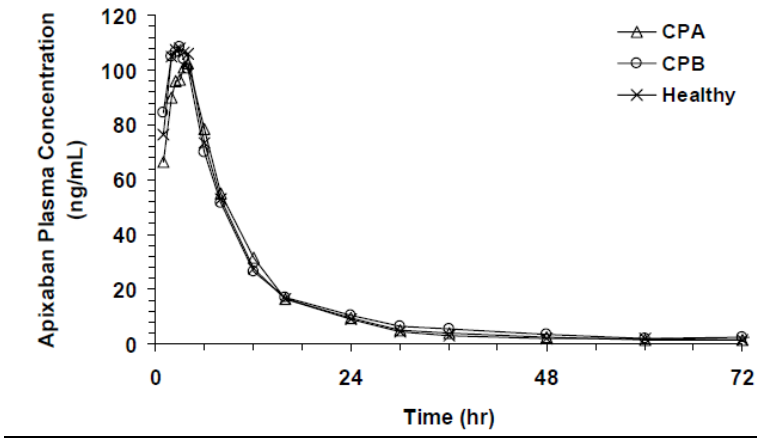


Table 4: Summary Statistics for Apixaban Pharmacokinetic Parameters by Hepatic Function Group

Hepatic Function Group	Apixaban Pharmacokinetic Parameters								
	Cmax (ng/mL) Geom. Mean (CV%)	Tmax (h) Median (Min, Max)	AUC (INF) (ng·h/mL) Geom. Mean (CV%)	AUC (0-T) (ng·h/mL) Geom. Mean (CV%)	CLT/F (L/hr) Geom. Mean (CV%)	CLR (L/hr) Geom. Mean (CV%)	%UR (%) Mean (SD)	T-HALF (h) Mean (SD)	MR[a] Geom. Mean (CV%)
Treatment Group A (n = 8)	104 (29)	3.25 (2.00, 4.00)	1083 (30)	1054 (30)	4.62 (34)	0.89 (29)	19.4 (4.8)	14.7 (7.0)	0.13 (72)
Treatment Group B (n = 8)	115 (25)	3.00 (2.00, 4.00)	1152 (28)	1116 (27)	4.34 (41)	0.56 (49)	13.8 (5.5)	17.1 (16.8)	0.16 (75)
Treatment Group C (n = 16)[b]	123 (26)	2.50 (1.00, 4.00)	1054 (35)	1021 (37)	4.74 (35)	0.59 (41)	12.8 (4.6)	14.8 (10.2)	0.08 (102)

[a] MR (molar ratio of M1 metabolite / apixaban recovered in urine)

[b] n=15 for MR

Treatment Group A: Mild hepatic impairment (Child-Pugh class A)
B: Moderate hepatic impairment (Child-Pugh class B)
C: Healthy subjects

Statistical analysis of the pharmacokinetics parameters of apixaban is shown below.

Table 5: Results of Statistical Analyses of Apixaban Cmax, AUC(INF) and AUC(0-T)

Pharmacokinetic Variable	Group	Adjusted Geometric Mean	Ratio of Geometric Means	Point Estimate	90% C.I.
Cmax (ng/mL)	Treatment Group A (n = 8)	104.3	CPA vs. Healthy	0.85	(0.69, 1.05)
	Treatment Group B (n = 8)	115.3	CPB vs. Healthy	0.94	(0.76, 1.16)
	Treatment Group C (n = 16)	122.9			
AUC(INF) (ng·h/mL)	Treatment Group A (n = 8)	1082.8	CPA vs. Healthy	1.03	(0.80, 1.32)
	Treatment Group B (n = 8)	1152.1	CPB vs. Healthy	1.09	(0.85, 1.41)
	Treatment Group C (n = 16)	1054.3			
AUC(0-T) (ng·h/mL)	Treatment Group A (n = 8)	1053.9	CPA vs. Healthy	1.03	(0.80, 1.33)
	Treatment Group B (n = 8)	1115.5	CPB vs. Healthy	1.09	(0.85, 1.41)
	Treatment Group C (n = 16)	1020.7			

Treatment Group A: Mild hepatic impairment (Child-Pugh class A)
B: Moderate hepatic impairment (Child-Pugh class B)
C: Healthy subjects

- There were no statistically significant differences between the healthy subjects and either of the two hepatically impaired groups.

Protein binding

Table 11.2.1C: Summary of Apixaban Protein Binding in Serum from Subjects with Hepatic Impairment and Healthy Subjects

Group	Mean Fraction Unbound (%) (SD)
Treatment Group A (n = 8)	6.8 (1.4)
Treatment Group B (n = 8)	7.9 (1.8)
Treatment Group C (n = 16)	7.1 (1.3)

Source: Appendix 11.2.1E

Treatment Group A: Mild hepatic impairment (Child-Pugh class A)
B: Moderate hepatic impairment (Child-Pugh class B)
C: Healthy subjects

- Apixaban serum protein binding was similar between healthy subjects and subjects with mild or moderate hepatic impairment.

Reviewer's note: The unbound fraction appears to be ~50% lower in this study including healthy subjects (7% vs ~13% where the sponsor stated apixaban is ~87% protein bound). No explanation was provided. The assay method and results don't seem to have major problems.

Pharmacodynamics

INR

Figure 11.3.1: Plot of Mean INR Percent Change From Baseline Profile

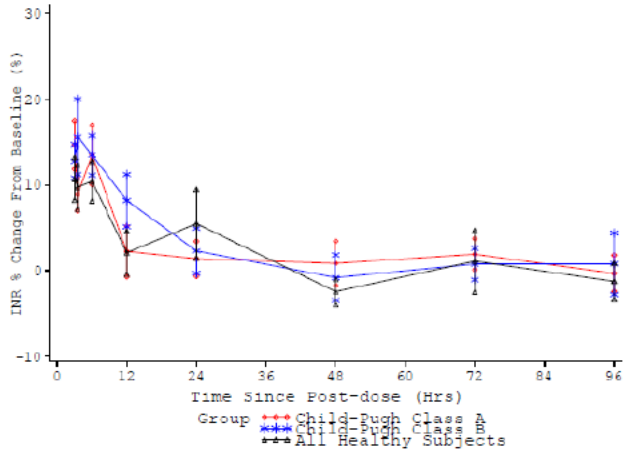
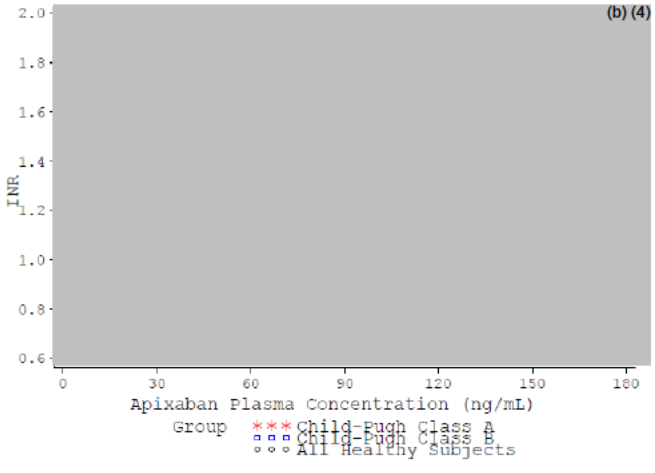


Figure 8.11.3.1C:
Plot of Individual INR and Apixaban Plasma Concentration

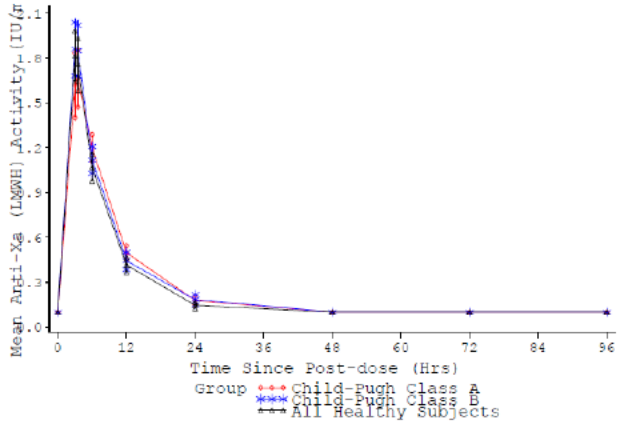


- Mean (SD) INR at baseline was 1.17 (0.19), 1.15 (0.16), and 1.04 (0.08) for CPA, CPB, and healthy subjects, respectively.
- No relevant differences among the groups with respect to changes from baseline INR were observed.

- No subject had an INR greater than or equal to 2.

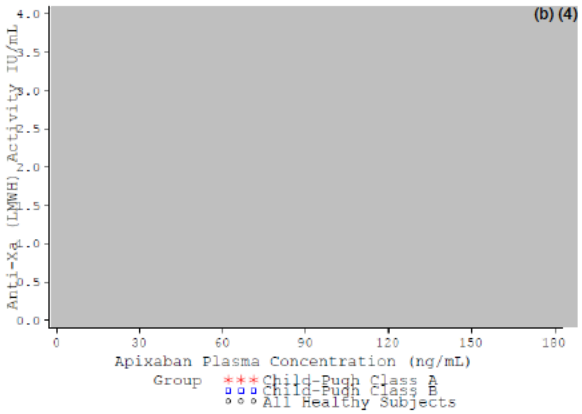
Anti-Xa

Figure 11.3.3A: Plot of Mean Anti-Xa (LMWH) Activity Profiles



Note: Values < LLQ are treated as 1/2 LLQ
Error bar represents one standard error

Figure 11.3.3B: Plot of Individual Anti-Xa (LMWH) Activity and Apixaban Plasma Concentration



Note: Anti-Xa Activity Values < LLQ are excluded

- No apparent differences in anti-Xa activity are observed in both mild and moderate hepatically-impaired groups, compared to healthy group.
- A linear relationship between anti-Xa activity and apixaban plasma concentration was observed.

Safety

Was there any death or serious adverse events? ☐ Yes ☑ No ☐ NA

- AEs are few and mostly mild.
- There were few bleeding related AEs which might be of clinical interest, 1 positive fecal occult blood (mild hepatic impaired patient) and 1 hematochezia (moderate hepatic impaired patient). All were mild in intensity and resolved without treatment.

Reviewer's note: Although these bleeding related AEs were mild, they occurred after one single dose of 5 mg apixaban. The bleeding risk after chronic use of apixaban as 5 mg BID in this patient population is unclear.

Conclusions

Should the apixaban dose be adjusted in subjects with hepatic impairment?
No dose adjustment is required for mild hepatic impairment. Recommendation for dose adjustment in patients with moderate hepatic impairment can not be provided due to insufficient clinical data and lack of understanding of the exposure-outcome relationship in patients with moderate hepatic impairment.

Body Weight

Report # CV185059	**Study Period** 11/18/08-1/26/09
Title	Effects of Body Weight on the Single-Dose Pharmacokinetics of Apixaban (BMS-562247) in Healthy Subjects

Study Design

Single-Dose	Non-Randomized	Open-Label	Parallel	Multi-Center(2 sites)	
No. of Groups	**3**	≤ 50 kg (low weight)	65-85 kg (reference group)	≥ 120 kg (height weight)	
ourNo. of Subject /Completed/evaluable for PKPD analysis	**55/54/53**	18	18/17/16[a]	19	
Males/Females	**26/29**	2/16	8/10	16/3	
Age, Mean(range)		23(18-31)	28(18-43)	29(19-41)	
Body Weight, kg, Mean(range)		46.3 (37.7-49.8)	75.1 (67.2-83.8.4)	137.4 (120.0-175.1)	
Dose	10 mg (5 mg x2)	10 mg	10 mg	10 mg	
Sampling Times: PK plasma: Pre-dose and 0.5, 1, 2, 3, 4, 6, 9, 12, 18, 24, 36, 48, 60 and 72 hours post dose PD (anti-Factor Xa activity) plasma: pre-dose and 2, 12, and 24 hours post dose					

[a,] one subject withdrew consent and one subject had plasma concentration of apixaban near LLOQ or below LLOQ

Table 1: Investigational Product Information

Treatment	Formulation	Route	Product ID Information	Product Batch Number	Label Batch/Lot Number
Apixaban (BMS-562247) 5 mg	Tablet	Oral	562247-K005-027	6J14405	6L21084

- Dosing is long enough to obtain steady state ☐ Yes ☐ No☑ Not Applicable
- Sample size was determined based on statistical analysis ☐ Yes ☑ No
- The overall study design acceptable: ☑ Yes ☐ No

Analytical Method

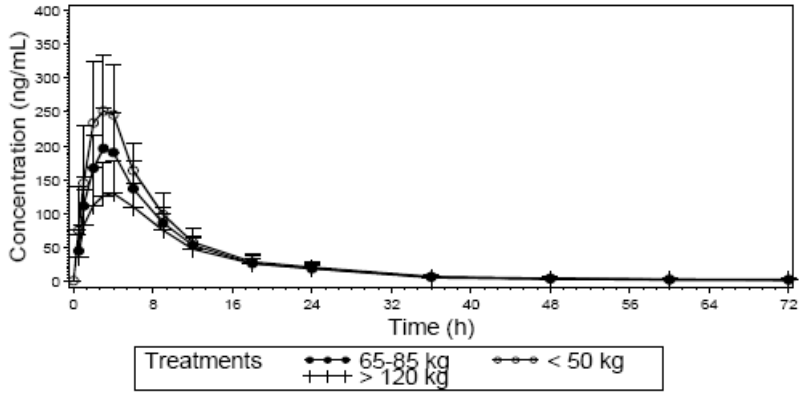
- Study samples were analyzed within the established stability period: ☑ Yes ☐ No
- Quality control samples range is acceptable ☑ Yes ☐ No
- Internal standard was used ☑ Yes ☐ No
- Method was validated prior to use ☑ Yes ☐ No
- Chromatograms were provided ☑ Yes ☐ No
- Overall performance is acceptable ☑ Yes ☐ No

The performance of the assay method during study sample analysis is acceptable and is summarized in the table below.

