CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202155Orig1s002

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Clinical Pharmacology/Biopharmaceutics Review
Labeling Supplement

PRODUCT (Generic Name):	Apixaban
NDA:	202-155
PRODUCT (Brand Name):	ELIQUIS®
DOSAGE FORM:	Tablets
DOSAGE STRENGTHS:	2.5 mg and 5 mg
INDICATION:	(b) (4) of stroke, systemic embolism, (b) (4) in patients with non-valvular atrial fibrillation
SUBMISSION DATE:	4/29/2013
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

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1. EXECUTIVE SUMMARY

In this submission, the applicant proposes [redacted] (b) (4) the results of a dedicated study in ESRD subjects maintained on hemodialysis. In addition, the applicant also proposes to include the PK/PD information based on the results of a dedicated PK/PD drug interaction study of apixaban with prasugrel.

Apixaban was approved in December 2012 as a factor Xa inhibitor anticoagulant indicated to reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation. In the original submissions, an activated charcoal study showed that half-life of apixaban decreased from ~13h to ~ 5h when charcoal is administered 2 hours post apixaban. Since no clear hypothesis explaining the effect of charcoal (not systemically absorbed), Agency felt the need to explain this finding in the US package insert. With available information at the time, we reflected our thoughts in the approved label. The rationale is summarized below.

Apixaban has an absolute bioavailability (BA) of 50%. ~ 50 % of apixaban was recovered in the feces after an oral dose. Distal small bowel and ascending colon have absorption capacity up to ~50 % of that absorbed from oral administration. Activated charcoal administered 2 h after apixaban resulting in ~50% decrease in exposure of apixaban. The biliary excretion of apixaban is minimal (2.4%). Our understanding was that activated charcoal binds/adsorbs apixaban in the gastrointestinal (GI) preventing additional absorption from the remaining drugs in the GI tract. In this sense, elimination of apixaban from systemic circulation was not expected to change by activated charcoal therefore half-life change was not expected. However, half-life of apixaban decreased from ~13h to ~ 5h with charcoal. When looking into IV data, the half-life is apparently shorter (~6 h) suggesting a possibility of prolonged absorption causing a longer apparent half-life after oral administration.

The applicant believes that direct intestinal excretion (IE) and entero-enteric recirculation (EER) play a significant role on apixaban excretion/disposition. It is noted that this is a new proposal and is contrary to the applicant's understanding of the pharmacokinetics of apixaban in the original submission, i.e., there is insignificant intestinal and biliary excretion for apixaban. Based on this information, the applicant claims that the half-life reduction of apixaban when charcoal is administered is justified.

Based on the findings from the two dedicated studies i.e., impact of ESRD and the interaction between apixaban and prasugrel, the applicant is seeking to update sections 12.2 and 12.3 of the US package insert.

We have reviewed the submitted information and conducted additional literature search. We conclude that neither mechanisms proposed by the applicant can be confirmed without additional clinical studies. We find the results of the dedicated study in ESRD subjects maintained on hemodialysis and the interaction study with prasugrel acceptable.

1.1 Recommendations

The Office of Clinical Pharmacology has reviewed this submission and has the following recommendations:

- (b) (4)
- The impact of charcoal administration on the AUC but not the half-life findings will be included in the label.
- Dosing instructions for patients with ESRD maintained on hemodialysis will be provided in the label. The recommended dose of apixaban in ESRD patients is 5 mg b.i.d. In ESRD patients either age≥80 years or body weight≤ 60 kg, the recommended dose is 2.5 mg b.i.d.

Detailed labeling recommendations are presented in Section 3.

2. CLINICAL PHARMACOLOGY SUMMARY

(b) (4)

(b) (4)

[redacted]

2.2 Impact of ESRD and Hemodialysis on the Pharmacokinetics of Apixaban

Compared to healthy subjects, apixaban AUC was 36% greater in ESRD subjects after hemodialysis. This increase is slightly lower than that previously reported in subjects with severe impairment in renal function (CrCl of 15 - 30 mL/min - exposure 50% greater compared to normal renal function). It should be noted, currently there is no dose adjustment recommended in patients with severe impairment of renal function.

In subjects with end-stage renal disease (ESRD), a 4-hour hemodialysis session with a dialysate flow rate of 500 mL/min and a blood flow rate in the range of 350 to 500 mL/min started 2 hours

(b) (4)

[redacted]

after administration of a single 5 mg dose of apixaban, the AUC of apixaban was 17% greater compared to those with normal renal function. As expected the dialysis clearance of apixaban is approximately 18 mL/min resulting in a 14% decrease in exposure due to hemodialysis.

Protein binding was similar between healthy controls and the two periods: 93.2%, 91.5% and 94.1%. So the impact of protein binding is not significant.

The concentration-anti-Xa activity relationship in the ESRD subjects is reasonably similar compared to healthy subjects with normal renal function.

3. DRAFT LABELING RECOMMENDATIONS

Only Sections contain clinical pharmacology related changes are provided. Sponsor's new proposal is marked in **Blue**. Sponsor proposed deletions are shown as ~~**strikethroughs**~~. The OCP's recommendations are shown as track changes in **Red**. The rationale supporting the reviewer's edits are provided below the specific edits as ***Reviewer's Comments***.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dose

The recommended dose of ELIQUIS for most patients is 5 mg taken orally twice daily (b) (4)

Reviewer's Comments: (b) (4)

8 USE IN SPECIFIC POPULATIONS

8.6 ESRD Patients Maintained with hemodialysis

The recommended dose for ESRD patients maintained with hemodialysis is 5 mg orally twice daily. For the ESRD patients maintained with hemodialysis having either one of the risk factors of age ≥80 years or body weight ≤ 60kg, the recommended dose should be reduced to 2.5 mg twice daily. There is no clinical experience for this dosing regimen in this patient population.

Reviewer's Comments: *As ESRD patients were not enrolled in the pivotal trial, there is no clinical experience for this patient population. The dose recommendation is based on the similar apixaban exposure and similar anti-FXa activity observed in the new PK/PD study report in this submission when compared to the data from severe renal impaired patients.*

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 AUC by 50% and 27%, respectively.- (b) (4)

Thus, administration of activated charcoal may be useful in the management of apixaban overdose or accidental ingestion (b) (4)

Reviewer's Comments: (b) (4)

12 CLINICAL PHARMACOLOGY

12.2 Pharmacodynamics

(b) (4)

Reviewer's Comments: (b) (4)

Pharmacodynamic Drug Interaction Studies

Pharmacodynamic drug interaction studies with aspirin, clopidogrel, aspirin and clopidogrel, prasugrel, enoxaparin, and naproxen were conducted. No pharmacodynamic interactions were observed with aspirin, (b) (4) clopidogrel, or prasugrel. (b) (4) - A 50% to 60% increase in anti-FXa activity was observed when apixaban was coadministered with enoxaparin or naproxen.

Reviewer's Comments: *Addition of PD interaction information with prasugrel is acceptable. As the bleeding related AEs were significantly more frequent in the co-administered group, additional language to describe the findings will be provided by the medical officer.*

12.3 Pharmacokinetics

(b) (4)

Absorption

The absolute bioavailability of apixaban is approximately 50% for doses up to 10 mg of ELIQUIS. Food does not affect the bioavailability of apixaban. Maximum concentrations (C_{max}) of apixaban appear 3 to 4 hours after oral administration of ELIQUIS (b) (4)

Apixaban demonstrates linear pharmacokinetics with dose-proportional increases in exposure for oral doses up to 10 mg. At doses ≥25 mg, apixaban displays dissolution-limited absorption with decreased bioavailability.

