CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204886Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY REVIEW ADDENDUM

Individual Study Reviews

NDA	204886
Submission Date	May 10, 2013
Submission Type	Original, NME – Standard Review
Brand Name	ZONTIVITY®
Generic Name	Vorapaxar Sulfate
Sponsor	Merck, Sharp and Dohme Corp.
Therapeutic Class	Protease Activated Receptor-1 [PAR-1] antagonist [anti-platelet]
Formulation	Oral immediate release tablet
[Strengths]	[2.5 mg]
Dosing Regimen	2.5 mg once-daily
Proposed Indication	Reduction of atherothrombotic events in patients with a history of myocardial infarction [MI] and no prior history of stroke or transient ischemic attack [TIA]
Review Divisions	DCP I and DCRP
Reviewers	Sudharshan Hariharan, Ph.D. AbuAsal Bilal, Ph.D
Team Leader	Rajanikanth Madabushi, Ph.D.

This document is an addendum to the original clinical pharmacology question based review checked in DARRTS on 12/16/2013. This addendum contains reviews for 17 individual in vivo clinical pharmacology studies discussed in the question based review. This addendum does not discuss a pivotal bioequivalence study[1] and in vitro clinical pharmacology related studies[2] as they are reviewed elsewhere.

[1] Reviewed by Dr. Hariharan, IND 71384, DARRTS date: 06/06/2012

[2] Reviewed by Dr. Harlow, NDA 204886, DARRTS date: 12/17/2013

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LIST OF ABBREVIATIONS

ACT	Activated Clotting Time
ADME	Absorption, Distribution, Metabolism, Elimination
ADP	Adenosine di phosphate
AE	Adverse Event
ALT	Alanine transaminase
AMS	Accelerated Mass Spectrometry
ANOVA	Analysis of variance
aPTT	Activated Prothrombin Time
AST	Aspartate transaminase
AUC	Area Under Curve
BMI	Body Mass Index
CI	Confidence Interval
CL/F	Apparent clearance
C_{max}	Maximum plasma concentration
C_{min}	Concentration at the inter-dosing interval
C-P	Child-Pugh
CSR	Clinical Study Report
CV	Coefficient of variation
DDI	Drug-Drug Interaction
ECG	Electrocardiogram
ECT	Ecarin Clotting Time
ESRD	End Stage Renal Disease
FSA	Flow Scintillation Analysis
GGT	Gamma-glutamyl transpeptidase
GMR	Geometric Mean Ratio
IC_{50}	Inhibitor concentration corresponding to 50% of maximal inhibition
INR	International Normalized Ratio
LC	Liquid Chromatography
LLOQ	Lower Limit of Quantification
MS	Mass Spectrometry
NLT	No Less Than

NMT	No More Than
PD	Pharmacodynamics
P-gp	P-glycoprotein
PK	Pharmacokinetics
PPACK	(D-phenylalanyl-L-propyl-L-arginine chloromethyl ketone
PRP	Platelet Rich Plasma
PT	Prothrombin Time
QC	Quality Control
QD	Once-daily
SAE	Serious Adverse Event
SCH 2046273	Metabolite of vorapaxar (M20)
SCH 530348	Vorapaxar
SD	Standard Deviation
SE	Standard Error
$t_{1/2}$	Half-Life
T_{max}	Time to reach maximum concentration
TRA	Vorapaxar
TRAP	Thrombin Receptor Activating Peptide
TT	Thrombin Time
Vd/F	Apparent volume of distribution

PHARMACOKINETICS/PHARMACODYNAMICS/BIOPHARMACEUTICS STUDIES

Characterization of ADME		
Study report: P03454	**Study period:** 08/18/2005 - 09/22/2005	**EDR Link**[3]
OBJECTIVE		
To characterize the absorption, metabolism, pharmacokinetics and excretion of vorapaxar		
STUDY DESIGN		
Open label, single center, single dose ADME study in healthy adult male volunteers. *Dosing*: Vorapaxar sulfate was administered as 9.3 mg single dose containing approximately 100 μCi of total radioactivity as oral solution (20% w/v hydroxypropyl-β-cyclodextrin) following an overnight fast. Subjects were confined to the study center until at least day 7 followed by a weekly 36 h confinement for 3 consecutive weeks.		
Population/Sample size		
N=6; Healthy adult male subjects (age=18-50 y, BMI=19-29 kg/m^2, 100% caucasians)		
PK Sampling		
Blood samples for pharmacokinetic evaluation of vorapaxar were collected pre-dose, and at 0.5, 1, 1.5, 2, 4, 6, 12, 24, 36, 48, 72, 96, 120 and 144 h post-dose and on days 14, 21 and 28 post-dose. Urine samples were collected prior to dosing and in block intervals: 0-12, 12-24, 24-36, 48-72, 72-96, 96-120, 120-144, 144-168 h post-dose, and in 24 h block intervals during the in-patient sample collections: 312-336, 480-504 and 648-672 h post-dose. Fecal samples were collected prior to dose and then daily as individual bowel movements up to 168 h post-dose, and during the in-patient sample collections: 312-336, 480-504 and 648-672 h post-dose.		
Statistical method		
Descriptive statistics		
Bioanalysis		
All samples were assayed for radioactivity using liquid scintillation spectrometry. Plasma samples for vorapaxar were assayed using a validated LC-MS/MS method. Metabolite profiling was performed using LC-MS or LC-MS/MS or LC-MS/FSA.		

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RESULTS

Bioanalysis assay method

	Vorapaxar
Method	**UPLC-MS/MS**
LLOQ (ng/mL)	0.1
Range (ng/mL)	0.1 to 50
QCs (ng/mL)	0.3, 7.5, 37.5

Comment: The analytical assay method is acceptable since the accuracy and precision for at least 2/3^{rds} of the QC and LLOQ samples are within the acceptable limits of ±15% and ± 20%, respectively, as specified in 'Guidance for Industry: Bioanalytical Method Validation'.