Analyte	**Apixaban**	
Method	LC-API/MS/MS	LC-API/MS/MS
Matrix	Plasma	Urine
LOQ	1.00 (ng/mL)	1.00 (ng/mL)
Range	1.00 to 1000 (ng/mL)	1.00 to 1000 (ng/mL)
QCs	3.00, 35.0, 400, 800 (ng/mL)	3.00, 35.0, 400, 750 (ng/mL)
Accuracy/Bias	2.54%	6.71 %
Precision (CV%)	7.27%	4.88 %

Pharmacokinetics

Figure 9.2A: **Mean (+SD) Plasma Concentration-Time Profiles of Apixaban Following a Single, 10-mg Apixaban Dose in Subjects with Low, Normal (Reference), and High Body Weight, on a arithmetic (top frame) and logarithmic (lower frame) scale**



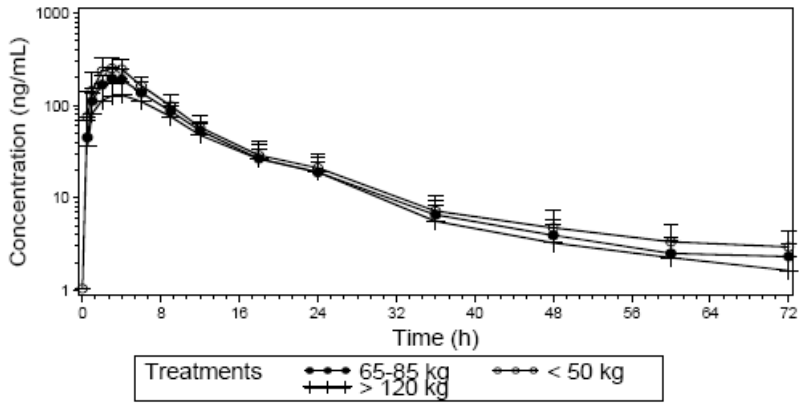


Table 5: Summary Statistics for Apixaban Pharmacokinetic Parameters by Body Weight Group

Body Weight Group	Apixaban Pharmacokinetic Parameters								
	Cmax (ng/mL) Geom. Mean (CV %)	AUC(INF) (ng·h/mL) Geom. Mean (CV %)	AUC(0-T) (ng·h/mL) Geom. Mean (CV %)	CLR (mL/min) Geom. Mean (CV %)	%UR (%) Mean (SD)	T-HALF (h) Mean (SD)	Tmax (h) Median (Min, Max)	CLT/F (mL/min) Geom. Mean (CV %)	VSS/F (L) Geom. Mean (CV %)
Low (n = 18)	264 (26)	2424 (26)	2357 (26)	14.09 (25.2)	21.25 (5.6)	15.8 (9.8)	3.00 (1.00, 6.00)	68.75 (40)	52.76 (45)
Reference (n = 16[a])	207 (24)	2024 (24)	1988 (23)	12.57 (45.0)	17.3 (8.6)	12.0 (5.35)	3.03 (2.00, 6.00)	82.34 (19)	61.02 (22)
High (n = 19)	144 (28)	1561 (31)	1534 (32)	17.77 (42.1)	17.8 (5.8)	8.8 (3.15)	3.98 (1.00, 6.00)	106.80 (35)	75.61 (28)

Table 6: Results of Statistical Analyses of Apixaban Cmax, AUC(INF) and AUC(0-T)

Pharmacokinetic Variable	Body Weight Group	Geometric Mean	Ratio of Geometric Means		
			Ratio	Point Estimate	90% CI
Cmax (ng/mL)	Low (n=18)	264	Low versus Reference	1.272	(1.075, 1.506)
	High (n=19)	144	High versus Reference	0.692	(0.586, 0.818)
	Reference (n=16[a])	207			
AUC(INF) (ng·h/mL)	Low (n=18)	2424	Low versus Reference	1.198	(1.011, 1.419)
	High (n=19)	1561	High versus Reference	0.771	(0.652, 0.912)
	Reference (n=16[a])	2024			
AUC(0-T) (ng·h/mL)	Low (n=18)	2357	Low versus Reference	1.186	(1.001, 1.405)
	High (n=19)	1534	High versus Reference	0.772	(0.653, 0.912)
	Reference (n=16[a])	1988			

[a] Two subjects, both in the reference group, were excluded from data analysis, summarization and figures (see Data Sets Analyzed: PK/PD for further details).

Pharmacodynamics

Table 7: Anti-Factor Xa Activity Summary Statistics by Body Weight Group and Timepoint

	3-h Postdose	12-h Postdose	24-h Postdose
Low Body Weight			
Mean (SD)	3.71 (1.34)	0.88 (0.29)	0.31 (0.15)
Min-Max	0.51 - 5.36	0.44 - 1.42	< LLOQ[a] - 0.70
Reference Body Weight			
Mean (SD)	2.79 (0.85)	0.77 (0.17)	0.26 (0.11)
Min-Max	0.97 - 4.44	0.54 - 1.20	< LLOQ - 0.48
High Body Weight			
Mean (SD)	1.85 (0.74)	0.70 (0.29)	0.27 (0.15)
Min-Max	0.41 - 3.45	0.28 - 1.15	< LLOQ - 0.58

[a] < LLOQ indicates the value is below the lower limit of quantification (0.20 U/mL).

Safety

Was there any death or serious adverse events? ☐ Yes ☑ No ☐ NA
Headache was the most frequently reported AE.

Conclusions

Is there a need to adjust the dose in patients with low body weight? ☐ Yes ☑ No

Dose adjustment based solely on low body weight may not be warranted; however, combination of additional risk factors for bleeding might lead to dose adjustment.

Is there a need to adjust the dose in patients with high body weight? ☐ Yes ☑ No

Although the impact of decrease in exposure on efficacy can not be determined in this study, the pivotal trial: ARISTOTLE suggested that lower exposure (25% lower) in patients with high body weight (>120 kg) did not result in loss of efficacy.

4.2 APPENDIX II
PHARMACOMETRICS (PM) REVIEW

OFFICE OF CLINICAL PHARMACOLOGY: PHARMACOMETRIC REVIEW

Application Number	NDA 202155
Compound	Eliquis (Apixaban)
Submission Date	28 September 2011
PM Reviewer	Tzu-Yun McDowell, PhD Dhananjay Marathe, PhD
PM Team Leader	Pravin Jadhav, PhD

1 SUMMARY OF FINDINGS

1.1 Key Review Questions

The purpose of this review is to address the following key questions.

1.1.1 What is the exposure-safety outcome relationship for apixaban?

The E-R analyses for safety explored the relationship between apixaban exposure [steady-state AUC (AUCss), derived from sponsor's population PK model] and International Society on Thrombosis and Hemostasis [ISTH] major bleed, the primary safety endpoint as defined as clinically overt bleeding accompanied by a decrease in hemoglobin ≥ 2 g/dl and/or a transfusion of ≥ 2 units of packed red blood cells or bleeding at critical sites or a fetal bleeding. The probability of ISTH major bleeding event increased with an increase in apixaban exposure (**Figure 7 & 8**). A similar positive relationship with apixaban exposure is observed for ISTH major bleeding event after excluding hemorrhagic stroke.

1.1.2 What is the exposure-efficacy outcome relationship for apixaban?

The E-R analyses for efficacy studied the relationship between apixaban exposure (AUCss) and ischemic stroke, a major component of the primary efficacy endpoint. The probability of ischemic stroke was independent from apixaban exposure at the dose level studied (**Figure 9**). The ability to observe a statistically significant relationship may be limited due to narrow exposure range and low event rate (n = 27 in the PK subset) observed in the current trial. Therefore, a reliable exposure-efficacy relationship for apixaban could not be established.

1.1.3 Is the dose adjustment of 2.5 mg BID for patients at increased bleeding risk appropriate?

Yes. Apixaban 2.5 mg BID for AF patients at increased bleeding risk based on the sponsor's criteria (prospectively evaluated in the pivotal trial- ARISTOTLE)- two of any following criteria: age ≥ 80 years, body weight ≤ 60 kg and serum creatinine ≥ 1.5 mg/dL is acceptable. This conclusion is based on the following:

- The ARISTOTLE trial demonstrated that apixaban was effective in reducing stroke/systemic embolism (SE) as well as risk of major bleeding compared to warfarin both within the 2.5 mg BID and the 5 mg BID (Table 1). However, it should be noted that a relatively small sample size in 2.5 mg BID group led to an unstable estimate for the efficacy results as illustrated with a wider confidence interval.
- While the observed event rate for major bleeding after 2.5 mg apixaban treatment is lower than that of warfarin for subjects with similar risk factors (event rate was 3.29 and 6.71 per 100 patient-years respectively), the exposure-safety relationship predicted the probability of major bleeding risk within a year to be doubled if dose is adjusted to 5 mg. The predicted bleeding event rate of 3.55% (2.26-4.62) in high risk patients receiving 2.5 mg BID would increase to 6.33% (4.43-8.20) if patients were to receive 5 mg.
- Further, we also found a subset of patients that achieved lower concentrations (equivalent to 2.5 mg BID) after 5 mg BID. A ~25% lower apixaban exposure was observed in high body weight (≥ 120 kg) subjects receiving 5 mg BID. In this subset, a robust efficacy results were also found despite lower concentrsations [HR: 0.34 (0.11-1.06)]. These findings are also consistent with the efficacy findings in the 2.5 mg BID group.

Overall, these results suggest that a 25% decrease in apixaban exposure due to a dose adjustment or an intrinsic factor may not compromise efficacy.

1.1.4 Is a dose adjustment needed when apixaban is co-administered with moderate/strong CYP3A4 and/or Pg-p modulators?

Dose adjustment of apixaban should be based on the following findings:

- Empirical evidence suggests that apixaban retained efficacy effect at 25% lower exposure.
- The impact of greater than a 25% decrease in exposure on efficacy is unknown.
- The risk of ISTH major bleeding increased with apixaban exposure.

To ensure the efficacy effect of apixaban and reduce major bleeding risk, 2.5 mg BID (half dose) is recommended for interacting drugs resulting in more than 50% increase in apixaban exposure.

1.1.5 Are the labeling claims based on population PK analyses reasonable?

Yes. The sponsor's labeling claim that there is no discernible difference in apixaban pharmacokinetics between White/Caucasian, Asian, and Black/African American subjects is reasonable. The PPK analysis result for phase 3 AF patients (**Figure 11**) is consistent with the claim from combined Phase 1 results.

1.2 Recommendations

- Apixaban 2.5 mg BID for patients at increased risk of bleeding based on the sponsor's criteria is acceptable and should be approved.
- No dose adjustment of apixaban is recommended for drugs that affect apixaban exposure by 75% -150%.
- Dose adjustment to 2.5 mg BID when apixaban is co-administered with strong CYP3A4 and P-gp inhibitors.
- No dose adjustment of apixaban is recommended based on race

2 PERTINENT REGULATORY BACKGROUND

Apixaban is an orally-active, selective and direct factor Xa inhibitor being developed by Bristol-Myers Squibb (BMS) and Pfizer as an anticoagulant. The proposed indication is "to reduce risk of stroke, systemic embolism, (b) (4) in patients with nonvalvular atrial fibrillation". An efficacy and safety trial (ARISTOTLE) comparing apixaban (2.5 and 5 mg) to blinded warfarin is the pivotal study supporting the application. The sponsor (b) (4) . The proposed dose is 5 mg orally twice daily or 2.5 mg twice daily for selected patients who fulfill any two of the following criteria: age ≥ 80 years, body weight ≤ 60 kg and serum creatinine ≥ 1.5 mg/dL. The current submission (NDA 202-155) for apixaban that is most relevant to this review is the pivotal efficacy and safety trial (ARISTOTLE) comparing apixaban (2.5 and 5 mg) to blinded warfarin titrated to a target INR of 2 to 3.

The sponsor also provided a pharmacometric report which included a population PK model as well as exposure-response analyses that are subject to the review.

3 RESULTS OF SPONSOR'S ANALYSIS

3.1 Dose selection

Dose selection for the pivotal phase 3 trials (ARISTOTLE and AVERROES) was primarily based on the results from two phase 2 studies for different indications. [CV185010 for venous thromboembolism prevention (VTEp) and CV185017 in deep vein thrombosis (DVT)]. The dose ranging study in VTEp (CV185010) studied 8 treatment groups in a total of 1,238 subjects undergoing total knee replacement surgery (~150 subject/group): apixaban doses of 5, 10 and 20 mg with both QD and BID regimen; blinded enoxaparin and open-label warfarin (titrated to INR 1.8-3.0). The study results showed a dose-response for both efficacy and bleeding endpoints and demonstrated a trend for better efficacy with BID compared to QD dosing regimen (**Figure 1**). Clearly, there is no further gain in efficacy at doses > 5 mg BID, however, there is an increase in bleeding as compared to the control arm for doses > 5 mg BID. The sponsor concluded that 5 mg BID provided a favorable balance of efficacy and safety for AF indication. The selection of 5 mg BID was also supported by a DVT treatment study (CV 185017) where 3 apixaban groups (5 mg BID, 10 mg BID, and 20 mg QD) were effective in preventing recurrent VTE and consistent with an acceptable safety profile compared to an open-label VKA group.