Elimination

Apixaban is eliminated in both urine and feces. Renal excretion accounts for about 27% of total clearance. Biliary and direct intestinal excretion contributes to elimination of apixaban in the feces.

(b) (4)

Apixaban has a total clearance of approximately 3.3 L/hour and an apparen (b) (4)
half-life of approximately 12 hours following oral administration, (b) (4)

Apixaban is a substrate of transport proteins: P-gp and breast cancer resistance protein.

Reviewer's Comments: (b) (4)

Drug Interaction Studies

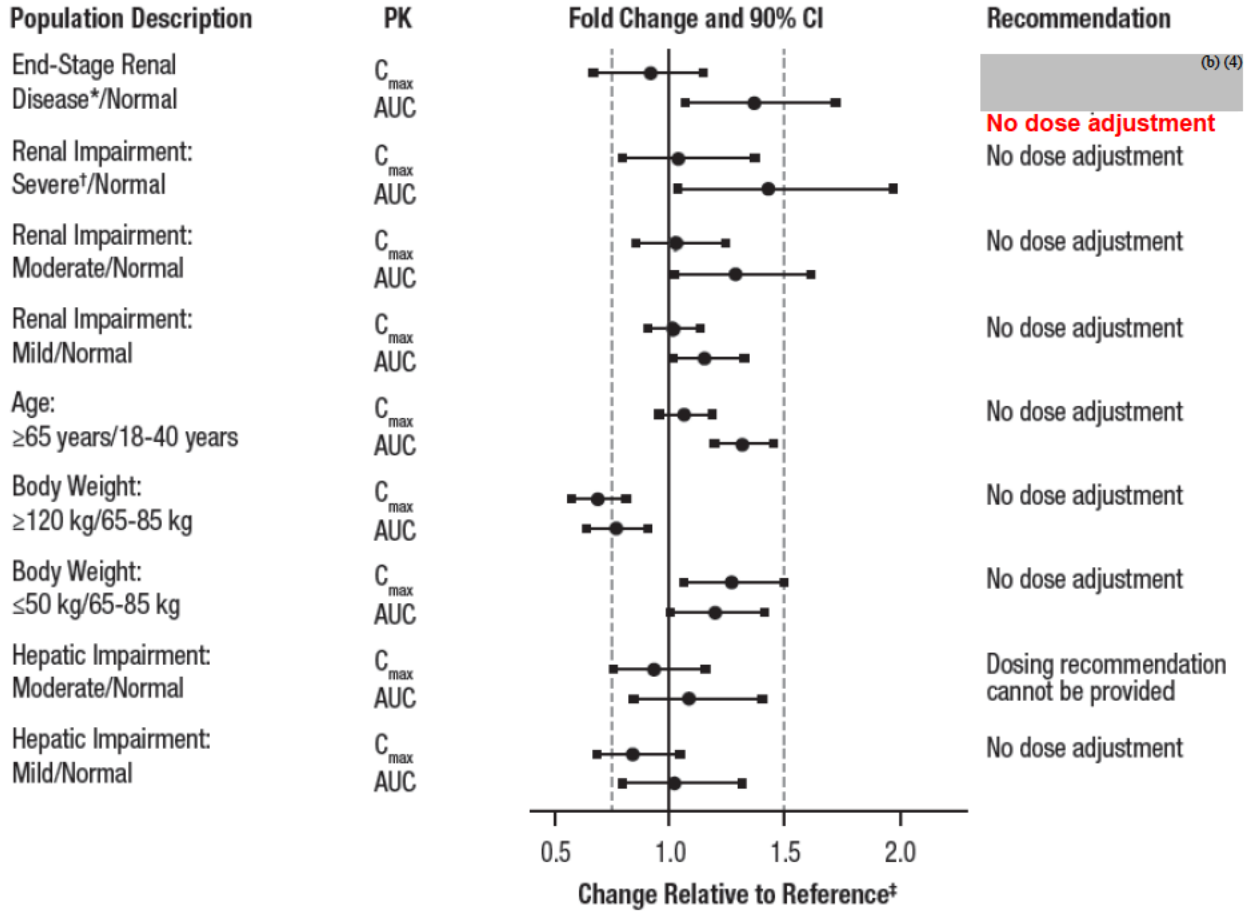
In dedicated studies conducted in healthy subjects, famotidine, atenolol, prasugrel, and enoxaparin did not meaningfully alter the pharmacokinetics of apixaban.

In studies conducted in healthy subjects, apixaban did not meaningfully alter the pharmacokinetics of digoxin, naproxen, atenolol, prasugrel, or acetylsalicylic acid.

Reviewer's Comments: *Addition of PK interaction information with prasugrel is acceptable.*

Specific Populations

The effects of level of renal impairment, age, body weight, and level of hepatic impairment, (b) (4) on the pharmacokinetics of apixaban are summarized in Figure 3.



* ESRD subjects maintained with chronic and stable hemodialysis; Reported PK findings are following single dose of apixaban post hemodialysis (b) (4)

Creatinine clearance 15 to 29 mL/min.

‡ Dashed vertical lines illustrate pharmacokinetic changes that were used to inform dosing recommendations.

A study in healthy subjects comparing the pharmacokinetics in males and females showed no meaningful difference.

The results across pharmacokinetic studies in normal subjects showed no differences in apixaban pharmacokinetics among White/Caucasian, Asian, and Black/African American subjects. No dose adjustment is required based on race/ethnicity.

In subjects with (b) (4) ESRD (b) (4) a 4-hour hemodialysis session with a dialysate flow rate of 500 mL/min and a blood flow rate in the range of 350 to 500 mL/min started 2 hours after administration of a single 5 mg dose of apixaban, (b) (4)

(b) (4) the AUC of apixaban was 17% greater compared to those with normal renal function. The dialysis clearance of apixaban is approximately 18 mL/min resulting in a 14% decrease in exposure due to hemodialysis compared to off-dialysis period.

Protein binding was similar between healthy controls and the on-dialysis and off-dialysis periods reported as 93.2 %, 94.1 % and 91.5 %, respectively.

Reviewer's Comments: *Addition of PK information in ESRD patients with dialysis is acceptable. As new information become available from the study, key findings are to be provided in the label and to support the label for ESRD patients on hemodialysis. Currently there is no dose adjustment recommended in patients with severe impairment of renal function. The proposed action is no different than what we currently have of patients with severe impairment of renal function (CrCl 15 - 30 mL/min). Details regarding the study are included in the individual study review in Section 4 in this review.*

4. APPENDIX- INDIVIDUAL STUDY REVIEWS

Renal Impairment – ESRD maintained with hemodialysis

Report # CV185087	**Study Period** 06/28/11-09/12/11
Title	Single-Dose Study To Evaluate the Pharmacokinetics, pharmacodynamics, and Safety of Apixaban in Subjects on Hemodialysis

EDR Link \\cdsesub1\evsprod\nda202155\0086\m5\53-clin-stud-rep\533-rep-human-pk-stud\5333-intrin-factor-pk-stud-rep\cv185087\study-cv185087-csr-final.pdf