PK

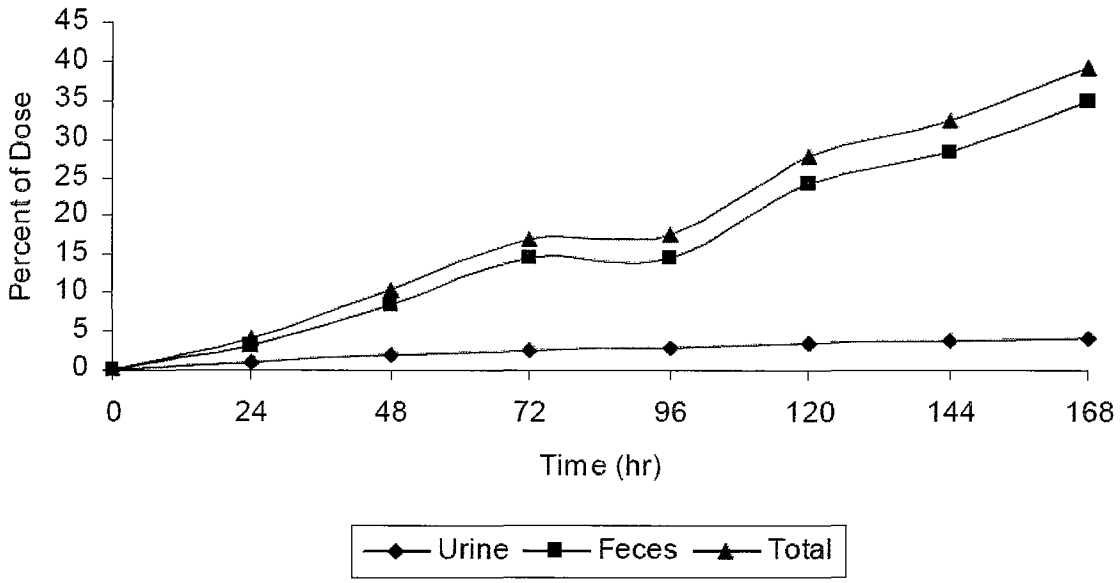

Figure 1: Mean cumulative drug derived radioactivity (0-168 h) following a single dose of 9.3 mg (100 μCi) ^{14}C-vorapaxar sulfate administered as oral solution [Source: P03454, Figure 3, Page 76]

Table 1: Mean plasma pharmacokinetic parameters/measures following a single dose of 9.3 mg (100 μCi) ^{14}C-vorapaxar sulfate administered as oral solution

	Mean (CV %)					
	C_{max} (ng/mL)	**T_{max}[a] (h)**	**AUC_{0-t} (ng*h/mL)**	**$t_{1/2}$ (h)**	**CL/F (L/h)**	**Vd/F (L)**
Plasma vorapaxar PK	117 (16)	1.75 (1.5 – 2.0)	5710 (13)	159 (34)	1.29 (13)	293 (33)

[a] Median (range)

Table 2: LC-MS/FSA characterized drug derived material in 0-168 h post-dose pooled urine and 0-168 h, days 13-14 and 20-21 post-dose pooled feces following a single dose of 9.3 mg (100 μCi) ^{14}C-vorapaxar sulfate administered as oral solution

Metabolite label	Metabolite name	m/z	% dose in urine	% dose in feces
NA	Unknown	--	0.11	--
M8	Monohydroxy-vorapaxar-gluc	685[a]	0.42	ND
M10	Monohydroxy-vorapaxar-gluc	685[a]	0.31	ND
M13	Monohydroxy-vorapaxar-sulfate	589[b]	0.11	ND
M14	Monohydroxy-vorapaxar-sulfate	589[b]	0.05	ND
M15	Monohydroxy-vorapaxar	509	0.21	ND
M16	Carboxylic acid metabolite	523	0.41	2.30
M17	M+34	527	1.40	0.87
M17a	Dihydroxy-vorapaxar	525[c]	ND	0.88
M17b/c	Dihydroxy-vorapaxar	525[c]	ND	2.30
NA	Unknown	--	--	1.08
NA	Unknown	--	--	1.15
M19	Amine metabolite	421	1.21	18.4
M19a	Monohydroxy-vorapaxar	509[d]	ND	3.51
M20	Monohydroxy-vorapaxar	509[d]	ND	0.68
M20b	Monohydroxy-vorapaxar	509[d]	ND	2.44
M21	Monohydroxy-vorapaxar	509[d]	ND	6.96
Parent	Vorapaxar	493	ND	1.59
Cumulative recovery (% of dose)			**4.23**	**42.2**

ND Not detected
[a] Retention times for M8 and M10 are 18.4 and 18.9 min, respectively
[b] Retention times for M13 and M14 are 21.6 and 22.7, respectively
[c] Retention times for M17a and M17b/c are 24.0 and 26.2 min, respectively
[d] Retention times for M19a, M20, M20b and M21 are 30.0, 30.7, 31.5 and 31.9 min, respectively