Based on the results of the two studies, sponsor concluded that 5 mg BID was appropriate for a wide range of patients with AF. Sponsor further implemented a dose adjustment strategy for AF patients who are at an increased risk of bleeding in their two phase 3 trials: 2.5 mg BID was given for subject who had any two of the following criteria: age ≥ 80 years, body weight ≤ 60 kg and serum creatinine ≥ 1.5 mg/dL. The rationale of this dose adjustment was based on a clinical judgment and the results of the available clinical pharmacology studies at the time this decision was made. The dose adjustment plan was included in the Special Protocol Assessment for the pivotal phase trial (CV 185030) submitted to the FDA in Oct 2006.

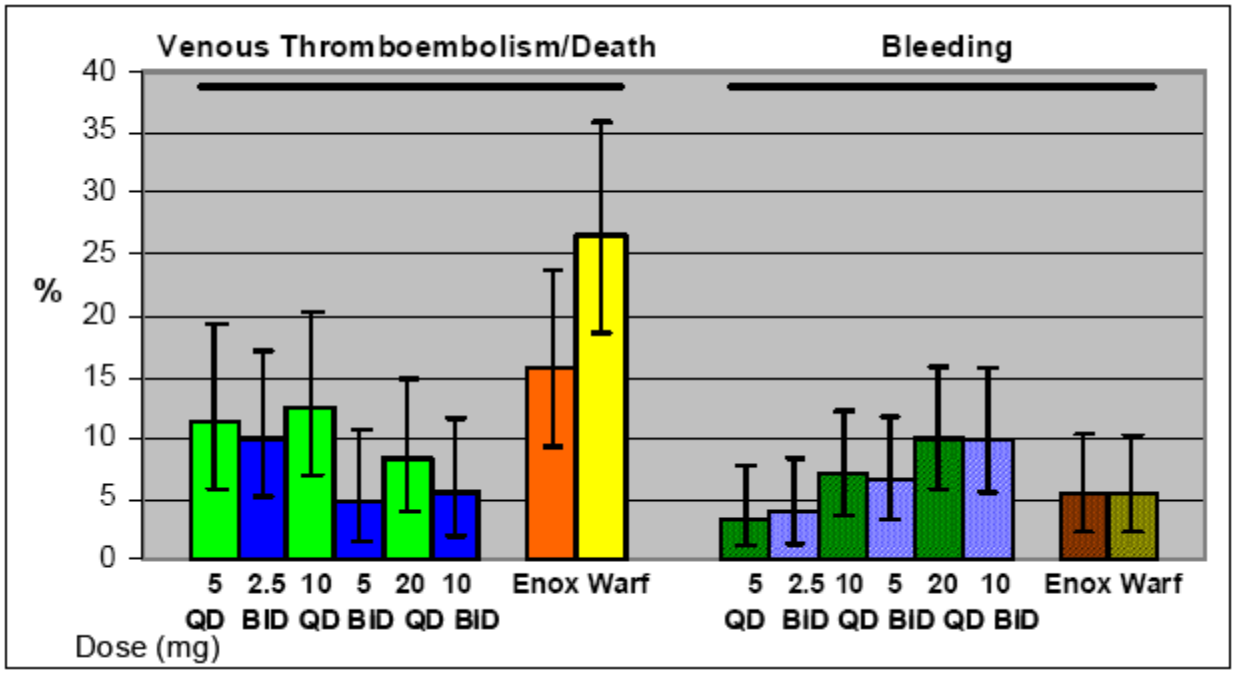


Figure 1. Efficacy and safety outcomes in apixaban phase 2 VTE prevention after keen replacement in CV185010 *Source:* CV185010*, CSR.pdf*

3.2 Phase 3 Pivotal Trial: ARISTOTLE (CV185030)

An active (warfarin)-controlled, randomized, double-blind study to evaluate efficacy and safety of apixaban in preventing stroke and systemic embolism (SE) in patients with non-valvular atrial fibrillation (AF). A total of 18,201 subjects with at least one risk factor for stroke were randomized to either apixaban (n = 9,120) 5 mg BID [or 2.5 mg BID in selected subjects] or to warfarin (n=9,081) titrated to a target INR of 2 to 3. The treatment arms were well balanced for baseline characteristics and had the average duration of exposure about 1.7 years. The primary efficacy endpoint was confirmed stroke (ischemic, hemorrhagic or of unspecified type) or SE during the intended treatment period. The primary safety endpoint was confirmed ISTH major bleeding during the treatment period

(last dose plus 2 days). Apixaban was superior to warfarin for prevention of stroke and SE [HR = 0.79 (95% CUI: 0.66-0.95), p=0.0114) and for ISTH major bleeding [HR = 0.69 (95% CI: 0.60-0.80), p <.0001]. The sequential analyses also showed that apixaban was superior to warfarin for prevention of all-cause death (HR = 0.89, p = 0.0465).
There were about 4.6% of subjects receiving apixaban 2.5 mg BID (n = 428) and placebo 2.5 mg (n = 403). **Table 1** shows the summary results of primary efficacy and safety endpoints by subgroup. These results suggest that both efficacy and safety of apixaban were preserved in the 2.5 mg BID subgroup. Interestingly, the hazard ratio for 2.5 mg BID subgroup is 0.5 compared to 0.82 for 5 mg BID. While these are two distinct populations based on the underlying risk factors, it must be noted that the dose adjustment to 2.5 mg in patients with certain risk factors should lead to concentrations similar to that of 5 mg. In fact, 2.5 mg leads to 25% lower concentration for subjects with identified risk factors (See section 3.3).

Table 1 Event rate and hazard ratio for primary efficacy endpoint and ISTH major bleeding by dose subgroup

Stroke or SE	Apixaban	Warfarin
APIXABAN DOSE		
APIX/PLACEBO 2.5 MG BID, n/N (%)	12/428 (2.80)	22/403 (5.46)
EVENT RATE (%/YR)	1.70	3.33
HAZARD RATIO (APIXABAN/WARFARIN)	0.50	
95% CI FOR HAZARD RATIO	(0.25, 1.02)	
APIX/PLACEBO 5 MG BID, n/N (%)	200/8692 (2.30)	243/8678 (2.80)
EVENT RATE (%/YR)	1.25	1.53
HAZARD RATIO (APIXABAN/WARFARIN)	0.82	
95% CI FOR HAZARD RATIO	(0.68, 0.98)	

ISTH Major Bleeding	Apixaban	Warfarin
APIXABAN DOSE		
APIX/PLACEBO 2.5 MG BID, n/N (%)	20/ 424 (4.72)	37/ 402 (9.20)
EVENT RATE (%/YR)	3.29	6.71
HAZARD RATIO (APIXABAN/WARFARIN)	0.50	
95% CI FOR HAZARD RATIO	(0.29, 0.86)	
APIX/PLACEBO 5 MG BID, n/N (%)	307/ 8664 (3.54)	425/ 8650 (4.91)
EVENT RATE (%/YR)	2.09	2.95
HAZARD RATIO (APIXABAN/WARFARIN)	0.71	
95% CI FOR HAZARD RATIO	(0.61, 0.82)	

Source: CV185030, CSR.pdf, Table S.5.4.A & S.6.2.B

A subset of subjects in ARISTOTLE had a single random PK (n= 3231) or/and PD (n = 3125) sample collected at month 2. Apixaban plasma concentration and anti-Fxa activity was found to be lower (15-20% reduction) in 2.5 mg group compared to 5 mg. There appeared to be a good correlation between apixaban plasma concentration and anti-FXa activity (see **Figure 2**), which is consistent with observations from other apixaban clinical studies.

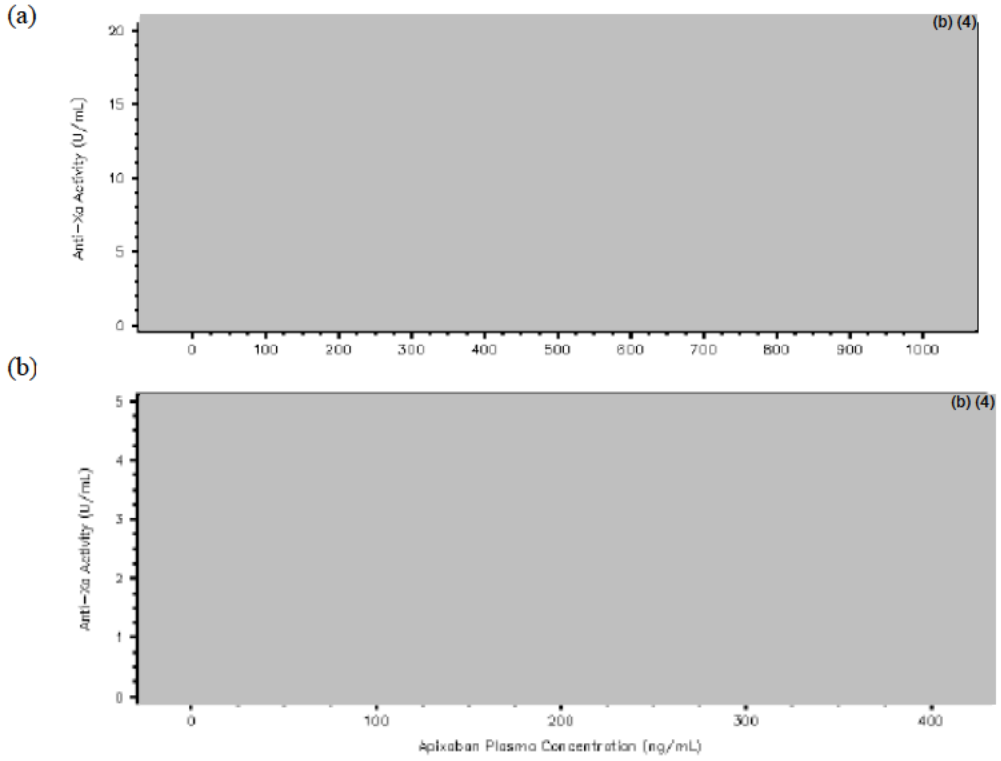


Figure 2 Plot of Anti-Fxa activity versus Apixaban plasma concentration in ARISTOTLE (a) 5 mg BID and (b) 2.5 mg BID PK/PD subset *Source: CV185030, CSR.pdf, Figure 10.2 A*

3.3 Population PK Analysis

The sponsor performed population pharmacokinetic (PPK) analyses in healthy subjects and patients to explore the influence of covariates (healthy/AF/ACS state, sex, age, renal function, race, weight, time of administration (diurnal variation), and concomitant medication) on apixaban exposure (

Table).

Table 2 Summary of clinical studies used in population pharmacokinetic analysis and Exposure-Response analyses

Study	Phase	Type of Study	Doses	# of Subjects	# of Samples	Analyses
CV185002A	1	safety, tolerability, PD, and PK; healthy subjects	10, 25 mg qd, 2.5, 5, 10, 25 mg bid	36	1052	PPK
CV185013	1	PK, PD, safety and tolerability; healthy subjects (Japanese, Caucasian)	2.5, 10, 25, and 50 mg	24	1440	PPK
CV185018	1	Renal Impairment; healthy subjects	10 mg	32	523	PPK, PK/ Anti-Xa
CV185022	1	Age and gender; healthy subjects	20 mg	79	1121	PPK
CV185023	2b	ACS patients	2.5 and 10 mg bid, 10 and 20 mg qd	951	1510	PPK
CV185030	3	AF patients	5 mg bid (2.5 mg bid in few subjects)	2932	2932	PPK, PK/ Anti-Xa, ER
CV185046	1	PK, PD, safety and tolerability; healthy subjects (Japanese)	2.5, 5, and 10 mg bid	18	639	PPK, PK/ Anti-Xa
CV185058	1	PK, PD, safety and tolerability; healthy subjects (Chinese)	10 mg bid	12	356	PPK, PK/ Anti-Xa
CV185059	1	Weight; healthy subjects	10 mg	55	693	PPK, PK/ Anti-Xa
CV185067	2b	AF patients (Japanese)	2.5 and 5 mg bid	139	680	PPK, PK/ Anti-Xa, ER
CV185070	2	ACS patients (Japanese)	2.5 and 5 mg bid	93	726	PPK
CV185074	1	Comparison with Rivaroxaban; healthy subjects	2.5 mg bid	14	296	PPK, PK/ Anti-Xa

Source: Sponsor's Pop PK and ER in AF Report, Table 3.1, Page 28-31 and Table 3.3.1.1, Page 33

3.3.1 Methods

Data from eight Phase 1 studies, three Phase 2 studies (one in AF; two in ACS), and one Phase 3 AF study were pooled for the AF PPK. A total of 11968 measurable apixaban observations were available from 4385 subjects. 2932 were AF subjects from pivotal phase 3 study CV185030 (ARISTOTLE).

A two-stage approach was utilized for PPK model. In the first stage, Stage 1 model was developed using phase 1 and phase 2 studies. In the second stage, the model was adapted to include data from phase 3 study and covariates for the concomitant medication to form the final Stage 2 full model.