Study Design

Single-Dose	Non-Randomized	Open-Label		Parallel		Single-Center
No. of Groups	**2**	☑Normal (A)	☐Mild	☐Moderate	☐Sever	☑ESRD (B)
No. of Subject /Completed	**16/16**	8/8				8/8
Males/Females	**12/4**	6/2				6/2
Age, Mean(range)		47.0(34-59)				46.9(36-63)
Body Weight, kg, Mean(range)		87.4 (66.3-114.7)				92.5 (62.2-126)
Dose	5 mg	5 mg				5 mg
Enrollment and pre-classification of subjects was based upon the estimated CLcr value determined using Cockcroft-Gault formula at the time of screening and baseline. Estimation of GFR was also performed on day -1 using MDRD equation.						
All subjects received apixaban after at least a 10-hr fast. Group A: Subjects received a single oral dose of 5 mg apixaban Group B: Subjects requiring dialysis followed a thrice-weekly dialysis schedule. Apixaban was dosed twice in hemodialysis subjects (Day 1 of Periods 1 and 2) separated by a washout of at least 7 days. On Day 1 of Period 1, a 4-hour hemodialysis session was started 2 hours after apixaban						

administration. On Day 1 of Period 2, apixaban was dosed immediately after completion of a 4-hour hemodialysis session.
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, 60 and 72 hours post dose. **PK, urine:** Pre-dose and 0-12, 12-24, 24-48 and 48-72 hours post dose. **PD, plasma**: Pre-dose and 0.5, 1.5, 3, 6, 12, 24, 48 and 72 hours post dose. **Dialysate:** 2, 2-3, 3-4, 4-5 and 5-6 hours post dose.

Table 3.4.2: Study Drug Information

Formulation	Unit	Route	Product Identification No.	Batch Product No.	Label Batch No.
Apixaban tablet	5 mg	Oral	562247-K005-027 562247-K005-041	7L26408	0E56753

- Classification of renal function is consistent with the FDA Guidance Recommendations:

☑ Yes ☐ No

Group	Description	Creatinine Clearance (ClCr)[a]
A (8 Subjects)	Normal Renal Function	> 80 mL/min
B (8 Subjects)	ESRD maintained with hemodialysis	Not Applicable

[a] CLCr (Cockroft-Gault) = (140-age) x (Wt in kg) x (0.85 if female) / (72 * S_{cr})

- Renal function was determined via ☑ C-G formula for healthy subjects at screening and Day -1
  ☑ MDRD formula on Day -1
- 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: ☑All ☐Limited (in all subjects)
  Sampling Times: 4 hours after apixaban dose
  Method: Equilibrium dialysis
- 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

☑ Yes ☐ No

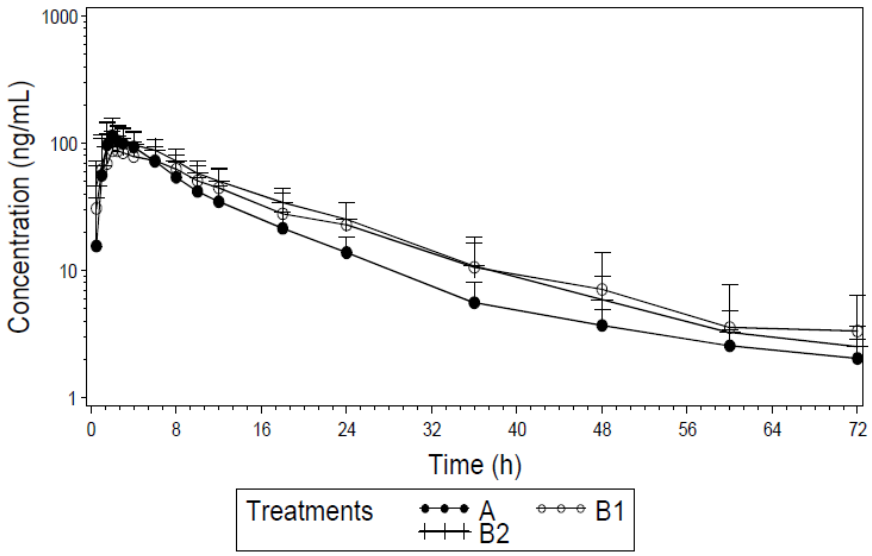
LC-API/MS/MS methods were utilized for determination of apixaban and its metabolite, BMS-730823 (M1). Assay performances are provided below:

Analyte	Matrix	LLOQ (ng/mL)	ULOQ (ng/mL)	Between-run %CV[a]	Within-run %CV[a]	Mean % Deviation from Nominal Concentration[a]
BMS-562247	Human Plasma	1.00	1000	≤6.41	≤6.50	±4.47
	Human Urine	1.00	1000	≤3.10	≤4.00	±8.49
	Human Dialysate	1.00	500	≤3.38	≤1.63	±3.60
	Human Serum:Buffer	1.00	200	≤3.61	≤4.89	±8.44
BMS-730823	Human Plasma	5.00	1000	≤5.89	≤6.81	±1.17
	Human Urine	5.00	1000	≤6.21	≤10.7	±5.28
	Human Dialysate	1.00	500	≤5.09	≤5.71	±2.75

[a] Maximum value from analysis of analytical QCs (Tables 4, 7, 10, 14,17, 21, and 25).

Pharmacokinetics of Apixaban

1. Is there a relationship between creatinine clearance and AUC? ☐Yes ☐No ☑NA, if yes explain
2. Is there a relationship between creatinine clearance and C_{max}? ☐Yes ☐No ☑NA, if yes explain



Treatments:

TRT A = Group A: normal renal function (n=8)

TRT B1 = Group B P1: ESRD with hemodialysis started 2 hr after apixaban administration (n=8)

TRT B2 = Group B P2: ESRD with apixaban administered immediately after completion of hemodialysis (n=8)

Table 9.2.1.1A: Summary Statistics for Total Apixaban Pharmacokinetic Parameters

	Plasma Parameters (Total)					
Treatment	**Cmax (ng/mL) Geo Mean (%CV)**	**AUC(0-T) (ng•hr/mL) Geo Mean (%CV)**	**AUC(INF) (ng•hr/mL) Geo Mean (%CV)**	**Tmax (h) Median (Min-Max)**	**T-HALF (h) Mean (SD)**	**CLT/F (mL/min) Geo Mean (%CV)**
Group A	125.6	1205	1265	2.00	20.0	65.9
	(29)	(29)	(30)	(1.0-4.0)	(14.45)	(33)
Group B P1	98.9	1430	1474	2.00	12.5	56.6
	(29)	(41)	(44)	(1.0-6.0)	(3.14)	(24)
Group B P2	113.6	1673	1717	2.00	12.7	48.5
	(31)	(24)	(24)	(2.0-6.0)	(3.40)	(22)

	Urine Parameters		
Treatment	**CLR (mL/min) Geo Mean (%CV)**	**UR (0-72) (ng) Mean (SD)**	**%UR (%) Mean (SD)**
Group A	11.263	919873	18.397
	(44)	(427723.1)	(8.5545)
Group B P1*	0.020	7250	0.145
	(70)	(4406.5)	(0.0881)
Group B P2*	0.020	9073	0.181
	(80)	(6956.7)	(0.1391)

	Dialysate Parameters					
Treatment	**AUC(2-6) entering (ng•hr/mL) Geo Mean (%CV)**	**AUC(2-6) exiting (ng•hr/mL) Geo Mean (%CV)**	**DR(2-6) (ng) Mean (SD)**	**%DR (%) Mean (SD)**	**CLD (mL/min) Geo Mean (%CV)**	**Extraction Ratio (%) Mean (SD)**
Group B P1	309	312	334124	6.68	17.7	-1.1
	(29)	(28)	(70402.5)	(1.408)	(19)	(5.65)

Source: Tables S.8.2.2A, S.8.2.2B, S.8.2.2C

Table 9.2.1.1B: Results of Statistical Analyses on Apixaban (Total) Group B Period 1 vs. Group A and Group B Period 2 vs. Group A