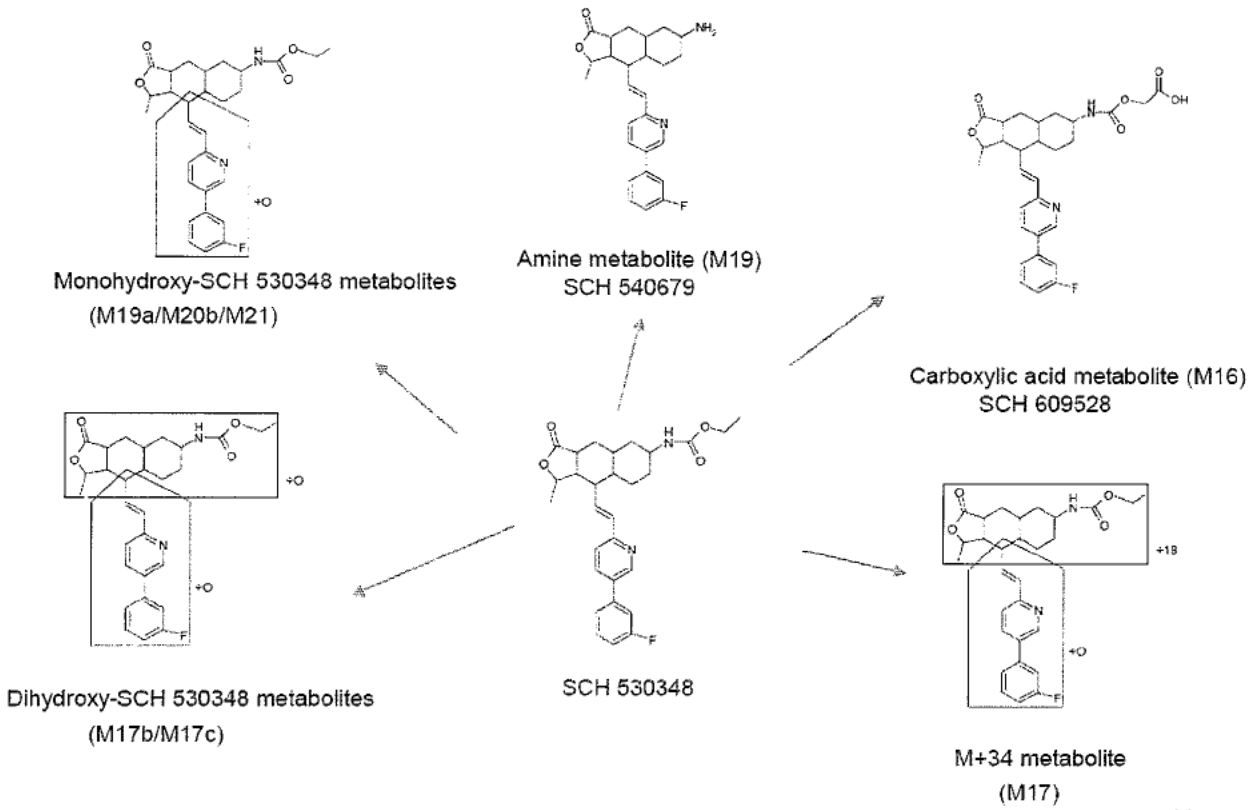

Figure 2: Proposed major biotransformation pathway following single dose of 9.3 mg (100 μCi) ^{14}C-vorapaxar sulfate administered as oral solution. Metabolites shown represent >1% of administered dose [Source: CSR P03454, Figure 8, Page 81].

- Measured recovery of drug derived radioactivity was greater in feces (35.0%) than in urine (4.23%), adding up to a total recovery of 39.2% of dose through 168 h post-dose (Table 1). Interpolation of excretion data suggests that it may require at least 6 weeks for near complete recovery of radioactivity (95%) due to the long terminal elimination half-life of vorapaxar.
- Parent drug, vorapaxar, was not detected in the urine (Table 2). This suggests that renal excretion is not the primary route of drug clearance.
- The mean blood-to-plasma radioactivity ratio ranged from 0.56-0.60 over 120 h (data not shown). This suggests minimal sequestering of drug derived radioactivity into red blood cells over time.
- In samples collected at 2, 4 and 24 h post-dose, parent drug was the major moiety at all time points with trace amounts of metabolite M20 detected in 6 and 24 h post-dose samples (data not shown).
- Major biotransformation pathways included oxidation and carbamate hydrolysis (Fig. 2). None of the metabolites were human specific and were earlier detected in rat, mouse and/or monkey.

Safety

No deaths or serious adverse events were noted in this study. All mild adverse events resolved spontaneously and no subject discontinued the study due to adverse events.

SUMMARY

- This 7-day ADME study accounts for only 40% of the drug derived radioactivity due to the long terminal elimination half-life of vorapaxar. Nevertheless, based on the collected data, fecal excretion appears to be the major route of elimination of drug related radioactivity.

- No parent drug was measured in urine in samples collected through 168 h post-dose. This suggests that renal excretion is not the primary route of drug clearance.

- Major biotransformation pathways were oxidation and carbamate hydrolysis. No new human specific metabolites were detected.

Absolute Bioavailability		
Study report: P07045	**Study period:** 06/28/2010 - 08/27/2010	**EDR Link**[4]
OBJECTIVE		
(i) To determine absolute bioavailability of vorapaxar (ii) To characterize the mass balance and cumulative recovery of vorapaxar over a 6-week period		
STUDY DESIGN		
Open label, single center study in healthy adult male volunteers. *Dosing*: Vorapaxar sulfate was administered as a single oral dose (1 x 2.5 mg) followed by single intravenous micro-dose (72.7 μg, 82.2 nCi) at 60 min following oral administration. Concentrations of unlabeled vorapaxar in plasma, urine and feces were measured using LC-MS/MS. Radiolabeled ^{14}C-vorapaxar in plasma, urine and feces was first separated by HPLC and measured by accelerated mass spectrometry (AMS).		
Population/Sample size		
N=6; Healthy adult male subjects (age=18-50 y, BMI=19-29 kg/m^2)		
PK Sampling		
Blood samples for pharmacokinetic evaluation of vorapaxar were collected pre-dose, and at 0.5, 1, 1.25, 1.5, 2, 2.5, 3, 4, 6, 12 and 24 h post-dose. Additional blood samples were collected on days 7, 14, 21, 28, 35 and 42 post-dose. Urine samples were collected prior to dosing and then as individual voids pooled in block collections every 24 h until the morning of day 43 post-dose. Fecal samples were collected prior to dose and then daily as individual bowel movements until the morning of day 43.		
Evaluations		
Plasma PK measures: C_{max}, T_{max}, AUC_{0-t}, AUC_{0-inf}, V_d/F, V_d, CL/F, CL, $t_{1/2}$ *Urine/Feces PK measures*: Ae_{cum} – cumulative vorapaxar excreted up to last collection interval *Absolute bioavailability*: Calculated as the ratio of dose-normalized oral to *i.v.* vorapaxar AUC		
Statistical method		
Descriptive statistics for plasma, urine and feces PK measures. To estimate the absolute bioavailability, the log transformed, dose-normalized AUC_{0-inf} was analyzed using a mixed effect ANOVA model extracting the effect due to treatment as a fixed effect and subject as a random effect. The geometric mean ratio between oral *vs* intravenous AUC was calculated as an estimate of absolute bioavailability and 90% CI for the ratio estimate was provided.		

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RESULTS

Bioanalysis assay method

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

	Vorapaxar
Method	**UPLC-MS/MS**
LLOQ (ng/mL)	1
Range (ng/mL)	1 to 1000
QCs (ng/mL)	3, 80, 800

Reviewer's comment: The analytical assay method is acceptable since the accuracy and precision of at least 2/3^{rds} of the QC and LLOQ samples are within ±15% and ±20%, respectively, as specified in 'Guidance for Industry: Bioanalytical Method Validation'.

PK summary statistics

Table 1: PK measures following single oral administration of unlabeled vorapaxar sulfate 2.5 mg and intravenous bolus of ^{14}C-vorapaxar sulfate 73.7 µg [Source: CSR P07045, Table 12, Page 62]

Mean (CV %) SCH 530348 Pharmacokinetic Parameters Following a Single Oral Administration of 2.5 mg SCH 530348 and IV Bolus of 73.7 µg ^{14}C-SCH 530348 to Healthy Subjects

Dose Group	Cmax (ng/mL)	Tmax[a] (hr)	AUC(tf) (ng·hr/mL)	AUC∞/D[b,c] (ng·hr/mL/mg)	t½ (hr)
Oral dose 2.5 mg (n=6)	27.0 (14)	1.25 (1.00-2.00)	1300 (19)	663 (19)	196 (35)
IV Micro dose 73.7 µg (n=6)	1.17 (11)	0.30 (0.25-0.50)[d]	43.2 (25)	624 (24)	159 (22)

a: Median (Range)

b: Mean dose normalized (dose = 73.7 µg for IV, 2.08 mg free base for oral SCH 530348) AUC∞ values for oral and IV administration

c: % Absolute bioavailability as calculated by dose normalized AUC(Oral)/AUC(IV) based on exposures to infinity is 108%

d: First sample collected was at 0.25 hr post IV bolus administration.