3.3.2 Results

The final model was a two-compartment model with first-order absorption and first-order elimination. Apixaban clearance (CL/F) was separated into renal (CL_R/F) and non-renal (CL_{NR}/F) components and the effect of calculated creatinine clearance (CRCL) was fixed such that CL_R/F and baseline CRCL were directly proportional. The covariates tested for inclusion in the final model are listed in **Table** .

Table 3 Covariates included in the final population pharmacokinetic model

Covariate	Apparent Renal Clearance (CL_R/F)	Apparent Non-renal Clearance (CL_{NR}/F)	Apparent Volume of Central Compartment (V2/F)	Absorption Rate (Ka)
Age	NT*	+	NT	NT
Sex	NT*	+	NT	NT
Baseline body weight	NT*	+	+	NT
Concomitant medication**	+	+	NT	NT
Race (White, Black, Asian, other)	+	+	NT	NT
Patient status (ACS, AF)	+	+	+	NT
Dosing time (diurnal variation)	+	+	NT	+

NT: not tested

* Base model will include cCrCL on CL_R/F using the Cockcroft-Gault formula

** Evaluated in Stage 2 after incorporation of the Phase 3 data.

Source: Sponsor's Pop PK and ER in AF Report, Table 3, Page 176

A summary of the parameter estimates of the final Stage 2 model is provided in **Table** . The goodness of fit plots for the combined data across all studies and for pivotal Phase 3 study data alone are provided in **Figure A** and **Figure B**, respectively.

Table 4 Pharmacokinetic and covariate parameter estimates of the final model

Fixed Effects Parameters	Estimate ± SE Updated Stage 1 Final	Estimate ± SE Stage 2 Full Model	Estimate ± SE Stage 2 Final Model
OFV	-5878.214	-5888.432	-5888.403
ka (θ_1) (1/hr)	0.471±0.0204	0.473±0.0213	0.473±0.0208
Evening Dosing (AMPM=2) on ka (θ_{10})	-0.434±0.0234	-0.433±0.0237	-0.433±0.0236
CL_R/F (θ_2) (L/hr)	1.57±0.118	1.57±0.118	1.57±0.117
cCLcr on CL_R/F (θ_7)	1 FIXED	1 FIXED	1 FIXED
CL_{NR}/F (θ_6) (L/hr)	2.02±0.11	2.02±0.114	2.02±0.108
Age on CL_{NR}/F (θ_{14})	-0.429±0.0681	-0.429±0.0683	-0.429±0.0678
Female Subjects on CL_{NR}/F (θ_{15})	-0.215±0.0263	-0.216±0.0263	-0.216±0.0263
CL/F			
Asian Subjects on CL/F (θ_{16})	-0.12±0.0184	-0.119±0.0184	-0.119±0.0183
AF Patients on CL/F (θ_{17})	-0.149±0.0298	-0.139±0.0312	-0.139±0.0305
ACS Patients on CL/F (θ_{18})	-0.217±0.0284	-0.215±0.0292	-0.215±0.0286
Strong/Moderate Inhibitors on Total Clearance (θ_{19})	NE	-0.145±0.0421	-0.146±0.0421
Strong/Moderate Inducers on Total Clearance (θ_{20})	NE	-0.0243±0.146	NE
V_c/F (θ_3) (L)	29.8±0.981	30±0.999	30±0.971
D_WTB on V_c/F (θ_{11})	0.806±0.0649	0.79±0.0646	0.79±0.0645
AF Patients on V_c/F (θ_{12})	-0.0217±0.0501	-0.0407±0.0495	-0.0405±0.0491
ACS Patients on V_c/F (θ_{13})	-0.177±0.0449	-0.18±0.0452	-0.18±0.0446
Q/F (θ_4) (L/hr)	1.89±0.151	1.91±0.169	1.91±0.163
V_p/F (θ_5) (L)	26.7±1.89	27±2.1	27±2.03
Shape Parameter for $F_{REL}(\gamma)$ (θ_9)	0.853±0.0693	0.857±0.0725	0.857±0.0684
Logit for Reduction in F_{REL} at 50 mg (I_{50}) (θ_9)	-0.321±0.0512	-0.322±0.0514	-0.322±0.0512
Interindividual Variance Components	**Estimate ± SE (%CV[a])**	**Estimate ± SE (%CV[a])**	**Estimate ± SE (%CV[a])**
ω^2-ka	0.271±0.0319 (52.1)	0.263±0.031 (51.3)	0.263±0.0311 (51.3)
ω^2-k	0.101±0.00989 (31.8)	0.0953±0.00961 (30.9)	0.0954±0.00964 (30.9)
ω^2-V_c/F	0.0287±0.0055 (16.9)	0.0294±0.00553 (17.1)	0.0294±0.00553 (17.1)
ω^2-k_{21}	0.243±0.0412 (49.3)	0.24±0.0406 (49)	0.24±0.0404 (49)
ω^2-k_{12}	1.49±0.163 (122)	1.55±0.17 (124)	1.55±0.169 (124)

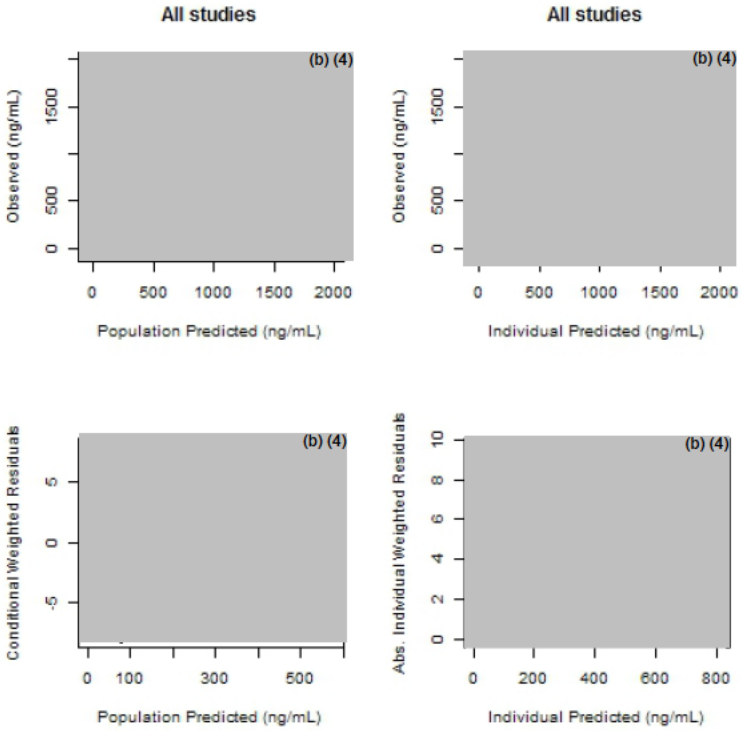
Residual Variance Components	Estimate ± SE (%CV[b])	Estimate ± SE (%CV[b])	Estimate ± SE (%CV[b])
σ HV and Studies CV185067, CV185070 (θ_{21})	0.31±0.00282 (31)	0.31±0.00282 (31)	0.31±0.00282 (31)
σ Study CV185023 (θ_{22})	0.666±0.0182 (66.6)	0.668±0.0183 (66.8)	0.668±0.0183 (66.8)
σ Study CV185030 (θ_{23})	0.451±0.0169 (45.1)	0.46±0.0163 (46)	0.46±0.0163 (46)

[a] Approximate %CV reported as 100·ω

[b] Approximate %CV reported as 100·σ

Source: Sponsor's Pop PK and ER in AF Report, Table 5.1.1.5B, Page 87

A.



B.

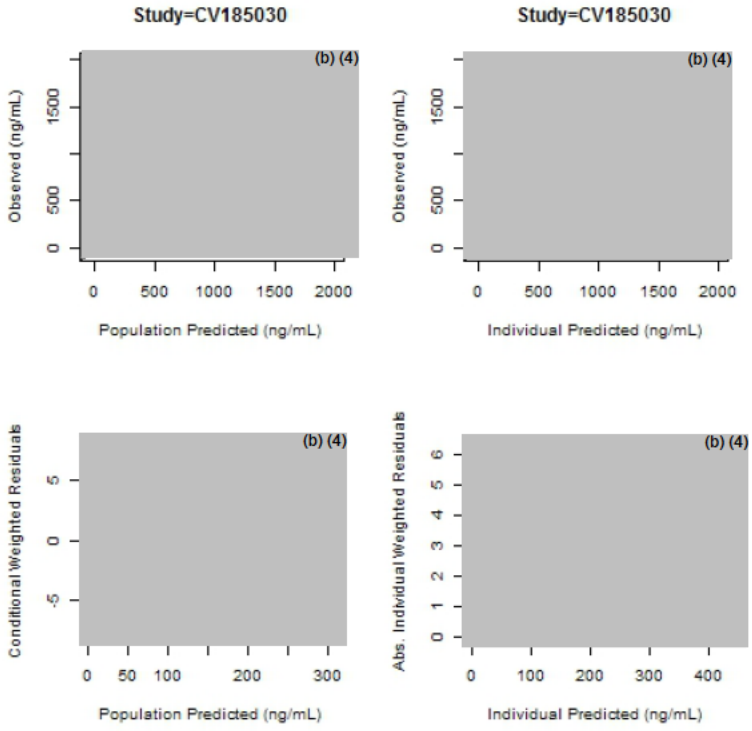
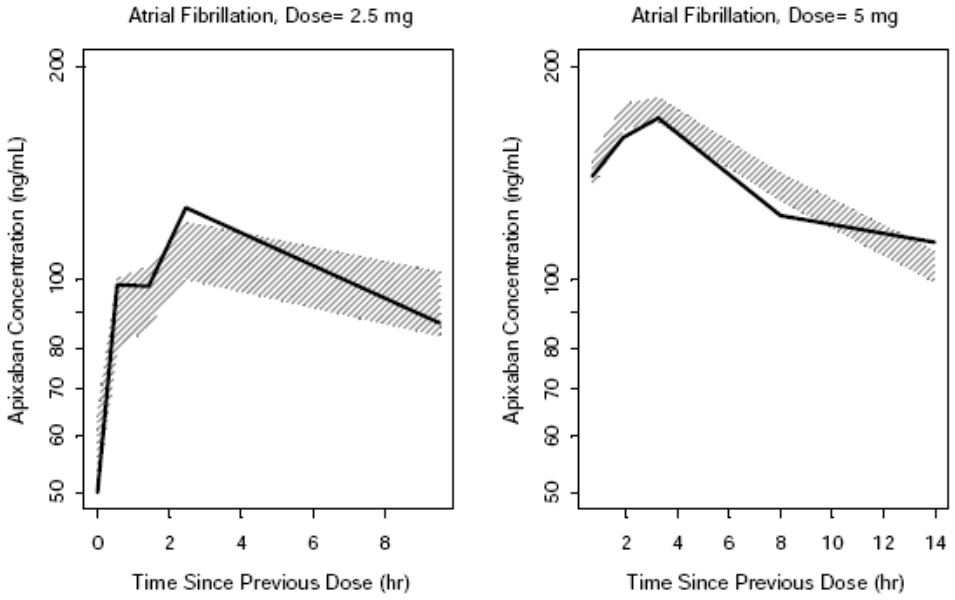


Figure 3 Goodness of fit plots of the final pharmacokinetic model for (A) combined data from all studies, and (B) phase 3 (ARISTOTLE) data alone. *Source: Reviewer's analysis of stage 2 final model provided by the Sponsor*

For external validation, the final model was used to predict steady state apixaban concentrations for the AF patients and compared with the actual observations (
Figure). The model appeared to capture the general shape of the apixaban concentration-time profile in AF patients despite some instances where the observed data are not contained within the 90% prediction interval. Since there were no systematic trends in the AF patient data, the model was deemed suitable to predict individual steady state AUCss for the ER safety and efficacy analyses.



Caption: Solid line represents geometric mean observed and shaded region represents the 90% prediction interval.

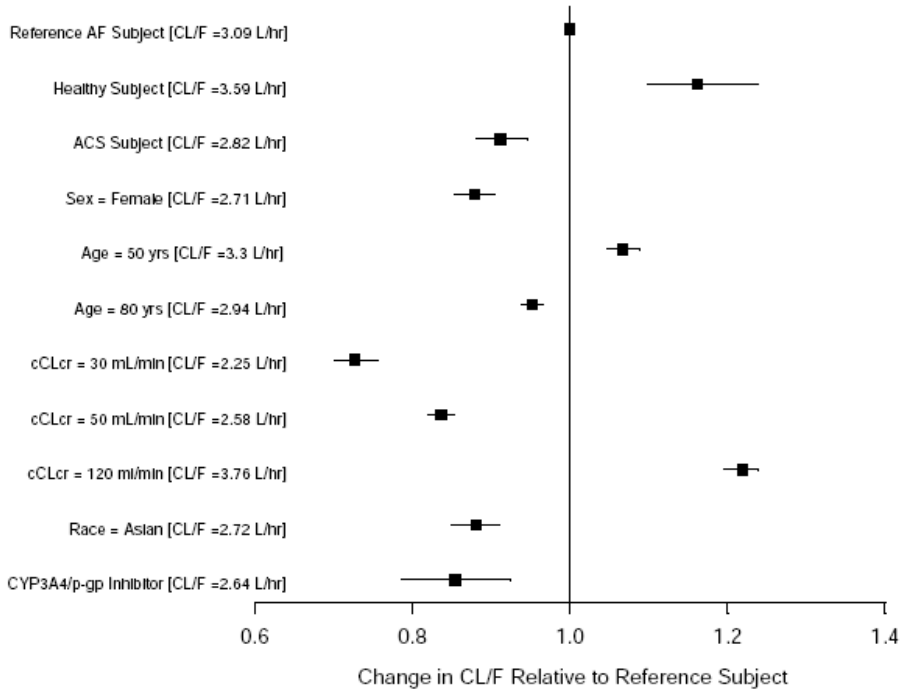
Figure 4 Posterior predictive check for atrial fibrillation patients for apixaban at steady-state. *Source: Sponsor's Pop PK and ER in AF Report, Figure 5.1.2C, Page 94*

3.3.3 Covariate Effects

The effect of covariates on apparent clearance of apixaban is summarized in
Figure .