Treatment and Comparison	Cmax (ng/mL) Adjusted Geometric Mean	AUC(0-T) (ng•hr/mL) Adjusted Geometric Mean	AUC(INF) (ng•hr/mL)) Adjusted Geometric Mean
Group A	125.6	1205	1265
Group B P1	98.9	1430	1474
Group B P2	113.6	1673	1717
	Geometric Mean Ratio (90% CI)		
Group B P1 vs. Group A	0.787 (0.616, 1.006)	1.187 (0.907, 1.553)	1.165 (0.880, 1.543)
Group B P2 vs. Group A	0.904 (0.697, 1.173)	1.389 (1.097, 1.758)	1.357 (1.066, 1.728)
Group B P1 vs. Group B P2	0.871 (0.723, 1.049)	0.855 (0.707, 1.033)	0.858 (0.707, 1.042)

Source: Tables S.8.2.3.1A, S.8.2.3.1B, S.8.2.3.1E S.8.2.3.2A, S.8.2.3.2B, S.8.2.3.2E, S.8.2.3.3A, S.8.2.3.3B and S.8.2.3.3E

- Compared to healthy subjects, apixaban AUC(INF) and AUC(0-T) were 36% and 39% higher in ESRD subjects, respectively, after hemodialysis; whereas apixaban Cmax was 10% lower in these subjects but the 90% CI includes 1, when apixaban was administered immediately after completion of hemodialysis (Group B, Period 2).
- Hemodialysis appears to reduce apixaban Cmax, AUC(INF) and AUC0-T by 13%, 14% and 14%, respectively, in ESRD subjects, respectively, when apixaban was administered 2 hr before the start of the dialysis session (Group B, Period 1) compared to when apixaban was administered immediately after completion of hemodialysis. Thus, compared to healthy subjects,apixaban AUC(INF) and AUC(0-T) appeared to be only 17% and 19% higher, respectively, in ESRD subjects when hemodialysis was started 2 hr after apixaban administration; apixaban Cmax appeared to be 21% lower than that observed in healthy subjects.

Pharmacokinetics of Metabolite (M1, BMS-730823)

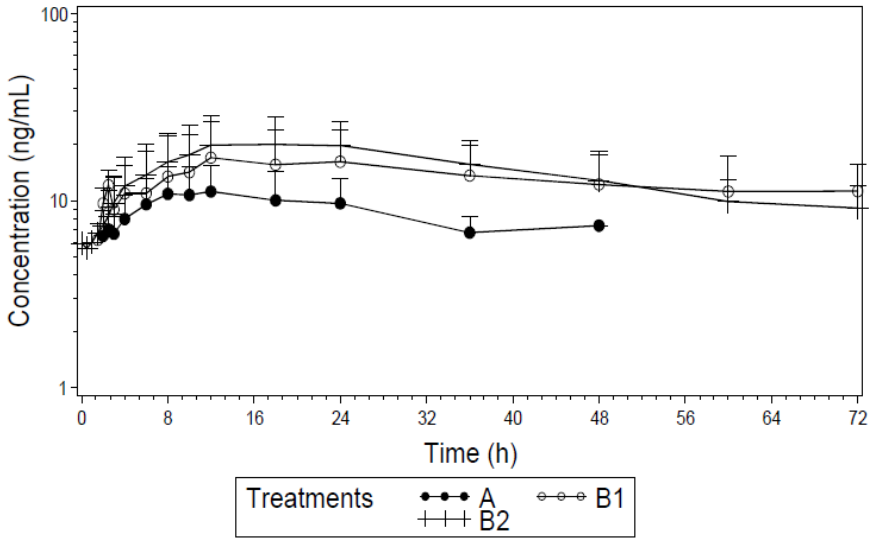


Table 9.2.2: Summary Statistics for BMS-730823 Pharmacokinetic Parameters

	Plasma Parameters		
Treatment	Cmax (ng/mL) Geo Mean (%CV)	AUC(0-T) (ng•hr/mL) Geo Mean (%CV)	Tmax (h) MEDIAN (MIN-MAX)
Group A	10.8	205	9.00
	(38)	(69)	(6.0-12.0)
Group B P1	15.9	746	15.00
	(48)	(56)	(8.0-60.0)
Group B P2	20.0	953	21.00
	(39)	(33)	(12.0-36.0)

	Urine Parameters	
Treatment	CLR[a] (mL/min) Geo Mean (%CV)	UR (0-72)[a] (ng) Mean (SD)
Group A	6.36	88342
	(62)	(43038)
Group B P1	NA	NA
Group B P2	NA	NA

	Dialysate Parameters					
Treatment	AUC(2-6) entering (ng•hr/mL) Geo Mean (%CV)	AUC(2-6) exiting (ng•hr/mL) Geo Mean (%CV)	DR(2-6) (ng) Mea (SD)	%DR (%) Mean (SD)	CLD mL/min) Geo Mean (%CV)	Extraction Ratio (%) Mean (SD)
Group B P1	15.0	17.7	ND	ND	ND	-19.9
	(102)	(96)				(25.32)

Source: Table S.8.2.2D

- Exposure to BMS-730823 was low, with geometric means of maximum plasma concentrations ≤ 20 ng/mL across the 3 groups.
- BMS-730823 geometric mean Cmax and AUC(0-T) was approximately 1.85- and 4.6-fold higher in ESRD subjects with apixaban administered immediately after completion of hemodialysis than that observed in subjects with normal renal function.
- BMS-730823 geometric mean Cmax and AUC(0-T) were approximately 1.47- and 3.6-fold higher in ESRD subjects when hemodialysis was started 2 hr after apixaban administration than that observed in subjects with normal renal function.
- BMS-730823 Tmax was also increased in ESRD subjects.
- Metabolite exposure was lower in ESRD subjects when hemodialysis was started 2 hr after apixaban administration; BMS-730823 concentration in dialysate was negligible (i.e. below the lower limit of quantitation, LLOQ).

Protein binding

Table 9.2.1.2A: Summary Statistics for Percentage of Apixaban Plasma Protein Binding and Apixaban Free Fraction

Treatment	PB (%) Mean (SD)	Fu (%) Mean (SD)
Group A	93.2	6.82
	(0.71)	(0.706)
Group B P1	94.1	5.94
	(0.97)	(0.968)
Group B P2	91.5	8.54
	(1.24)	(1.239)

Table 9.2.1.2B: Summary Statistics for Unbound Apixaban Plasma Pharmacokinetic Parameters

Treatment	Cmax (ng/mL) Geo Mean (%CV)	AUC(0-T) (ng•hr/mL) Geo Mean (%CV)	AUC(INF) (ng•hr/mL) Geo Mean (%CV)	CLT/F (mL/min) Geo Mean (%CV))
Group A	8.52	81.8	85.8	971
	(19)	(24)	(24)	(31)
Group B P1	5.80	83.8	86.4	965
	(24)	(16)	(18)	(14)
Group B P2	9.61	141.5	145.2	574
	(30)	(18)	(18)	(18)

Source: Table S.8.2.2A

Table 9.2.1.2C: Results of Statistical Analyses on Apixaban (Unbound) Group B Period 1 vs. Group A and Group B Period 2 vs. Group A