Table 2: Statistical analysis – Absolute bioavailability [Source: CSR 07045, Table 11, Page 59]

Statistical Analysis of SCH 530348 Pharmacokinetic Parameters Following Single Oral Administration of 2.5 mg SCH 530348 and IV Bolus of 73.7 µg ^{14}C-SCH 530348 (n=6)

Parameter	Treatment	n	LSMean[a]	90% CI	Comparison	GMR	90% CI	rMSE[b]
AUC∞[c]	Oral	6	653	545-783	Oral vs IV	1.073	0.997-1.156	0.064
	IV	6	608	507-730				
Cmax[d]	Oral	6	12.8	11.5-14.3	Oral vs IV	0.812	0.697-0.945	0.131
	IV	6	15.8	14.2-17.6				

a: Model-based (least squares) geometric mean: based on mixed effect model extracting the effect due to Treatment as fixed effect and subject as random effect

b: Square root of conditional mean squared error (residual error) from the linear mixed effects model. rMSE·100% approximate the within-subject %CV on the raw scale

c: Dose normalized AUC∞ (for Oral: AUC∞/2.08mg; for IV: AUC∞/0.0737mg

d: Dose normalized Cmax (for Oral: Cmax/2.08mg; for IV: Cmax/0.0737mg

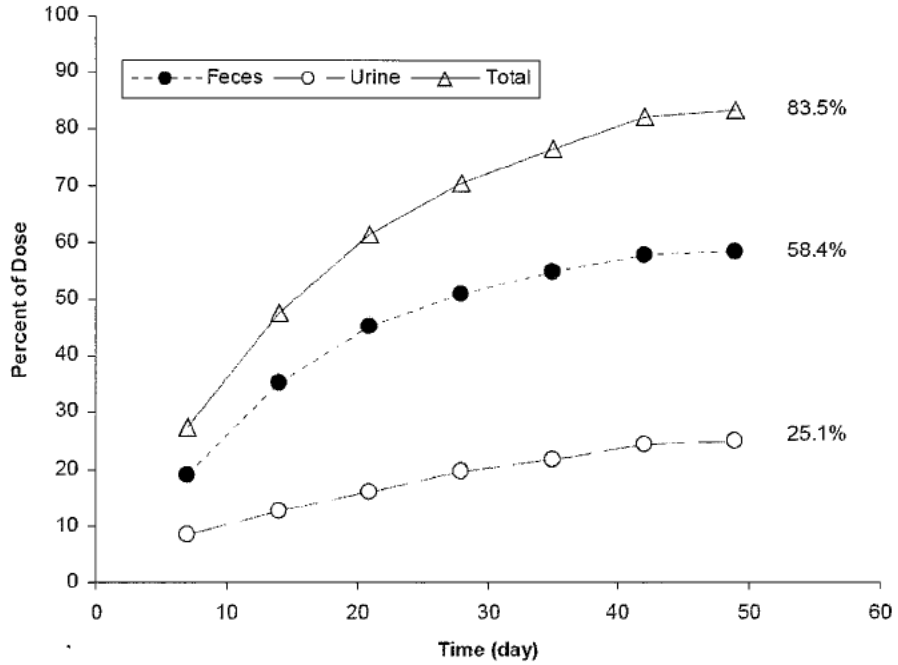

Figure 1: Mean cumulative recovery of vorapaxar in urine and feces by end of the study [Source: P07045, Figure 6, Page 67]

Comment: When these results were extrapolated using Michaelis-Menten kinetics, the projected duration for near about 100% recovery was about 72 days.

Concentration-time profile

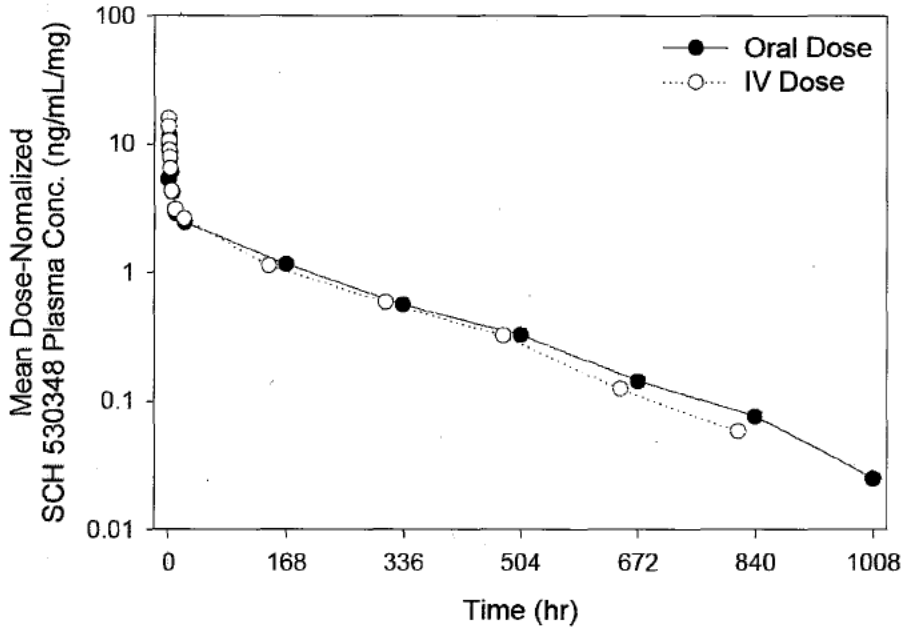

Figure 2: Mean vorapaxar plasma concentration-time profile following administration of single oral unlabeled vorapaxar sulfate 2.5 mg and intravenous ^{14}C-vorapaxar sulfate 73.7 µg [Source: CSR P07045, Figure 5, Page 62]

Comment: Note the parallel slopes of elimination for both profiles which suggests no non-linearity in the clearance process thus validating assumption of dose-proportionality for the calculation of absolute bioavailability.

SUMMARY

- Approximately, 83% of total radioactivity was recovered in this 6-week study. Extrapolation using Michaelis-Menten kinetics, projects 100% recovery in about 72 days. The duration and the sample collection in this study is commendable for a drug with such a long half-life.
- Absolute bioavailability of vorapaxar is approximately 100%.
- Renal excretion is a minor component to the clearance of vorapaxar and its metabolites. We know from study P03454 that the role of renal pathway in the excretion of unchanged vorapaxar is insignificant.