1. **Typical reference patient:** The total apixaban apparent clearance was estimated to be 3.09 L/hr for a 65 year-old, non-Asian, male, AF patient that weighed 70 kg and had a creatinine clearance of 80 mL/min.
2. **Dose:** The effect of dose was included on relative bioavailability but the effect was small in the clinical dose range (<4% difference between 2.5 and 5 mg).
3. **Age and Gender:** Non-renal apixaban apparent clearance (CL_{NR}/F) decreased with age, and was lower in females relative to males. A 50 year old subject would have a 11.9% increase and an 80 year old subject would have a 8.5% decrease in CL_{NR}/F relative to the typical 65 year old subject. Female subjects would have a 21.6% reduction in CL_{NR}/F relative to male subjects.
4. **Race:** Asian race had a decrease of 11.9% in apparent clearance (CL/F) of apixaban relative to the reference population.

5. **Disease State:** AF patients and recent ACS patients resulted in decreases of 13.9% and 21.5%, respectively in apparent clearance (CL/F) of apixaban relative to the reference population. Also patients with recent ACS had an 18% decrease in V_c/F while patients with AF had a 4% decrease in V_c/F relative to healthy subjects.
6. **CYP3A4/p-gp Inhibitors**: Strong/moderate CYP3A4/p-gp inhibitors resulted in a decrease of 14.6% in apparent clearance (CL/F) relative to the reference population.
7. **Weight:** The effect of baseline body weight on V_c/F was less than directly proportional with a 23.3% reduction for a 50 kg subject and a 22% increase for a 90 kg subject relative to the typical 70 kg individual.
8. **Renal Impairment:** A subject with severe renal impairment (CLCR = 15 mL/min) was predicted to have a 55% higher steady state AUC than the reference subject (male, non-Asian, 65 year-old, 70 kg, CLCR = 80 mL/min). The associated risk of bleeding in this typical subject was lower than that predicted for typical individuals meeting dose modification criteria based on age and serum creatinine (SCr) or weight and SCr (from ER analysis).



Solid squares represent the ratio of the typical predicted CL/F relative to the reference subject. The black line represents the 90% confidence interval of the ratio. The reference subject is a 65 year old, non-Asian, male subject with AF that has a cCLcr of 80 mL/min and did not receive a concomitant strong or moderate CYP3A4/p-gp inhibitor.

Figure 5: Illustration of covariate effects on CL/F for Apixaban

Source: Sponsor's Pop PK and ER in AF Report, Table 5.1.1.5, Page 89

Reviewer's Comments:

1. *The sponsor's PPK model provides reasonable description of apixaban concentrations for individual predictions (observed vs. individual predicted concentrations in* ***Figure*** *). Visual inspection shows that the model reasonably predicts individual data over a range of dose/concentration with combined data from all studies (****Figure A****). There is some under-estimation at higher observed concentrations in the phase 3 trial data (****Figure B****).*
2. *The individual predictions can be used for calculating the exposures (for subsequent ER analysis) in only the subjects belonging to the PK subset. The model can not be extrapolated for predicting the apixaban exposures in the rest of the subjects in the phase 3 trial owing to high unexplained variability.*
3. *Sponsor's conclusion that none of the covariates by themselves alone warranted any dosing changes is reasonable. The magnitude of each covariate effect generally resulted in less than a 25% change relative to the reference population. This change was not associated with any appreciable reduction in benefit or increase in bleeding risk (see section 3.4).*
4. *The effect of covariates (age, gender, body weight and renal function) described in apixaban label, based on results of dedicated Phase 1 studies, are in general agreement with results of population PK.*

3.4 Exposure-Response Analysis

To explore the relationship between apixaban exposure and efficacy and safety endpoints, sponsor conducted a proportional hazard time-to-event models using AF patients (n = 3071) with at least one measurable apixaban concentration from the Phase 2 (CV185067) and 3 (CV185030) studies. The steady-state total daily apixaban exposure (AUCss) was obtained for each individual from the population PK model. The efficacy endpoint is time to first occurrence of stroke or SE, and the safety endpoints are time to first occurrence of (1) ISTH major bleeding and (2) a composite bleeding event (major or clinically relevant non-major bleeding event).

Efficacy

The proportional hazard model for efficacy indicated a trend for a decreasing risk of stroke or SE with increasing in apixaban exposure, and the relationship appeared to be very shallow. Sponsor concluded that a robust E-R relationship for efficacy could not be established considering a number of limitations in the analysis including small number of events in the PK subset in addition to a flat relationship.

Safety

The proportional hazard model for both safety endpoints revealed for a greater risk of bleeding with increasing apixaban exposure. Sponsor has investigated a set of covariates including aspirin and aspirin-containing products (ASA) use, non-ASA antiplatelet use, non-ASA NSAID, anticoagulant use during apixaban treatment. In addition, the dichotomized variables for the protocol-specified cutoffs criteria: age ≥ 80 years, body weight ≤ 60 kg and serum creatinine ≥ 1.5 mg/dL were also included in the full model. **Figure 6** showed the predicted 3 year probability of events for efficacy and safety endpoints from sponsor's ER base models. Sponsor also evaluated their dose adjustment algorithm for ARISTOTLE based on the model predicted estimates. The predicted changes in apixaban exposure among the majority of typical individuals with various demographic factors was

less than 30% of the reference subject defined as male, non-Asian, 65 years of age, 70 kg body weight with CLCR = 80 ml/min. **Table 5** shows the predictions of major bleeding events and relative risk for dose groups defined in the protocol and for scenarios where dose adjustment has not been made. The predictions show that there were similar event rates in 5 mg BID apixaban and 2.5 mg BID apixaban. The 3-year probability of major bleeding event would be 7.8 %-years in 2.5 mg group if they were to receive 5 mg instead of 4.1 %-year with protocol-specified dose modification.

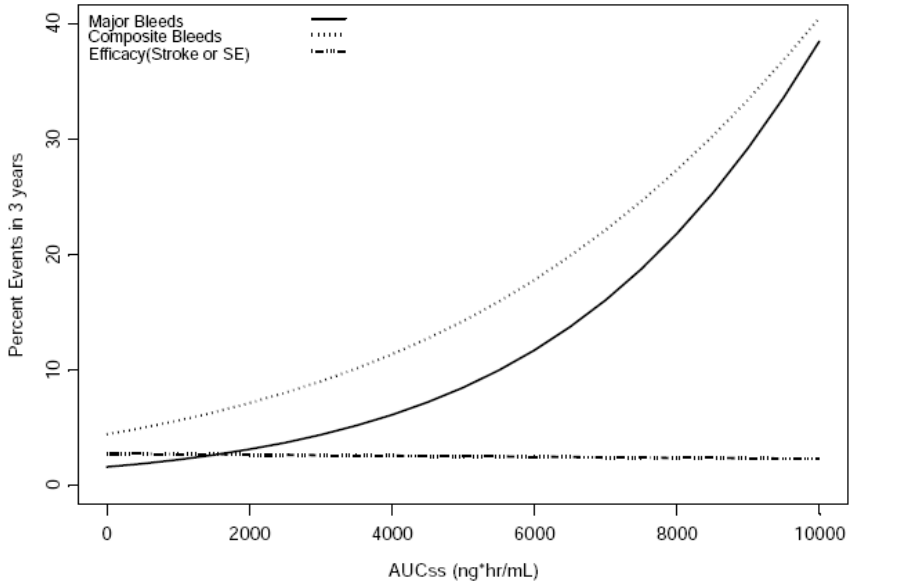


Figure 6 Probability of efficacy and safety events within 3 years predicted by sponsor's E-R models *Source: Sponsor's report for population PK and exposure-response analyses in subjected with AF, Figure 5.5.2A*

Table 5 Predictions of Major bleeding events and relative risk for dose groups defined by the protocol and other dose scenarios. *Source: Sponsor's report for population PK and exposure-response analyses in subjected with AF, Table 5.5.2.2A*

Group[a]	Apixaban Dose	Prediction (90% CI)	
		Probability of an Event within 3 Years (%)	Relative Risk
5 mg Reference (per protocol)	5 mg BID	4.3 (3.4 – 5.4)	1
5 mg (reduced dose)	2.5 mg BID	2.2 (1.4 – 3.5)	0.5 (0.4 – 0.7)
2.5 mg (no dose adjustment)	5 mg BID	7.8 (4.2 – 14.7)	1.8 (1.0 – 3.3)
2.5 mg (per protocol)	2.5 mg BID	4.1 (1.9 – 8.5)	0.9 (0.5 – 1.9)

[a] Predictions were made for each group assuming no concomitant use of ASA, NSAIDs, antiplatelets or anticoagulants

*Reviewer's comments: The sponsor's dose adjustment algorithm was not based on exposure matching or any quantitative assessment.2.5 mg BID instead of 5 mg BID was assigned to patients at increased risk of bleeding with two of three following criteria: age ≥ 80 years, body weight ≤ 60 kg and serum creatinine ≥ 1.5 mg/*dL*. The fact that patients with these risk factors might also be at higher risk of thromboembolism raises a review question regarding the sponsor's dose adjustment criteria without a careful consideration about potential loss of efficacy due to overadjustment of the dose. Although the results of the ARISTOTLE trial in combination with the E-R relationships seem to support the recommendations, additional evidence is needed to ensure the legitimacy of the dose adjustment, especially the efficacy effect of 2.5 mg BID.*
Additionally, sponsor's E-R models did not adjust for other potential clinical factors such as prior history of stroke/TIA/SE that might impact or confound the E-R relationships. Independent analyses were necessary to evaluate sponsor's dose adjustment strategy and provide dose recommendations if required.

4 REVIEWER'S ANALYSIS

4.1 Introduction

Independent analyses were conducted to explore the relationships between apixaban exposure and efficacy/safety events in ARISTOTLE. The studied relationships in combination with other summary statistics from ARISTOTLE trial data were used to address the review questions related to the dose selection and adjustment.

4.2 Objectives

Analysis objectives are:

1. Evaluate the relationship between apixaban exposure and the probability of ischemic stroke
2. Evaluate the relationship between apixaban exposure and the probability of ISTH major bleed
3. Use exposure-outcome relationships in combination with ARISTOTLE trial data to explore the impact of dose modification on safety and efficacy events
4. Use exposure-outcome relationships to provide recommendations when apixaban is co-administered with moderate/strong modulators of CYP3A4 and Pg-p

4.3 Exposure-Response Analyses for Safety

4.3.1 Data and Methods

A single PK sample was collected randomly in a subset of patients in ARISTOTLE (n= 3231). Considering the limitation of using the random concentration data, steady-state AUC [AUCss (ng*hr/ml)], derived from sponsor's population PK model was chosen as the exposure metric in the analyses (Sponsor's dataset: mjbld.xpt). The safety endpoint is ISTH major bleeding event among safety population (subject received at least on treatment) in ARISTOTLE.

A logistic regression was performed to initially examine the relationship between apixaban exposure and the probability of (1) ISTH major bleeding and (2) ISTH major bleeding excluding hemorrhagic stroke in ARISTOTLE PK subset. The observed probability for a major bleeding stratified by apixaban exposure quartile was calculated. An overlay-plot with observed probability in each quartile of apixaban AUC as well as a predicted probability from the regression model was used to display the relationship between AUCss and ISTH major bleeding.

A Cox proportional hazard model was further performed to model time to first occurrence of ISTH major bleeding as a function of the logarithm of AUCss and a set of covariates. To approximate an on-treatment analysis, the time period from the first dose to the last dose of study medication plus 2 days were chosen. If an outcome event did not occur during this timeframe, time was censored at the last dose of study medication plus 2 days. Only time to the first event was considered in the analysis (sponsor's dataset: adbs.xpt)

Because dose adjustment to 2.5 mg BID was assigned to patients at increased risk of bleeding (i.e. age >=80 and weight ≤ 60 kg) and apixaban concentration is correlated with these risk factors, studying apixaban patients alone in the analysis is not sufficient to evaluate an independent impact of exposure and the individual risk factors on bleeding risk[10]. As a result, to appropriately examine the effect of each risk factor on bleeding risk and dissect the influence of these confounded factors on exposure, warfarin-treated patients were included in the exposure-safety analysis. Warfarin patients are titrated to INR of 2 to 3, which provides a means to evaluate other risk factors on major bleeding independent of warfarin exposure. The risk factors are assumed to have the same effects on bleeding risk in warfarin-and apixaban- treated patients. The logarithm of AUCss in warfarin-treated subjects was set to be 0.001.