Treatment and Comparison	Cmax (ng/mL) Adjusted Geometric Mean	AUC(0-T) (ng•hr/mL) Adjusted Geometric Mean	AUC(INF) (ng•hr/mL) Adjusted Geometric Mean
Group A	8.52	81.8	85.8
Group B P1	5.80	83.8	86.4
Group B P2	9.61	141.5	145.2
Geometric Mean Ratio (90% CI)			
Group B P1 vs. Group A	0.680 (0.568, 0.815)	1.025 (0.853, 1.233)	1.007 (0.826, 1.226)
Group B P2 vs. Group A	1.127 (0.902, 1.409)	1.731 (1.421, 2.109)	1.692 (1.381, 2.074)
Group BP 1 vs. Group BP 2	0.603 (0.519, 0.701)	0.592 (0.510, 0.688)	0.595 (0.509, 0.695)

Source: Tables S.8.2.3.1C, S.8.2.3.1D, S.8.2.3.1F, S.8.2.3.2C, S.8.2.3.2D, S.8.2.3.2F, S.8.2.3.3C, S.8.2.3.3D, S.8.2.3.3F

- Unbound apixaban PK parameters followed similar trends to those observed for total drug concentration. Unbound apixaban Cmax, AUC(0-T), and AUC(INF) were 13%, 73%, and 69% higher, respectively, in ESRD subjects when apixaban was administered immediately after completion of hemodialysis, than that observed in healthy subjects.
- In ESRD subjects, unbound apixaban Cmax, AUC(0-T) and AUC(INF) were approximately 40% lower when hemodialysis started 2 hr after apixaban administration, resulting in unbound apixaban AUC comparable to that observed in healthy subjects and a 32% lower Cmax than that observed in healthy subjects.

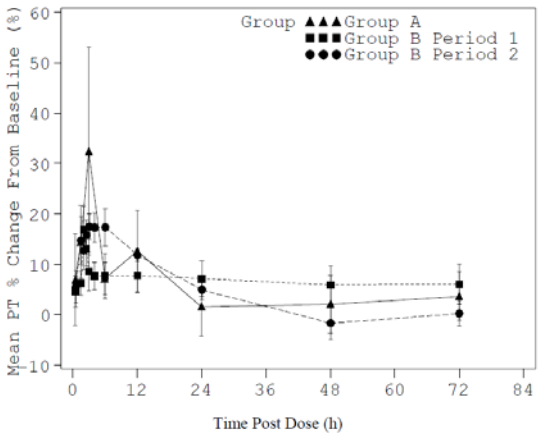
Pharmacodynamics

Table 10: Summary Statistics for the Pharmacodynamic Parameters INR, PT and aPTT

		Group A	Group B Period 1	Group B Period 2
INR	Baseline (SD)	0.97 (0.094)	1.07 (0.127)	1.09 (0.149)
	Maximum Percent Change from Baseline (%) (SD)	31.5 (56.59)	16.6 (10.60)	16.8 (7.15)
PT	Baseline (seconds) (SD)	11.49 (1.151)	12.78 (1.520)	13.03 (1.806)
	Maximum Percent Change from Baseline (%)(SD)	32.4 (58.31)	16.9 (10.98)	17.4 (7.28)
aPTT	Baseline (seconds) (SD)	34.33 (4.822)	36.43 (6.040)	31.46 (6.647)
	Maximum Percent Change from Baseline (%)(SD)	19.9 (20.40)	7.0 (9.62)	23.0 (14.81)

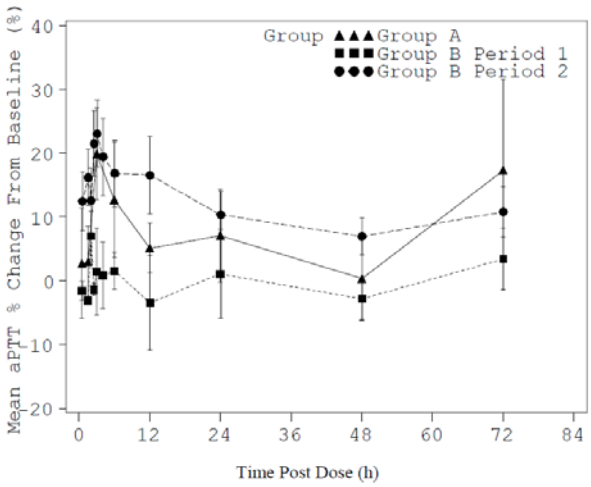
Source: Table S9.1, S.9.2 and S.9.3.

Figure 10.2B: Plot of Mean Prothrombin Time (PT) Percent Change from Baseline Versus Time



Source: Table S.9.2 and Figure S.9.2B

Figure 10.3B: Plot of Mean aPTT Percent Change from Baseline versus Time

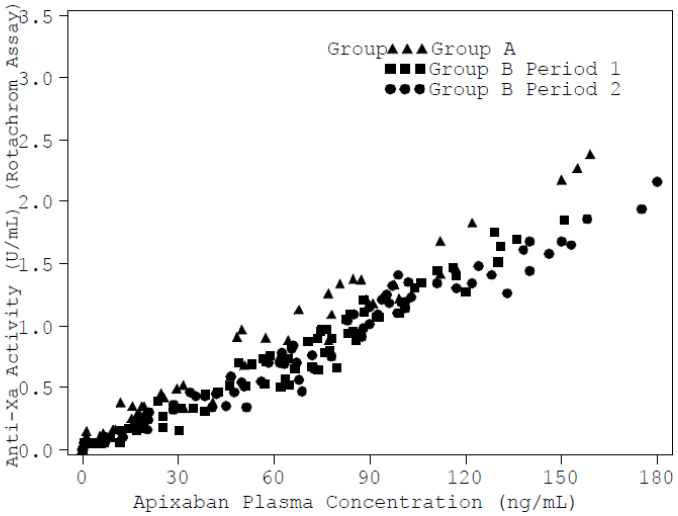


Source: Table S.9.3 and Figure S.9.3B

- Baselines of INR and PT in ESRD subjects appear to be higher than those in healthy subjects.
- Following administration of apixaban, INR and PT increased initially then returned to baseline in each group. The percent change from baseline appeared comparable across the three treatment groups.
- For aPTT, following administration of apixaban, aPTT increased initially then returned to baseline. Percent change from baseline varied slightly between Groups A and B, and between Periods for subjects in Group B. The largest mean increases (± SD) relative to baseline, were 19.85% (± 20.398) at 3 hr, 6.96% (± 9.624) at 2 hr, and 23.04%(± 14.811) at 3 hr for Group A, Group B Period 1, and Group B Period 2, respectively.

Anti-Factor Xa Activity

Figure 10.4B: Scatter Plot of Apixaban Plasma Concentrations versus Anti FXa Activity



Source: Figure S.9.5

- A direct linear relationship between anti-FXa activity values and apixaban plasma concentrations in all three groups

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 ☑NA
Exposure and anti-FXa activity of apixaban in ESRD patients maintained with hemodialysis appeared to be similar to those with moderate to severe renal impaired patients. Dose adjustment based solely on this study may not be warranted; however, combination of additional risk factors might lead to dose adjustment.

- ESRD subjects had 36% higher apixaban exposure (AUC) than that observed in healthy subjects with normal renal function.
- Hemodialysis decreased apixaban exposure in ESRD subjects by ~14% resulting in an AUC that was approximately 17% higher than that in subjects with normal renal function.
- Apixaban Cmax was lower in ESRD subjects than that observed in subjects with normal renal function, with the greatest difference (21% lower Cmax) being observed when hemodialysis was started 2 hr after apixaban administration.
- Apixaban dialysis clearance was 17.7 mL/min.
- Apixaban protein binding was generally comparable between ESRD subjects with hemodialysis started 2 hr after apixaban administration (94.1% bound) and subjects with normal renal function (93.2% bound). Protein binding appears to be

slightly lower in ESRD subjects when apixaban administered immediately after completion of hemodialysis (91.5% bound).