Single and Multiple Dose Pharmacokinetics		
Study report: P06559	**Study period:** 07/19/2010 - 10/28/2010	**EDR Link**[5]

OBJECTIVES

To evaluate the safety, tolerability and pharmacokinetics of vorapaxar and metabolite M20 following a single dose of 120 mg and daily doses of 2.5 mg vorapaxar sulfate for 6 weeks in healthy subjects.

STUDY DESIGN

Single center, open label, two treatment, parallel group study in healthy adult volunteers

Treatment A: 120 mg (3 x 40 mg) vorapaxar sulfate administered as a single dose
Treatment B: 2.5 mg (1 x 2.5 mg) vorapaxar sulfate administered once daily for 6 weeks

All subjects were confined to the study center on day -1 and discharged the morning of day 2. Subjects in treatment B continued with dose administration in the morning on days 3 through 41 as outpatients and returned for confinement in the evening of day 41 and discharged the morning of day 43. At the study center, on days 1 and 42, vorapaxar sulfate was administered following an overnight fast.

Population

Enrolled: N = 37 (treatment A=14 subjects, treatment B=23 subjects)
Completed: N = 32 (treatment A=13 subjects, treatment B=19 subjects; 86% caucasians; 46% men)
One subject discontinued from treatment A (withdrew consent). One subject discontinued (due to an AE after 28 days of dosing) and three subjects were lost to follow up.
Healthy adult volunteers (age: 18-45 y; BMI: 19-27 kg/m^2)
Sample size was calculated based on a prior estimate of the inter-subject variability on C_{max} and AUC of vorapaxar such that the 90% CIs around the geometric mean is NLT 19% and NMT 23%.

PK Sampling

Blood samples were collected pre-dose, 0.5, 1, 1.5, 2, 4, 6, 12 and 24 h post-dose on day 1, and on days 7, 14, 21, 28, 35, and 42 for both treatments.
For subjects in treatment B, additional samples were also collected once weekly for 6 weeks after the last day of dosing i.e., on days 49, 56, 63, 70, 77, 84.

Statistical method

PK: Descriptive statistics. GMR and 90% CIs for accumulation ratio and metabolite/parent ratio. In addition, log transformed C_{min} was analyzed using an ANOVA model extracting the effects due to day as a fixed effect and subject as a random effect. GMR and 90% CIs were calculated for each day *vs* the average of subsequent days. Steady state was claimed to be achieved on day X if the 90% confidence interval for day X *vs* the average of subsequent days fell within the 80-125% range.

RESULTS

Bioanalysis assay method

	Vorapaxar	**M20**
Method	**UPLC-MS/MS**	**UPLC-MS/MS**
LLOQ (ng/mL)	1	0.5
Range (ng/mL)	1 to 1000	0.5 to 500
QCs (ng/mL)	3, 80, 800	1.5, 40, 400

Comment: The analytical assay method is acceptable since the accuracy and precision for at least $2/3^{rds}$ of the QC and LLOQ samples are within the acceptable limits of ±15% and ± 20%, respectively, as specified in 'Guidance for Industry: Bioanalytical Method Validation'.

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Pharmacokinetics

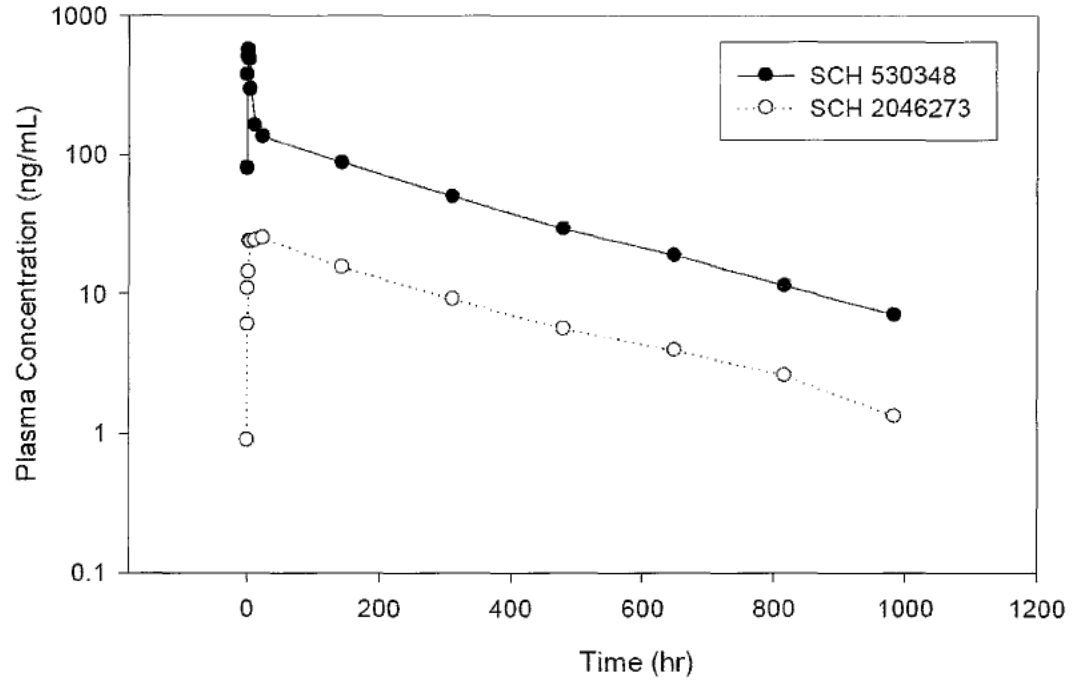

Figure 1: Mean plasma concentration of vorapaxar and metabolite M20 following a single oral dose of 120 mg vorapaxar sulfate in healthy volunteers [Source: CSR P06559, Figure 2, Page 59]