To identify the potential covariates in the model, a bivariate analysis of the association between covariates and survival time was performed. Potential covariates tested included age, sex, race, body weight, creatinine clearance, serum creatinine, prior stroke/TIA/systemic embolism, CHADS2 score, diabetes mellitus, hypertension, myocardial infarction, prior VKA use and aspirin use during double blind period. All covariates that were close to be significant in the bivariate analysis ($p < .20$) were selected in the final model fitting. The reduced model was then fitted and a covariate was considered to be significant at p value $< .05$. An alternative method using the stepwise selection was also employed to verify the covariate selection in the final model. The proportional hazard assumption was checked by plotting the weighted Schoenfeld residuals against the log survival time. All the analyses and plots were conducted and generated in SAS 9.2

4.3.2 Results

A subset of apixaban PK population [n = 2932/9088 (32%)], which included all apixaban subjects with an available AUCss was used in the logistic regression analysis. A total of 110 ISTH major bleeding events (7 is hemorrhagic stroke) were included in this subset [~34% of ISTH major bleeding (n = 327) in the apixaban safety population]. The observed and predicted probability (un-adjusted association) of ISTH major bleeding and ISTH major bleeding excluding hemorrhagic stroke by AUCss is shown in **Figure 7**. This analysis showed that risk of ISTH major bleeding with or without hemorrhagic stroke increased with apixaban concentration.

[10] Exposure-safety analysis using apixaban patients alone significantly underestimates the major bleeding risk in Cox-PH model.

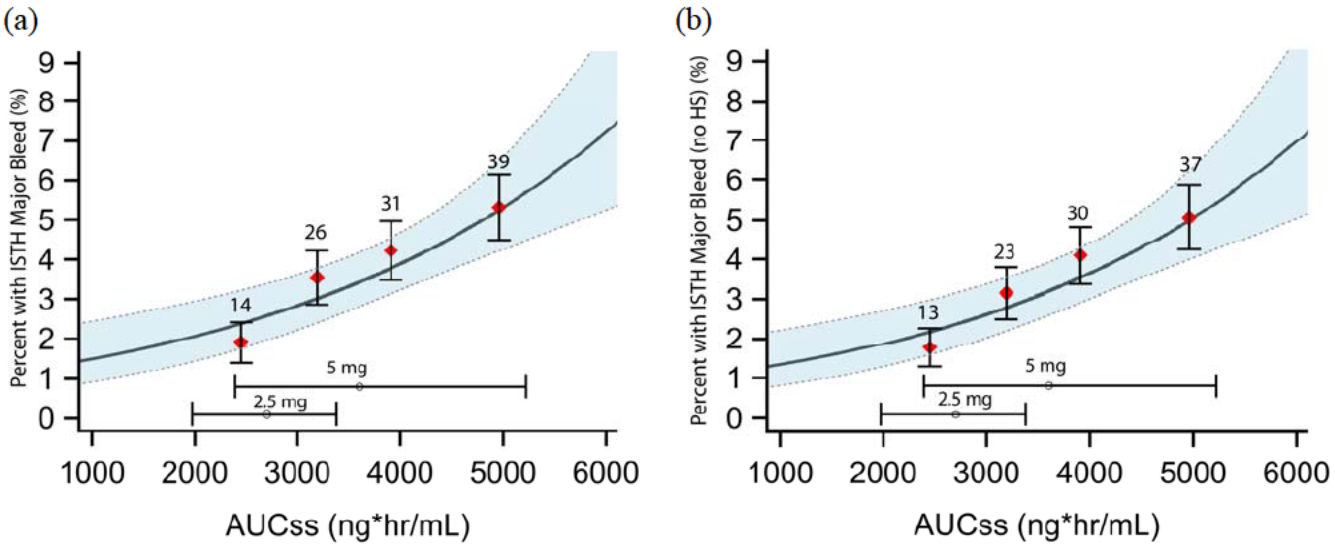


Figure 7 Probability of (a) ISTH Major bleeding and (2) ISTH Major bleeding excluding hemorrhagic stroke as a function of steady-state AUC. The solid line represents the predicted probability from an unadjusted linear logistic regression. The red markers represent the observed probability at the median AUCss for a given quartile. The bars on the bottom represents 5th to 95th percentiles of apixaban AUCss in the ARISTOTLE PK subset.

A Cox PH model was used to examine the relationship between AUCss and time to first ISTH major bleed while controlling for potential covariates. A total of 11,984 subjects were included in the analysis, which comprised all warfarin-treated population and apixaban-treated patients with available AUCss data. Age, serum creatinine, body weight, prior stroke/TIA/SE, aspirin use during double-blind period and treatment arm were identified as significant risk factors for ISTH major bleeding and included in the final Cox-PH model. After adjusting these covariates, the positive relationship between AUCss and risk of ISTH major bleeding remains significant. **Table 6** shows the parameter estimates and hazard ratios from the Cox PH model.

Table 6 Parameter Estimates and Hazard Ratios from Cox-Proportional Hazard model for the association between AUCss and ISTH Major Bleeding for Apixaban

Parameter	Estimate (SE)	P value
Age (years)	0.04 (0.005)	<.0001
Serum Creatinine	0.79(0.13)	<.0001
Body weight	-0.007 (0.002)	0.008
Aspirin use	0.18 (0.08)	0.04
Prior stroke/TIA/SE	0.21 (0.10)	0.04
logAUCss (ng*hr/mL)	0.75 (0.32)	0.02
Treatment	-6.62 (2.67)	<.0001

Parameter	Hazard ratio (95 % CI)
Age (5 units increase)	1.24 (1.18-1.30)
Serum Creatinine (0.5 unit increase)	1.49 (1.31-1.69)
Body weight (10 unit increase)	0.94 (0.89-0.98)
Aspirin use (Y vs N)	1.20 (1.01, 1.42)
Prior stroke/TIA/SE (Y vs N)	1.23 (1.01, 1.49)
logAUCss (ng*hr/mL) (1 unit increase)	2.12 (1.13-3.97)

4.3.3 Predictions

The mean predicted probability of ISTH major bleeding within one year according to AUCss was derived from the model and illustrated in **Figure 8**.

The population mean predictions and 95% confidence intervals of the probability of ISTH major bleeding within one year for the apixaban/placebo 5 mg BID, 2.5 mg BID groups as well as the observed event rates (per 100-patient year) in ARISTOTLE are shown in **Table 7**. In addition, the prediction of major bleeding risk within one year for 2.5 mg BID had they received 5 mg BID apixaban (no dose adjustment) is reported. The results indicate that the E-R model for safety predicted the risk of ISTH major bleeding reasonably well compared to the observed data in ARISTOTLE and the model predicted about 2 fold increase in major bleeding risk in 2.5 mg BID group if they were to receive 5 mg BID.

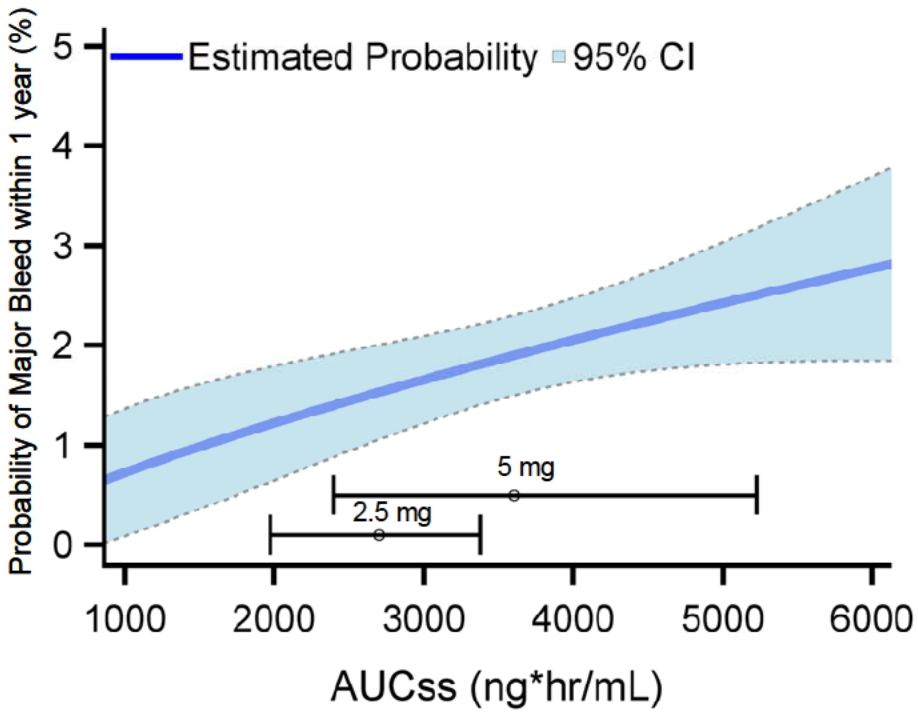


Figure 8 Probability of ISTH Major bleeding within 1 year as a function of the AUCss for apixaban. The shaded region represents the 95% confidence interval. The bars on the bottom represent 5th to 95th percentiles of apixaban AUCss by dose subgroup in the ARISTOTLE PK subset.

Table 7 Predictions of ISTH Major Bleeding risk in one year and observed event rates in ARISTOTLE

ISTH Major Bleeding	Model Predicted Apixaban	Model Predicted warfarin	ARISTOTLE Apixaban Event Rate	ARISTOTLE Warfarin Event Rate
Apixaban/placebo 2.5 mg	3.55 (2.26-4.82)	7.16 (6.05-8.26)	3.29	6.71
Apixaban/placebo 5 mg	1.79 (1.41-2.18)	2.87 (2.51-3.22)	2.09	2.95
2.5 mg receiving 5 mg (no dose adjustment)	6.33 (4.43-8.20)	----	----	----

4.4 Exposure-Response Analyses for Efficacy

4.4.1 Data and Methods

The E-R relationship for efficacy is performed using the same PK subset in ARISTOTLE with individual predicted AUCss as an exposure metric and ischemic stroke as the primary efficacy outcome.

A logistic regression was performed to initially examine the relationship between apixaban exposure and the probability of ischemic stroke in ARISTOTLE PK subset sponsor's dataset: strokese.xpt). The observed probability for an ischemic stroke stratified by apixaban exposure quartile was calculated. An overlay-plot with observed probability in each quartile of apixaban AUCss as well as a predicted probability from the regression model was used to display the relationship between AUCss and ischemic stroke.

A Cox proportional hazard model was further performed to model time to first occurrence of ischemic stroke as a function of the logarithm of AUCss and a set of covariates. To approximate an on-treatment analysis, the time period from the first dose to the last dose of study medication plus 2 days were chosen. If an outcome event did not occur during this timeframe, time was censored at the last dose of study medication plus 2 days. Only time to the first event was considered in the analysis (sponsor's dataset: adefs.xpt).

Because many risk factors for stroke (i.e. age) are correlated with apixaban exposure. For example, as age increases, the risk of stroke is expected to increase, even though apixaban exposure increases. To dissect the influence of confounded factors on exposure, warfarin-treated patients were included in the analysis. The logarithm of AUCss in warfarin-treated subjects was set to be 0.001.

To identify the potential covariates in the model, a bivariate analysis of the association between covariates and survival time was performed. Potential covariates tested included age, sex, race, body weight, creatinine clearance, serum creatinine, prior stroke/TIA/systemic embolism, CHADS2 score, diabetes mellitus, hypertension, myocardial infarction, prior VKA use and aspirin use during double blind period. All covariates that were close to be significant in the bivariate analysis ($p < .20$) were selected in the final model fitting. The reduced model was then fitted and a covariate was considered to be significant at p value $< .05$. An alternative method using the stepwise selection was also employed to verify the covariate selection in the final model. The proportional hazard assumption was checked by plotting the weighted Schoenfeld residuals against the log survival time. All the analyses and plots were conducted and generated in SAS 9.2

4.4.2 Results

A subset of apixaban ITT population [n = 2932/9120 (32%)], which included all subjects with an available AUCss was used in the logistic regression analysis. A total of 27 ischemic stroke were included in this subset [~22% of ischemic stroke (n = 123) in the apixaban ITT population]. The observed and predicted probability (un-adjusted association) of ischemic stroke by AUCss is shown in **Figure 9**. This analysis showed that risk of ischemic stroke is independent of apixaban exposure at the dose level studied.

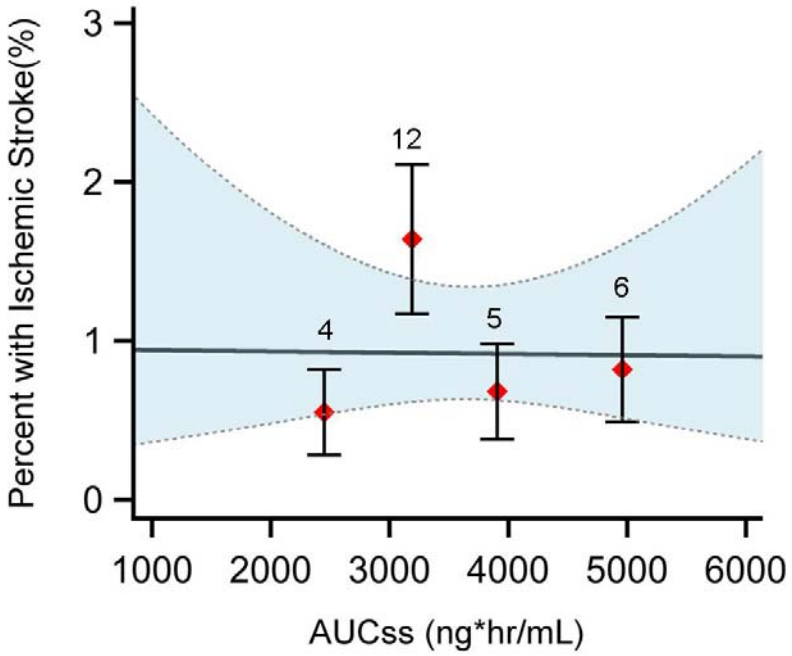


Figure 9 Probability of Ischemic stroke as a function of steady-state AUC. The solid line represents the predicted probability from an unadjusted linear logistic regression. The red markers represent the observed probability at the median AUCss for a given quartile.