- The metabolite, BMS-730823, Cmax and AUC(0-T) were approximately 1.9- and 4.6-fold higher in ESRD subjects than that observed in subjects with normal renal function, respectively. When hemodialysis was started 2 hr after apixaban administration, BMS-730823 Cmax and AUC(0-T) was approximately 20% and 22% lower, respectively, than when apixaban was administered immediately after hemodialysis.
- Anti-FXa activity demonstrated a linear relationship with apixaban plasma concentration within both healthy and ESRD subjects.
- The effect of apixaban on INR, PT, and aPTT appeared to be consistent between healthy subjects with normal renal function and ESRD subjects, however with large variability observed in these results.
- A single 5-mg oral dose of apixaban was safe and well tolerated in healthy subjects with normal renal function and subjects with ESRD maintained with hemodialysis in this study.

Reviewer's Comments:

- *The higher exposure of the metabolite, M1, is consistent with previous results from renal impairment study. Similarly, 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.*
- *Apixaban was administered during the dialysis as well as during off-dialysis period. The exposure and anti-FXa activity of apixaban in ESRD patients maintained with hemodialysis appeared to be similar to those with moderate to severe renal impaired patients. As previously approved, no dose adjustment is required for patients with moderate to severe renal impairment. Hence, dose adjustment based solely on renal impairment or ESRD disease state is not warranted.*
- *In addition, given the available data in this report, we thought there is enough information to label ESRD patients on hemodialysys.*
    - *The recommended dose for ESRD patients maintained with hemodialysis is 5 mg orally twice daily.*
    - *For the ESRD patients maintained with hemodialysis having either one of the risk factors of age ≥80 years or body weight ≤ 60kg, the recommended dose should be reduced by half to 2.5 mg twice daily.*

DDI- Apixaban VS Prasugrel

Report # CV185073	**Study Period** 5/21/10 9/21/10	**EDR Link** \\cdsesub1\evsprod\nda202155\0086\m5\53-clin-stud-rep\532-rep-stud-pk-human-biomat\5322-rep-hep-metab-interact-stud\cv185073\study-cv185073-csr-final.pdf
Title	A RANDOMIZED, OPEN-LABEL APIXABAN AND PRASUGREL DRUG INTERACTION STUDY IN HEALTHY SUBJECTS	
Objectives	**Primary:** To assess the effect of prasugrel on the PK of apixaban and the effect of apixaban on the PK of the active metabolite of prasugrel, R-138727, when co-administered.	

Rationale: Prasugrel (Effient®) is a P2Y platelet inhibitor indicated for the reduction of thrombotic cardiovascular events (including stent thrombosis) in patients with acute coronary syndrome (ACS) who are to be managed with primary percutaneous coronary intervention (PCI). (b) (4) this study was conducted to provided assurance that these two medications did not influence the pharmacokinetics of each other.

Study Design Multiple-Dose Randomized Open-labelled Crossover Single-Center Three-Period Healthy Vonuteers

Subjects were randomized to 1 of the 6 treatment sequences as detailed in the table below.

	Period 1	**W/CF**	**Period 2**	**W/CF**	**Period 3**	**W/CF**
Sequence 1	A	3 days	B	14 days	C	8 days
Sequence 2	A	3 days	C	14 days	B	8 days
Sequence 3	B	14 days	A	3 days	C	8 days
Sequence 4	B	14 days	C	14 days	A	-
Sequence 5	C	14 days	B	14 days	A	-
Sequence 6	C	14 days	A	3 days	B	8 days

W = Washout; CF = Clinic Furlough

Screening: -21days **Washout:**≥3days, 14 days and 14 days following A, B and C, respectively

Treatments: (≥ 8 hr fast before morning doses, evening doses of apixaban were given regardless of evening meal time)

A: 5 mg Apixaban orally, BID on Days 1-4

B: 60 mg Prasugrel orally on Day 1 followed by 10 mg Prasugrel orally, QD on Days 2-4

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

Study medication

Active Substance	**Strength**	**Dosage Form**	**Batch Number**
Apixaban (BMS-562247)	5 mg	Film-coated tablets	8F37006
Prasugrel (Effient®)	10 mg	Film-coated tablets Expiration Date: Jan 2011 Expiration Date: Aug 2011	 A657074A A730401C

PK Sampling (Blood):

Apixaban and R-138727 (active metabolite of prasugrel):

- Pre-dose on days 2, 3 and 4 for each period
- Day 4: 0.25, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 9 and 12 hours post dose and one last sampling for R138727 at 24 hours post dose

PD Sampling (Blood) for Platelet Aggregation:

- Pre-dose on days 1, 2 and 4
- Day 1: 2, 4, 6, 9 hours post dose
- Day 4: post dose 4, 6, 9 and 12 hours

PD Sampling (Blood) for Anti-FXa Activity:

- Pre-dose on days 1 and day 4
- Day 4: 1, 2, 4, 6, 9 and 12 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	R-138727
Method	LC/MS/MS	LC/MS/MS
Matrix	Plasma	Plasma
LOQ	1.00 (ng/mL)	0.250 (ng/mL)
Range	1.00 to 1000 (ng/mL)	0.250 to 250 (ng/mL)
QCs	3.00, 35.0, 400, 800 (ng/mL)	0.750, 2.00, 7.50, 30.0, 190 (ng/mL)
Accuracy/Bias	4.51%	4.86%
Precision (CV%)	5.46%	4.99%

Statistical Method:

PK: To assess the effect of prasugrel on apixaban Cmax and AUC(TAU), a general linear model analysis was performed on log(Cmax) and log[AUC(TAU)] of apixaban. Point estimates and 90% CIs for differences on the log scale were exponentiated to obtain estimates for ratios of geometric means on the original scale. Similar analyses were conducted on log(Cmax) and log[AUC(TAU)] of R-138727.

PD: Summary statistics were tabulated by treatment and time for platelet aggregation and anti-FXa activity, along with corresponding changes from baseline for platelet aggregation. Linear and semi-logarithmic plots of the mean and individual platelet aggregation and anti-Factor Xa activity were plotted versus time by treatment, respectively.

Study Population :

Planned/Dosed/Completed/ Discontinued Due to AE	36/53[#]/35/1*
Age [range]	18-45 yr
Male/Female	34/19
Race (White)	53

17 subjects for whom multiple PK samples were not collected were discontinued and replaced as stated by the sponsor.

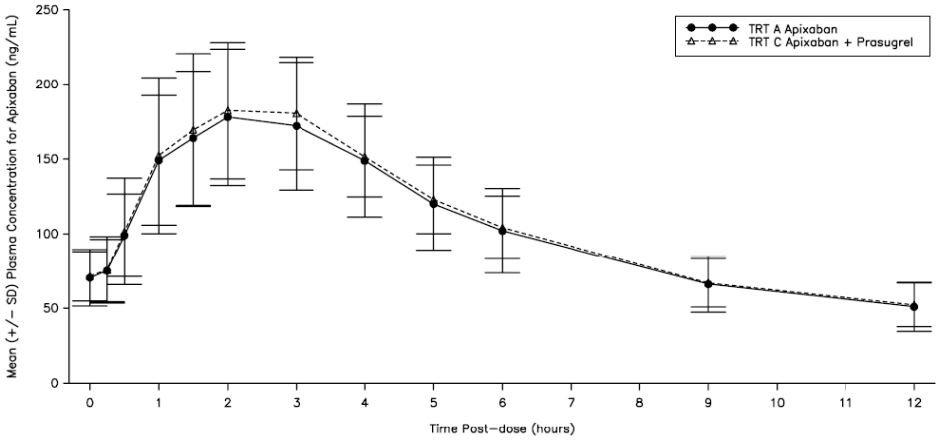
* 1 subject was discontinued due to a moderate AE (haematochezia).