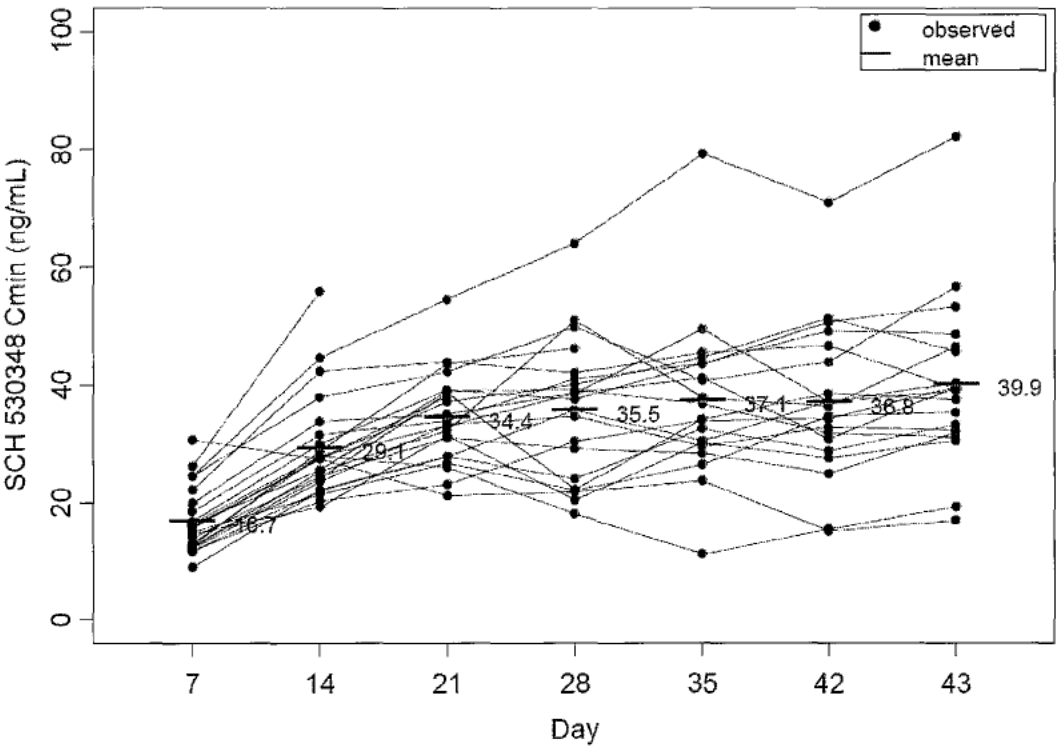

Figure 2: Individual and mean C_{min} values of vorapaxar following multiple oral dose of 2.5 mg vorapaxar sulfate for 6 weeks in healthy volunteers [Source: CSR P06559, Figure 5, Page 64]

Table 1: Mean PK parameters/measures following multiple oral dose of 2.5 mg vorapaxar sulfate for 6 weeks in healthy volunteers [Source: CSR P06559, Table 14, Page 63]

	SCH 530348				SCH 2046273			
	Day 1 (n=23)		Day 42 (n=20)		Day 1 (n=23)		Day 42 (n=20)	
PK Parameter	Mean	CV%	Mean	CV%	Mean	CV%	Mean	CV%
C_{max} (ng/mL)	25.7	28	67.0	26	1.77	36	10.9	48
T_{max} (hr)[a]	1.5	1-4	1.5	1-4	4	1.5-12	4	1.5-4.1
C_{min} (ng/mL)	-	-	36.8	35	-	-	7.87	53
AUC_{τ} (ng*hr/mL)	181	27	1020	31	32.2	36	218	49
AUC_{tf} (ng*hr/mL)	181	27	12500	42	32.2	36	2830	63
M/P Ratio (%)[b]	-	-	-	-	18	33	22	45
$t_{1/2}$ (hr)	-	-	197[d]	34[d]	-	-	187[e]	33[e]
$t_{1/2\ eff}$ (hr)	-	-	89.5	31	-	-	119	60
R_A[c]	-	-	5.90	28	-	-	7.67	56
CL/F (L/hr)	-	-	2.22	32	-	-	-	-
V_d/F (L)	-	-	634[d]	43[d]	-	-	-	-

AUC_{τ} = Area under the concentration-time curve during a dosing interval; AUC_{tf} = Area under the concentration-time curve from time 0 to last quantifiable sample; CL/F = Apparent total body clearance; C_{max} = Maximum observed concentration; C_{min} = Pre-dose plasma concentration; CV = Coefficient of variation; M/P Ratio = Metabolite to parent ratio; R_A = Accumulation ratio; $t_{1/2}$ = terminal phase half-life; T_{max} = Time of maximum observed concentration; V_d/F = Apparent volume of distribution.

a: Median (range).

b: M/P Ratio = $AUC_{\tau SCH\ 2046273}/AUC_{\tau SCH\ 530348}$ x100%

c: $R_A = AUC_{\tau Day\ 42}/AUC_{\tau Day\ 1}$

d: n=19. $t_{1/2}$ could not be determined for Subject 213 because % of extrapolated AUC is greater than 25% of total AUC. Therefore, V_d/F could not be determined for this subject.

e: n=16. t1/2 could not be determined for Subjects 205, 206, 207 and 219 either because % of extrapolated AUC is greater than 25% of total AUC or because square of linear regression coefficient (R^2) for the terminal phase is less than 0.9

Table 2: GMR and 90% CIs for metabolite to parent ratio following multiple oral dose of 2.5 mg vorapaxar sulfate for 6 weeks in healthy volunteers [Source: CSR P06559, Table 16, Page 67]

Metabolite/Parent Ratio after Multiple Doses of 2.5 mg SCH 530348						
Day	Analyte	n	AUC_{τ} LSMean (ng*hr/mL)[a]	90% CI (ng*hr/mL)	M/P Ratio	
					Ratio (%)	90% CI
1	SCH 530348	23	175[b]	157-196		
	SCH 2046273	23	30.3[b]	27.2-33.9	17.3	15.2-19.7
42	SCH 530348	20	980[b]	836-1149		
	SCH 2046273	20	194[b]	166-228	19.8	17.0-23.2

a: Model-based (least squares) geometric mean: based on mixed effect model extracting the effect due to Analyte as fixed effect and subject as random effect

b: Based on AUC_{τ}

- The terminal elimination half-life of vorapaxar and metabolite M20 are similar (Table 1). Slopes of the elimination phase of vorapaxar and M20 run parallel, suggesting that M20 is a formation rate limiting metabolite (Fig. 1).

- Metabolite-to-parent exposure ratio following treatment A and B is in the range of 17% to 20% (Table 2).

- Accumulation of vorapaxar upon once daily administration of 2.5 mg for 6 weeks is 5.6-fold. Based on accumulation, the effective half-life of vorapaxar is about 3-4 days.

- Graphical estimation (Fig. 2) as well as ANOVA (data not shown) of the weekly trough concentrations show that the steady state is achieved by day 21. It may be possible that the steady-state may have been achieved after week 2, but the sampling scheme does not allow for the precise determination.

Safety

There were no deaths or serious adverse events. One subject in treatment B had increased hepatic enzymes (AST, ALT and LDH) noted on day 28 which were considered related to the study drug and was discontinued from the study. After a follow up of 33 days since the last dose the liver function values returned to normal.

SUMMARY

- Exposure to the major active metabolite M20 is one-fifth of the parent drug exposure.

- Slopes of the elimination phases of metabolite M20 and vorapaxar run parallel, suggesting that M20 may be a formation rate limiting metabolite.