A Cox PH model was used to examine the relationship between AUCss and time to first ISTH major bleed while controlling for potential covariates. A total of 11,984 subjects were included in the analysis, which comprised all warfarin-treated population and apixaban-treated patients with available AUCss data. Age, prior stroke/TIA/SE, CHADS score and race were identified as significant risk factors. Treatment arm was not significant but was included in the model to allow a different estimate of the intercept. AUCss remained unassociated with risk of ischemic stroke after adjusting for covariates.

The E-R analyses for efficacy were limited by the small number of ischemic stroke event in the PK subset and the range of exposures available. In addition to the limitations, the slope was shallow and not precisely estimated; therefore, no further interpretation of the Cox PH model was made.

4.5 Additional Summary Statistics using ARISTOTLE Trial Data

Based on the E-R analyses, it is expected that 2.5 mg BID could significantly reduce major bleeding risk in selected patients based on sponsor's criteria; however, the efficacy effect in the 2.5 mg BID group has to be carefully evaluated using the ARISTOTLE trial data since a robust E-R efficacy relationship can not be established. **Figure 10** shows the efficacy results of apixaban compared to warfarin by dose group and types of stroke. The hazard ratios for ischemic/unspecified stroke and hemorrhagic stroke were 0.66 (0.29-1.48) and 0.32 (0.06-1.56) respectively in 2.5 mg BID group compared to 0.94 (0.75-1.17) and 0.52 (0.35-0.78) in 5 mg BID group. Although 2.5 mg BID group was small (~4.6% of randomized subjects), the efficacy effect of apixaban in reducing stroke/SE compared to warfarin was reasonably retained.

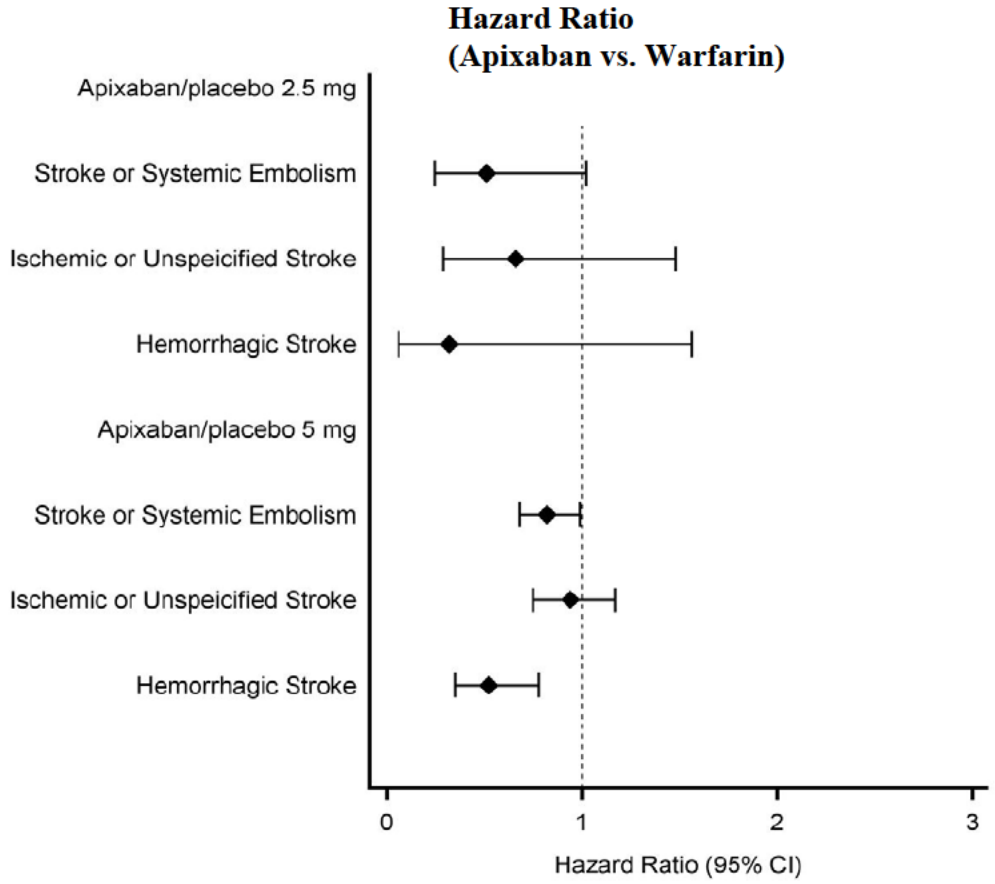


Figure 10 Forest Plot showing hazard ratios (warfarin as the reference) for different efficacy endpoints by dose groups during the intended treatment period-randomized subjects

4.5.1 Efficacy results among patients with lower apixaban exposure

To investigate the impact of lower apixaban exposure on efficacy, the event rate for primary efficacy endpoints was studied in subjects with high body weight (≥ 120 kg) in 5 mg (n = 1032) (**Table 8**). The median apixaban exposure in subjects with high body weight receiving the 5mg dose was similar to that in 2.5 mg. In both groups, the concentrations are ~25% lower compared to average 5 mg dose group. There was a robust effect in reducing stroke/SE in both 2.5 mg and high body weight group compared to warfarin. These results suggest that 25% decrease in apixaban exposure due to a dose adjustment or an intrinsic factor might not result in loss of efficacy.

Table 8 Event rate and hazard ratio for primary efficacy endpoint in 2.5 mg and high body weight subgroup.

	Median Apixaban AUCss (ng*hr/mL)	Apixaban n/N (% yr)	Warfarin n/N (% yr)	HR (95% CI)
2.5 mg	2703 (n = 128)	12/428 (1.70)	22/403 (3.33)	0.50 (0.20-1.02)
Weight ≥120kg in 5 mg	2690 (n = 179)	4/513 (0.40)	12/519 (1.19)	0.34 (0.11-1.06)
Weight <120kg in 5 mg	3662 (n = 2625)	196/8179 (1.30)	231/8159 (1.55)	0.84 (0.70-1.02)

4.5.2 Issues related to dose adjustment criteria

During the course of the review, a question was raised regarding the choice of serum creatinine instead of creatinine clearance (CRCL) as one of the dose adjustment criteria. The concern was CRCL is the clinical maker to evaluate renal function not serum creatinine and there would be possibility that patients with severe or moderate renal impairment (CRCL ≤ 50 ml/min) do not met sponsor's dose adjustment criteria and might be at higher risk of bleeding. **Figure 11** shows that sponsor's criteria reasonably adjusts for renal function as measured by baseline CRCL. 90% of 2.5 mg BID group had severe or moderate renal impairment with median CRCL of 37 ml/min while only 13% of 5 mg BID had CRCL below 50 ml/min with median of 80 ml/min. **Table 9** indicates that apixaban lower major bleeding risk among patients with severe or moderate renal impairment compared to warfarin within both 5 and 2.5 mg BID. Although patients with severe or moderate renal impairment receiving 5 mg had on average about 40% increase in exposure compare to a typical patient receiving 5 mg (median AUC: 3603 ng*hr/ml), the bleeding risk remained significantly lower in this subset of patients compared to warfarin patients, consistent with the findings in 2.5 mg subset. These results suggest that using the sponsor's criteria, majority of patients with severe or moderate renal impairment would receive 2.5 mg BID and bleeding risk remains relatively low in those who received 5 mg BID compared to warfarin.

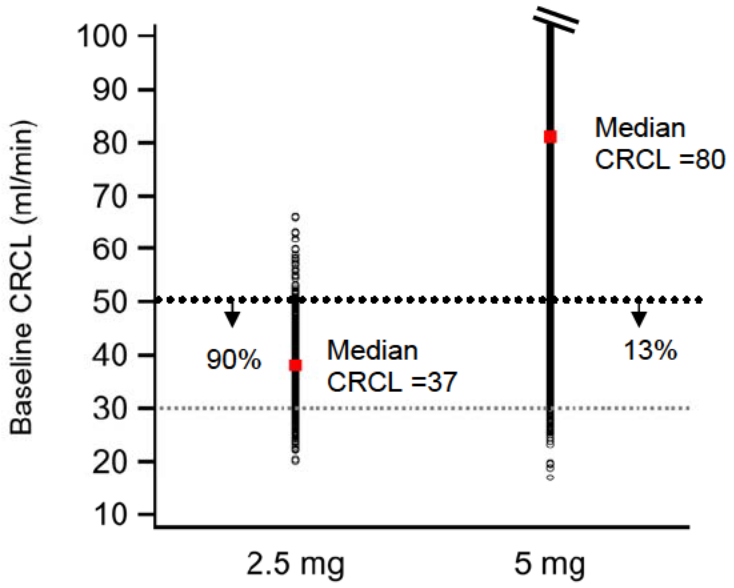


Figure 11 Baseline CRCL according to dose group

Table 9 Event rates and hazard ratios for patients with severe or moderate renal impairment (≤ 50 ml/min) according to dose group

Severe or moderate renal impairment	Median Apixaban AUCss(ng*hr/mL)	Apixaban n (% yr)	Warfarin n (% yr)	HR (95% CI)
Apixaban/placebo 2.5mg (N = 382/347)	2746	15 (2.70)	35 (7.44)	0.37 (0.20-0.68)
Apixaban/placebo 5mg (N=1111/1165)	4987	58 (3.37)	107 (6.16)	0.55 (0.40-0.76)

Considering the clinical utility of CRCL and a high correlation between body weight and CRCL, a simplified dose adjustment strategy based on two factors: age ≥ 80 years and CRCL ≤ 50 ml/min was explored. About 3% of patients (n = 281) receiving 5 mg (per protocol) would switch to 2.5 mg based on this new criteria, while 18% of patients (n = 77) would receive 5 mg instead of 2.5 mg (per protocol) in ARISTOTLE. The median and distribution of exposures using the new criteria dose not change much from the original criteria (per protocol) in the PK subset (see **Table 9** and **Figure 12**).

Table 9 Median apixaban exposure and patient allocation by dose group using the protocol-defined dose adjustment criteria and new criteria in the ARISTOTLE PK subset

Dose	Median Apixaban AUCss(ng*hr/mL) Per Protocol	Median Apixaban AUCss(ng*hr/mL) New Criteria
2.5 mg	2703 (n = 128)	2648 (n = 178)
5 mg	3603 (n =2804)	3579 (n = 2754)

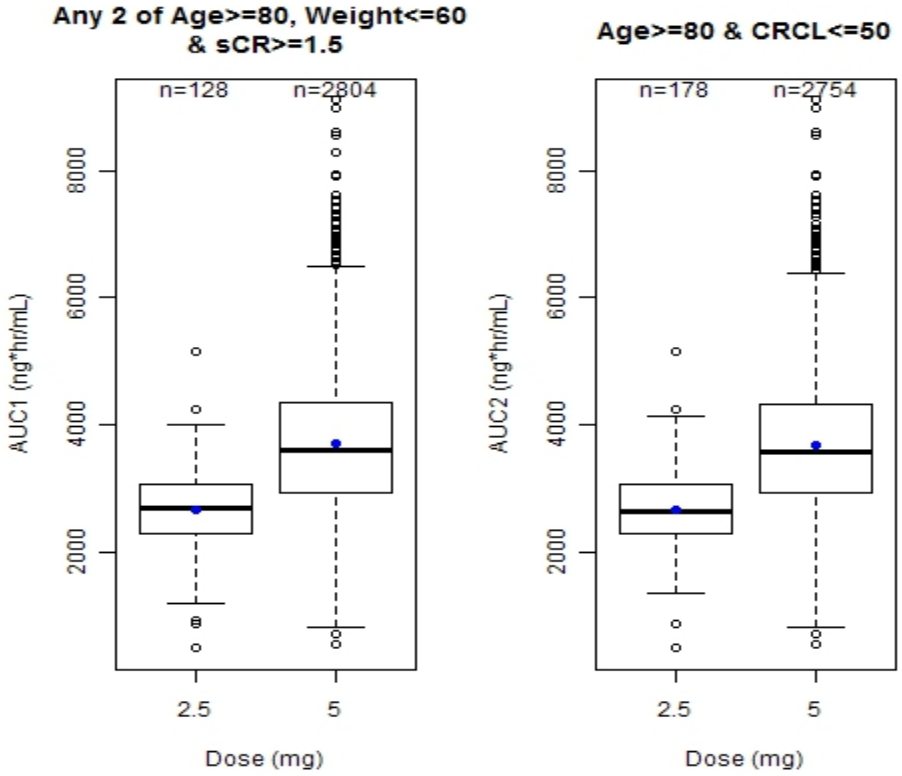


Figure 12 Distribution of apixaban exposure by dose group using the protocol-defined dose adjustment criteria and new criteria in the ARISTOTLE PK subset

Although it seems reasonable to use the new simplified dose adjustment criteria based on PK matching, there is no empirical evidence to support any new dose adjustment strategy. The changes in patient allocation for dose assignment using the new criteria, may not ensure the efficacy effect for those who would switch from 5 mg to 2.5 mg and the bleeding risk may increase among those switching from 2.5 mg to 5 mg. Considering that the sponsor's criteria reasonably adjusted for CRCL and the clinical impact of any new dose adjustment strategy is not evaluable, we do not recommend any modifications to the sponsor's dose adjustment criteria.