Results

Pharmacokinetics of Apixaban

- Apixaban exposure was not altered by co-administration with prasugrel when compared with apixaban alone; the 90% CIs for apixaban Cmax and AUC(TAU) geometric least squares (LS) mean ratios were contained within the predefined no effect interval of 0.8 - 1.25.

Apixaban mean plasma concentration-time profile on Day 4



Summary statistics of Apixaban PK

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

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

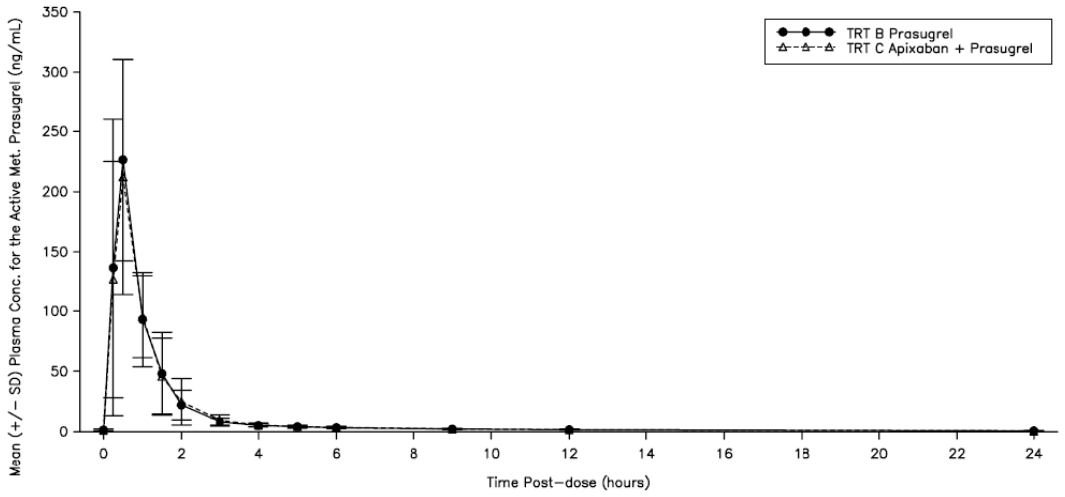
Treatment C: 5 mg Apixaban orally, BID on Days 1-4 and 60 mg Prasugrel orally on Day 1 followed by 10 mg Prasugrel orally, once daily (QD) on Days 2-4

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

Pharmacokinetics of R-138727

- The 90% CI for R-138727 AUC(TAU) geometric least squares (LS) mean ratios were contained within the predefined no effect interval of 0.8 - 1.25.
- For Cmax, geometric LS mean ratio was 0.885, with the upper bound of the 90% CI as 0.991 and the lower bound of the 90% CI as 0.789.

R-138727 mean plasma concentration-time profile on Day 4



Summary statistics of R-138727 PK

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

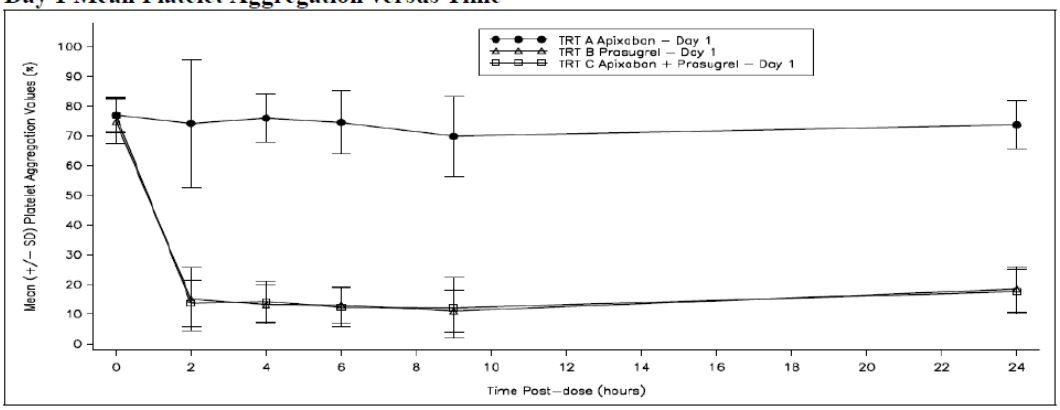
Treatment B: 60 mg Prasugrel orally on Day 1 followed by 10 mg Prasugrel orally once daily (QD) on Days 2-4
Treatment C: 5 mg Apixaban orally, twice daily (BID) on Days 1-4 and 60 mg Prasugrel orally on Day 1 followed by 10 mg Prasugrel orally QD on Days 2-4
LS = Least Squares; Trt = Treatment; CI =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

Pharmacodynamics

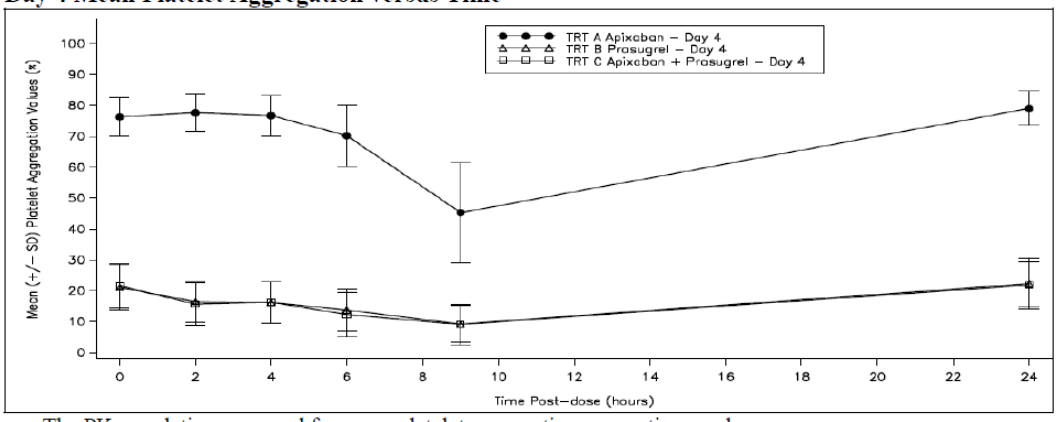
ADP-induced platelet aggregation

- Apixaban generally had no effect on ADP-induced platelet aggregation. However, it is noted that there was an apparent decrease in the ADP-induced platelet aggregation at the 9-hour time point following apixaban administration on Day 4. There are no clear reasons to explain this finding. It should be noted that platelet aggregation returned to baseline by the 24-hour time point.
- Prasugrel alone decreased ADP-induced platelet aggregation on Day 1 and maintained through Day 4 which was consistent with prasugrel's mechanism of action.
- Co-administration of apixaban with prasugrel did not alter ADP-induced platelet aggregation when compared with that of prasugrel alone.