Single Dose PK/PD		
Study report: P03449	**Study period:** 10/14/2003 - 03/08/2004	**EDR Link**[6]
OBJECTIVE		
To evaluate the pharmacokinetics, pharmacodynamics, safety and tolerability of 0.25, 1, 5, 10, 20 and 40 mg single-doses of vorapaxar sulfate in healthy volunteers.		
STUDY DESIGN		
Randomized, single-blind, placebo-controlled, sequential rising single-dose study After initial screening, subjects were confined at the study center for 5 days. At each dose level, subjects received a single dose of vorapaxar in a fasted state with PK, PD, safety and tolerability evaluations performed until 72 h post-dose. Escalation to the next dose level was based on establishment of safety and tolerability of previous dose level, including PK and PD data.		
Population		
N = 54; (90% caucasians; 9 per dose group; 2 : 1 = vorapaxar sulfate : placebo) Healthy adult male volunteers (age: 18-45 y, BMI: 19-29 kg/m^2) No formal estimation of sample size (exploratory)		
PK Sampling		
Plasma: Blood samples for pharmacokinetic evaluation of vorapaxar were collected pre-dose, and at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 16, 24, 36, 48, and 72 h post-dose. Additional blood samples were collected in the two highest dose groups i.e., 20 and 40 mg at pre-dose, and at 1 and 6 h post-dose for preliminary metabolite profiling. *Urine*: Urine was also collected in the two highest dose groups for qualitative metabolite profiling prior to drug administration (blank control) and as a single block 0-24 h post-dose.		
PD Sampling		
Platelet aggregation: Blood samples for platelet aggregation induced by TRAP[7] (15 μM) and ADP (10 μM) were collected at pre-dose, and at 1, 2, 4, 6, 12, 24, and 72 h post-dose. PPACK was the anti-coagulant used for the 0.25 mg dose group. However, the applicant claims that the PRP had low platelet counts consequently leading to poor and inconsistent platelet aggregation results. Hence, further dose cohorts used both PPACK and sodium citrate as the anti-coagulant, but, results using sodium citrate were considered primary by the applicant. *Coagulation tests*: Blood samples for coagulation tests such as TT, PT, aPTT, ACT, and ECT were collected at pre-dose, and at 2, 6, 12, 24, and 72 h post-dose. *Others*: Bleeding time and blood samples for serum soluble and membrane bound P-selectin concentrations were measured at pre-dose, and at 2, 24, and 72 h post-dose.		
Statistical method		
PK: descriptive statistics; to assess dose-proportionality, GMR and 90% CIs for log-transformed, dose-normalized C_{max} and $AUC_{0\text{-}72\ h}$ was performed extracting effects due to dose. *PD*: descriptive statistics; mean and 95% CI for treatment difference between pooled vorapaxar dose groups and placebo.		

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[7] Inhibition of platelet aggregation in response to thrombin is measured using 'thrombin receptor activating peptide (TRAP) as the agonist. The clinical development program for vorapaxar used TRAP at a concentration of 15 μM which is in the concentration range typically used (5 to 20 μM).

RESULTS

Bioanalysis assay method

	Vorapaxar
Method	**UPLC-MS/MS**
LLOQ (ng/mL)	0.1
Range (ng/mL)	0.1 to 50
QCs (ng/mL)	0.3, 7.5, 37.5

Comment: The analytical assay method is acceptable since the accuracy and precision for at least 2/3^{rds} of the QC and LLOQ samples are within the acceptable limits of ±15% and ± 20%, respectively, as specified in 'Guidance for Industry: Bioanalytical Method Validation'.

Pharmacokinetics

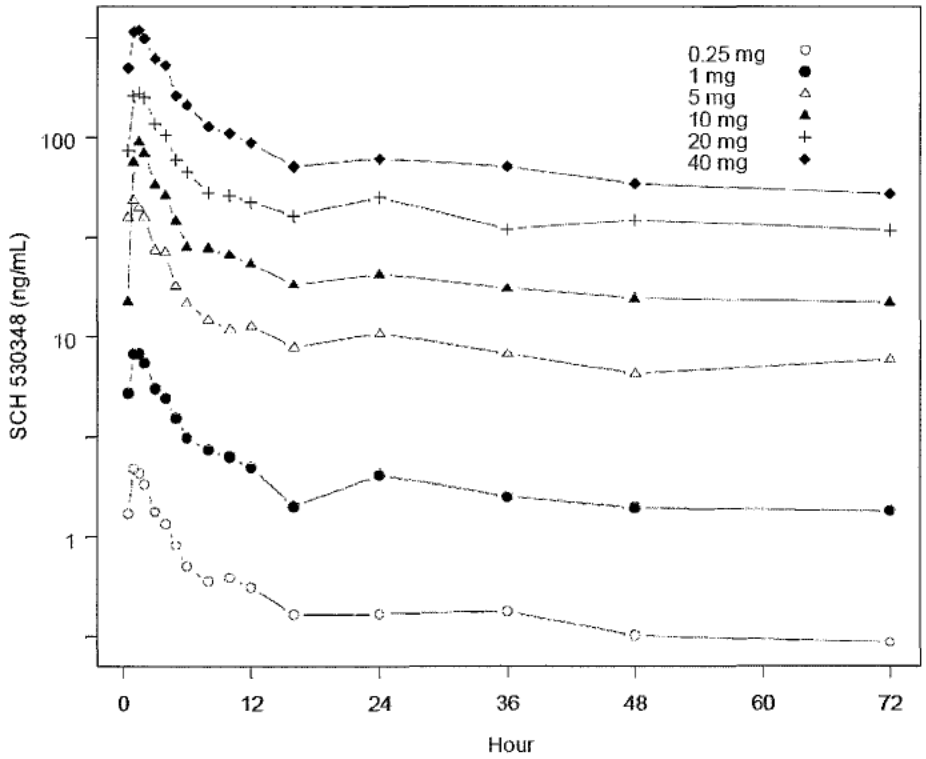

Figure 1: Mean vorapaxar plasma concentration-time profile following single oral doses of vorapaxar sulfate in healthy adult male subjects [Source: CSR P03449, Figure 6, Page 80]