4.5.3 Apixaban exposure by race

The Sponsor claims that there is no distinct difference in apixaban pharmacokinetics between White/Caucasian, Asian, and Black/African American subjects based on their phase 1 studies and the PPK analysis. **Figure 13** shows apixaban exposure according to race in the PK subset in ARISTOLE. This result is in agreement with the sponsor's labeling claims.

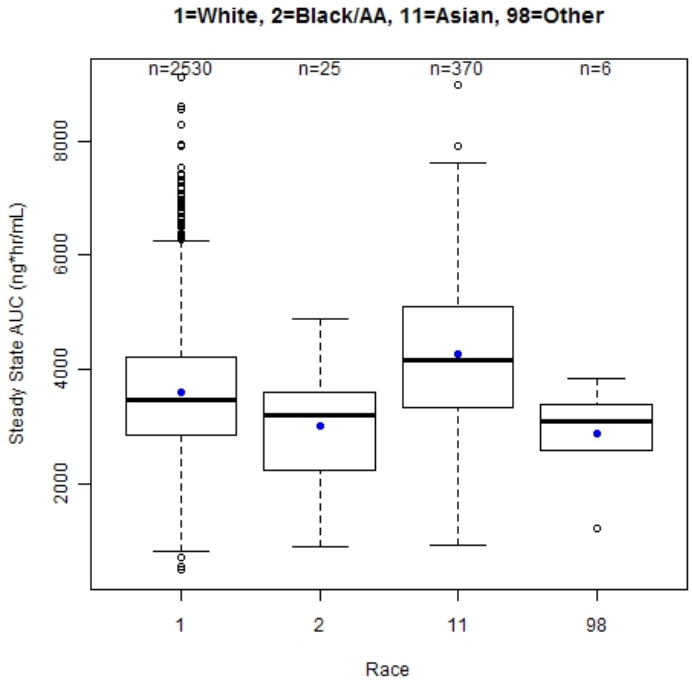


Figure 11 Distribution of apixaban exposure by race in the PK subset in ARISTOTLE

LISTING OF ANALYSES CODES AND OUTPUT FILES

File Name	Description	Location in \\cdsnas\pharmacometrics\
AUC_MB_Cox.sas	Exposure-Response Analysis for Major Bleeding	Reviews\Ongoing PM Reviews\Apixaban_NDA202155_DDM\ER Analyses
AUC_SE_Cox.sas	Exposure-Response Analysis for Ischemic Stroke	Reviews\Ongoing PM Reviews\Apixaban_NDA202155_DDM\ER Analyses
AUC_Check_review.R	Analysis of POP-PK output, plots	Reviews\Ongoing PM Reviews\ Apixaban_NDA202155_DDM\ PPK Analyses\final_stage2_model
run1.mod	Final Stage 2 model control file	Reviews\Ongoing PM Reviews\ Apixaban_NDA202155_DDM\ PPK Analyses\final_stage2_model
run1.lst	Final Stage 2 model output file	Reviews\Ongoing PM Reviews\ Apixaban_NDA202155_DDM\ PPK Analyses\final_stage2_model
Apixaban_plots_cond1.R	AUC-Event analysis for alternative dose adjustment scheme (age>=80 and CRCL<=50)	Reviews\Ongoing PM Reviews\ Apixaban_NDA202155_DDM\ ER Analyses
Apixaban_plots_cond2.R	AUC-Event analysis for alternative dose adjustment scheme (any two of age>=80, WT<=60, CRCL<=50)	Reviews\Ongoing PM Reviews\ Apixaban_NDA202155_DDM\ ER Analyses

4.3 APPENDIX III

PHARMACOGENOMICS REVIEW

OFFICE OF CLINICAL PHARMACOLOGY
GENOMICS GROUP REVIEW

NDA/BLA Number	202155
Submission Date	09/28/2011
Applicant Name	Bristol Myers Squibb
Generic Name	Apixaban
Proposed Indication	Reduce the risk of stroke, systemic embolism (b) (4) in patients with nonvalvular atrial fibrillation
Primary Reviewer	Hobart Rogers, Pharm.D, Ph.D.
Secondary Reviewer	Michael Pacanowski Pharm.D., M.P.H.

1 Background

Apixaban is an orally active, direct, reversible inhibitor of factor Xa. This NDA is being reviewed for the indication of reducing the risk of stroke, systemic embolism (b) (4) in patients with nonvalvular atrial fibrillation. The purpose of this review is to identify any significant role that genetic variation could play on the safety, efficacy, or disposition of apixaban.

2 Submission Contents Related to Genomics

The effects of genetic polymorphisms were not directly studied in the development of apixaban. The sponsor did not submit any genotype data or genotyping reports for any clinical trials. The sponsor did collect an optional pharmacogenomic blood sample in one phase 3 trial where warfarin was the comparator. Data regarding CYP2C9 and VKORC1 genotype, the major response determinants of the comparator warfarin, were not reported.

3 Key Question and Summary of Findings

3.1 Are pharmacogenomic studies indicated on the basis of the PK, safety, and efficacy profile of apixaban?

Apixaban exhibits low to moderate variability, with exposure parameters having intra- and inter-subject variability of ~20% (CV%) and ~30% (CV%), respectively. Apixaban is primarily metabolized by CYP3A4/5 (~80%) , with CYP1A2, 2C8, 2C9, 2C19 and 2J2 playing minor roles in its metabolism. While many of these enzymes are polymorphic, genetic variations are unlikely to have a clinically significant impact on apixaban exposure given major role of CYP3A4 and the redundancy of the metabolism. No racial differences in apixaban exposure or anti-Xa activity were observed in Phase 1 trials. No outliers were identified in multiple dose PK studies. Genetic variants in the drug target, factor Xa, are extremely rare and usually result in coagulation disorders with severe

phenotypes. Additionally, the variability in apixaban response as measured by the anti-Xa assay is very low.

The efficacy and safety of apixaban was evaluated in two Phase 3 trials. Both phase 3 trials enrolled subjects with atrial fibrillation. One phase 3 trial (CV185030) used warfarin as the comparator, while the other (CV185048) used aspirin in subjects who were unsuitable for warfarin. A composite endpoint of stroke and systemic embolism was the primary endpoint in both trials.

Apixaban significantly reduced rates of stroke and system embolism compared to warfarin (1.27% vs. 1.60%) and aspirin (1.62% vs. 3.63%). The efficacy of apixaban did not vary according to race, although a limited number of black/African-American subjects were enrolled. Geographic differences in efficacy were noted in trial CV185048, although this effect was not observed in CV185030. Warfarin control was reasonable (average time-in-therapeutic range was 60.5%), despite 43% of the population being treatment-naïve.

Apixaban had lower rates of major bleeding compared to warfarin (2.13% vs. 3.09%), although the rates of major bleeding were higher compared to aspirin (1.41% vs. 0.92%). Bleeding was correlated with drug exposure (see Pharmacometrics review); no significant heterogeneity in bleeding rates was observed across racial or geographic subgroups in either trial. No idiosyncratic AEs were observed.

4 Summary and Conclusions

Apixaban does not appear to have significant pharmacokinetic variability, race effects, or outliers that would be explained by polymorphic metabolism or transport.

Apixaban appears to reduce the rate of stroke and systemic embolic events compared to warfarin, without increasing bleeding rates.

Apixaban is likely to have superior efficacy and safety compared to warfarin in individuals with variant CYP2C9 and VKORC1 genotypes (the major determinants of warfarin response).

5 Recommendations

Overall, it is unlikely that common genetic variation plays any clinically significant role in the safety, efficacy or disposition of apixaban, based on its pharmacokinetic and pharmacodynamic profile and Phase 3 trial data, which suggest that apixaban is safe and effective when compared to warfarin or aspirin. Additional pharmacogenetic studies do not appear to be indicated.

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/s/

JU PING LAI
02/15/2012

DIVYA MENON ANDERSEN
02/15/2012

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CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS
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Office of Clinical Pharmacology
New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA/BLA Number	202-155	Brand Name	Eliquis
OCP Division(s)	DCP 1, DPM	Generic Name	Apixaban
Medical Division	DCRP	Drug Class	Factor Xa inhibitor
OCP Reviewer	Ju-Ping Lai, Tzu-Yun McDowell, Divya Menon-Andersen	Indication(s)	Stroke/SE prevention in AFib
OCP Team Leader	Raj Madabushi	Dosage Form	Tablet
Pharmacometrics Reviewer	Dhananjay Marathe, Pravin Jadhav (TL)	Dosing Regimen	BID
Date of Submission	09/28/2011	Route of Administration	Oral
Estimated Due Date of OCP Review	02/25/2012	Sponsor	BMS/Pfizer
Medical Division Due Date	03/28/2012	Priority Classification	Priority (6 month clock)
PDUFA Due Date	03/28/2012		

Clinical Pharmacology and Biopharmaceutics Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	**X**			
Tabular Listing of All Human Studies	**X**			
HPK Summary	**X**			
Labeling	**X**			
Reference Bioanalytical and Analytical Methods	**X**	**22**	**22**	20→ PK of Apx, metabolites (plasma, urine) and all conmeds/CYP substrates studied in DDIs 2→ mPT and anti Xa
I. Clinical Pharmacology				
(1) Mass balance:	**X**	**1**	**1**	
(2) Isozyme characterization:	**X**	**5**	**5**	
(3) Blood/plasma ratio:	**X**	**1**	**1**	
(4) Plasma protein binding:	**X**	**1**	**1**	
(5) Pharmacokinetics (e.g., Phase I) -	**X**			
(6) Healthy Volunteers-	**X**			
single dose:	**X**	**7**	**7**	
multiple dose:	**X**	**2**	**2**	
(7) Patients-	**X**			Sparse sampling in P2/P3
single dose:				
multiple dose:				
(8) Dose proportionality -	**X**			
fasting / non-fasting single dose:	**X**	**2**	**2**	Counted under (6)
fasting / non-fasting multiple dose:	**X**	**2**	**2**	
(9) Drug-drug interaction studies -				

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In-vivo effects on primary drug:	**X**	**11**	**11**	
In-vivo effects of primary drug:	**X**	**11**	**11**	
In-vitro:	**X**	**10**	**10**	
(10) Subpopulation studies -				
ethnicity:	**X**	**2**	**2**	
gender:	**X**	**1**	**1**	
body weight:	**X**	**1**	**1**	
pediatrics:				
geriatrics:	**X**	**1**	**1**	
renal impairment:	**X**	**1**	**1**	
hepatic impairment:	**X**	**1**	**1**	
(11) Pharmacodynamics -				
Phase 2:	×	**3**	**3**	CV185067 (P2 AFib), CV185010 and CV185017 (P2 Dose selection)
Phase 3:	×	**1**	**1**	ARISTOTLE
(12) PK/PD -				
Phase 1 and/or 2, proof of concept:	**X**	**6**	**6**	Counted under (6)
Phase 3 clinical trial:	×	**2**	**2**	ARISTOTLE (~30% with PK/PD) AVERROES (no PK/PD)
(13) Population Analyses -				
Data rich:	**X**	**1**	**1**	Population PK/PD-Outcomes analysis conducted using data collected in P1 - P3 studies
Data sparse:	×	**1**		
II. Biopharmaceutics				
(1) Absolute bioavailability	**X**	**2**	**2**	
(2) Relative bioavailability -				
solution as reference:	**X**	**1**	**0**	To support (b) (4), not to be reviewed
alternate formulation as reference:	**X**	**1**	**1**	
(3) Bioequivalence studies -				
traditional design; single / multi dose:	**X**	**1**	**1**	
replicate design; single / multi dose:				
(4) Food-drug interaction studies	**X**	**1**	**1**	
(5) Bio-waiver request based on BCS				
(6) BCS class	**X**	**4**	**4**	Permeability studies
(7) Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies				
(1) Genotype/phenotype studies				
(2) Chronopharmacokinetics				
(3) Pediatric development plan	Waiver requested for SPAF indication			
(4) Literature References	**X**			
Total Number of Studies		**71▲**	**70**	▲ studies contributing data to various categories are counted only once

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS
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On **initial** review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?			X	P3 formulation differs from TBM tablet in appearance only
2	Has the applicant provided metabolism and drug-drug interaction information?	X			
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?	X			
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	X			
5	Has a rationale for dose selection been submitted?	×			
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	X			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	X			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	×			
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
	Data				
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	X			
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			×	
	Studies and Analyses				
11	Is the appropriate pharmacokinetic information submitted?	X			
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	X			
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?	×			
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?	×			
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			X	
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			X	
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	X			
	General				
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	X			
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?	X			Japanese to English, where applicable

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE? YES

File name: 5_Clinical Pharmacology and Biopharmaceutics Filing Form/Checklist for NDA_BLA or Supplement

(b) (4)

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS
FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Ju-Ping Lai, Tzu-Yun McDowell, Divya Menon-Andersen	10/28/2011
Reviewing Clinical Pharmacologist	Date
Rajanikanth Madabushi	10/28/2011
Team Leader/Supervisor	Date

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/s/

DIVYA MENON ANDERSEN
10/31/2011

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