Day 1 Mean Platelet Aggregation versus Time[a]



Day 4 Mean Platelet Aggregation versus Time[a]

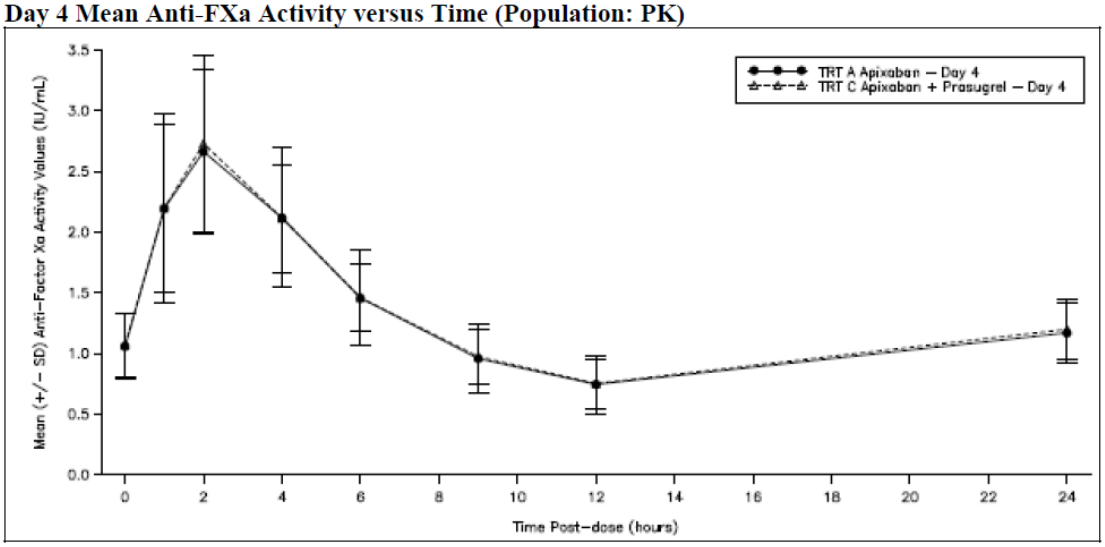


a The PK population was used for mean platelet aggregation versus time analyses.
TRT = Treatment

Anti-FXa Activity

- The anti-FXa activity was not altered by co-administration of prasugrel when compared with apixaban alone.
- All subjects receiving prasugrel alone had anti-FXa activity values under the detectable limit (<0.1 IU/mL).

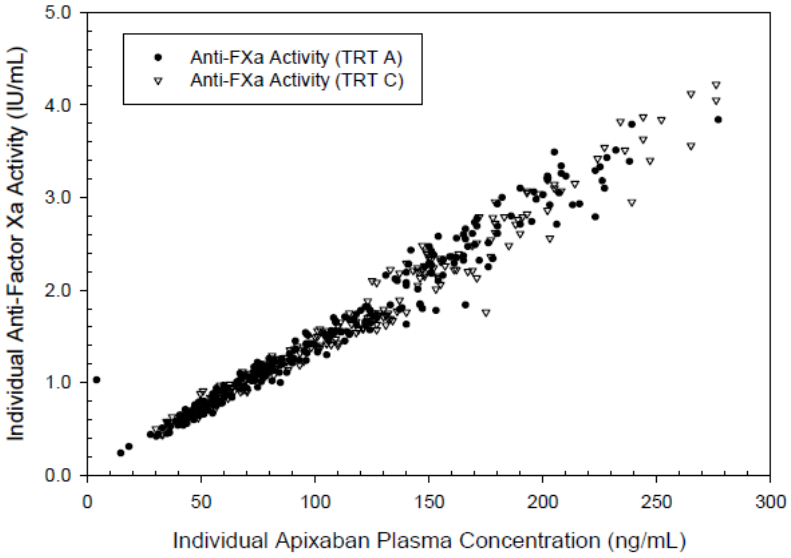
Day 4 Mean Anti-FXa Activity versus Time (Population: PK)



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

Relationship between apixaban concentration and anti-FXa activity

- A direct linear relationship was observed between the individual subject anti-Xa activity and apixaban plasma concentrations. This linear relationship was not impacted by co-administration of prasugrel.



Safety

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

19 subjects (35.8%) experienced adverse bleeding-related AEs which were considered to be related to study drug and mild in intensity with the exception of 1 event (haematochezia). The majority of the bleeding-related events were reported more frequently when apixaban was co-administered with prasugrel than when either agent was administered alone.

Table 14.3.1.6
Adverse Bleeding Event Summary
Population: Safety

System Organ Class (%) Preferred Term (%)	TRT A Apixaban N = 43	TRT B Prasugrel N = 44	TRT C Apixaban+Prasugrel N = 53	Total N = 53
TOTAL SUBJECTS WITH TEAE	3 (7.0)	4 (9.1)	18 (34.0)	19 (35.8)
GASTROINTESTINAL DISORDERS	0 (0.0)	0 (0.0)	4 (7.5)	4 (7.5)
Gingival bleeding	0 (0.0)	0 (0.0)	2 (3.8)	2 (3.8)
Haematochezia	0 (0.0)	0 (0.0)	1 (1.9)	1 (1.9)
Lip haemorrhage	0 (0.0)	0 (0.0)	1 (1.9)	1 (1.9)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	0 (0.0)	1 (2.3)	3 (5.7)	4 (7.5)
Vessel puncture site haematoma	0 (0.0)	1 (2.3)	3 (5.7)	4 (7.5)
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	0 (0.0)	0 (0.0)	1 (1.9)	1 (1.9)
Menorrhagia	0 (0.0)	0 (0.0)	1 (1.9)	1 (1.9)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	3 (7.0)	2 (4.5)	5 (9.4)	6 (11.3)
Epistaxis	1 (2.3)	1 (2.3)	4 (7.5)	5 (9.4)
Haemoptysis	2 (4.7)	2 (4.5)	1 (1.9)	3 (5.7)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	0 (0.0)	2 (4.5)	11 (20.8)	11 (20.8)
Ecchymosis	0 (0.0)	2 (4.5)	10 (18.9)	10 (18.9)
Petechiae	0 (0.0)	0 (0.0)	1 (1.9)	1 (1.9)

Program Name/Date: T_aeBE.sas 21JAN2011
MedDRA Version: 13.0
Cross-reference: Listing 16.2.7.2

Reviewer's note: Although PK and PD of apixaban and Prasugrel did not seem to be affected significantly by co-administration when compared to either drug alone, it is noted that ~ one third of the healthy subjects experienced the bleeding-related AEs in this study and majority occurred when both drugs were co-administered. Based on this data, an increased risk of bleeding in a higher risk patient population cannot be ruled out. As warning of bleeding when concomitant use of antiplatelet agents has been addressed in the Section 5.2 of the package insert of apixaban, no additional language will be added from clinical pharmacology perspective. Description of this finding might be provided by the medical officer..

Conclusion

- Co-administration of prasugrel with apixaban had no effect on the PK of apixaban.
- Apixaban did not have a clinically relevant effect on the PK of the active prasugrel metabolite, R-138727. Apixaban did not affect the AUC of R-138727, prasugrel's active metabolite, but did cause a small decrease (~11%) in R-138727 Cmax; the lower bound of the 90% CI was marginally lower than the lower bound of the no effect interval, and therefore didn't meet the criteria for equivalence.
- Apixaban did not appear to have an effect on ADP-induced platelet aggregation. Co-administration of apixaban and prasugrel on Days 1 and 4 did not alter prasugrel's effect on platelet aggregation.
- The anti-FXa activity when apixaban administered with prasugrel, was similar to that of apixaban was administered alone.

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/s/

JU PING LAI
10/25/2013

RAJANIKANTH MADABUSHI
10/25/2013