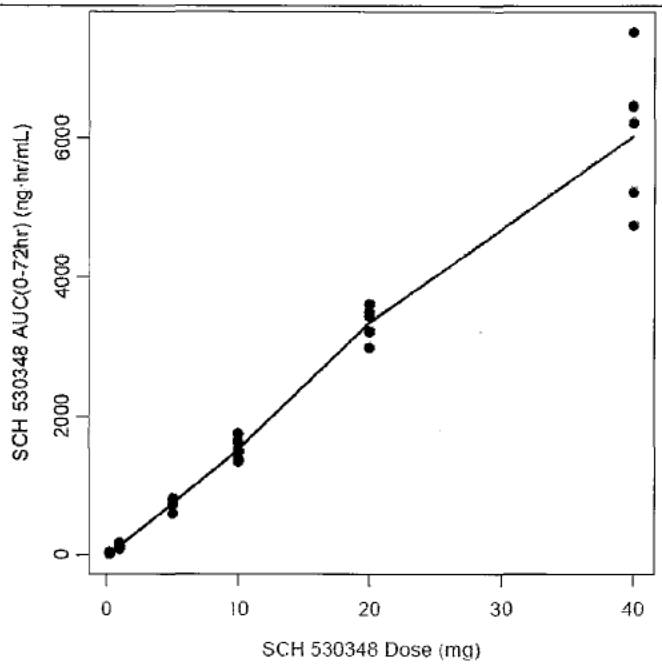

Figure 2: Assessment of dose-proportionality on $AUC_{0\text{-}72\ h}$ [Source: CSR P03449, Figure 8, Page 82]

- Vorapaxar is rapidly absorbed following oral administration. Time to reach peak concentration is 1-2 h across all dose groups.
- Pharmacokinetics of vorapaxar is characterized by a rapid distribution phase followed by slow terminal elimination phase.
- PK sample collection was extended up to 2 months post-dose in the 20 and 40 mg dose groups which showed that the terminal elimination half-life of vorapaxar might be in the range of 5 to 11 days.
- Inter-subject variability in PK measures of vorapaxar i.e., C_{max} and $AUC_{0\text{-}72\ h}$ is < 30%.
- Vorapaxar exhibits dose-proportional pharmacokinetics in the range of 0.25 mg to 40 mg.

Metabolite profiling:

- Unchanged drug was the primary circulating moiety with trace amounts of amine metabolite (M19) and two mono-oxy metabolites (M20, M21) in plasma.
- No unchanged parent drug was detected in urine collected until 24 h post-dose.

Pharmacodynamics

Platelet aggregation:

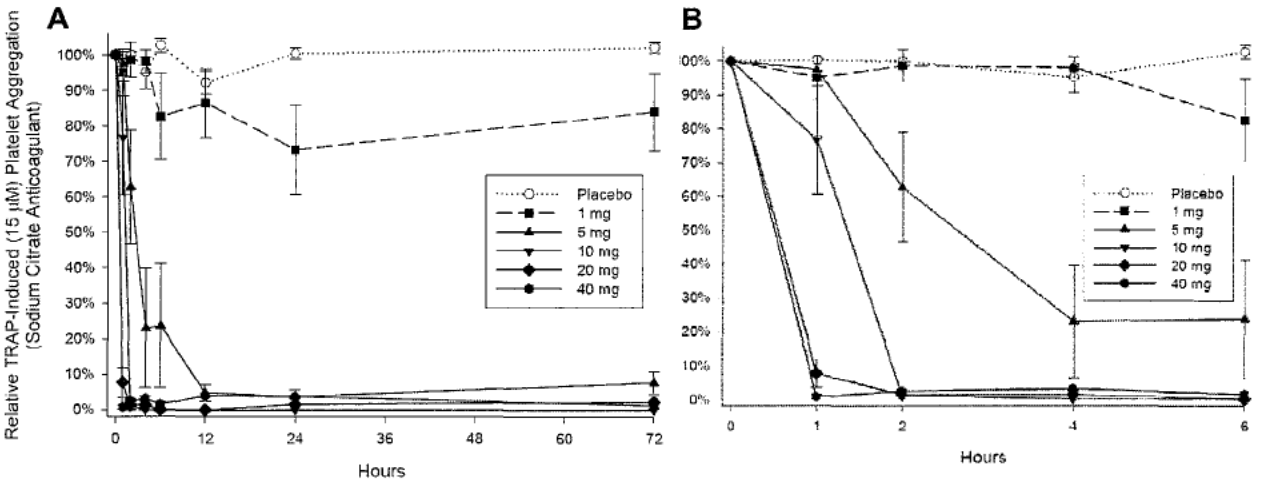

Figure 3: Time course of mean (±SE) % platelet aggregation in response to placebo and single doses of vorapaxar sulfate (A) 72 h post-dose (b) 6 h post-dose [Source: CSR P03449, Figure 3, Page 72]

- Vorapaxar did not inhibit platelet aggregation in response to ADP 20 µM.
- Platelet inhibition with PPACK as the anti-coagulant showed an inconsistent trend for 0.25 and 1 mg dose groups (data not shown). Moreover, the inhibition was more pronounced with PPACK than sodium citrate. As we would want the PD marker to have a relatively graded response with respect to vorapaxar plasma concentration, the choice of sodium citrate as the anti-coagulant serving as the primary results in this study and the use in subsequent studies seems reasonable.
- A single-dose of vorapaxar sulfate 5 mg produced less than 10% platelet aggregation by 12 h and doses higher than 5 mg achieved near maximal platelet aggregation inhibition by 2 h. All the dose groups continued to exhibit platelet aggregation values <10% at 72 h post-dose.
- As the platelet function did not recover by 72 h post-dose, subjects who received 20 or 40 mg vorapaxar sulfate were followed much longer. At the last measurement (35 to 64 days post-dose), 8 out of 10 subjects had % relative platelet aggregation between 80% to 95%, suggesting that complete recovery of platelet function may approximately take more than 1 month.

Coagulation parameters, P-selectin:

There were no significant changes in coagulation parameters (TT, PT, aPTT, ACT, and ECT) and membrane bound/ soluble P-selectin levels between placebo and the vorapaxar sulfate dose groups (data not shown).

Bleeding time:

Typical bleeding times using a modified Ivy method ranges between 3 to 9 min. However, the baseline bleeding times from this study were significantly lower, in the range of 40 to 80 sec. Following an

information request, the applicant clarified that they used a commercially available spring-activated puncture device (Glucoject Duo®; Italy – a lancet used to obtain blood sample to measure blood glucose levels), to produce standardized incisions on the surface of the forearm. The applicant also mentioned that there were no literature reports in support of using this puncture device to measure bleeding times. Moreover, no positive controls were employed in this study to test the sensitivity of the puncture device in measuring bleeding times (e.g., aspirin, a known agent to prolong bleeding time). Therefore, no conclusions can be drawn on the impact of vorapaxar on bleeding times as the applicant did not use a validated assay.

Safety

No subject died or had a serious adverse event. No subject discontinued participation for any reason. Although adverse events were reported for an apparently greater proportion of subjects who received vorapaxar than placebo, there was no particular pattern that emerged other than for flatulence.

SUMMARY

- Vorapaxar follows multi-exponential disposition characterized by a rapid distribution phase followed by slow terminal elimination phase.

- Onset of platelet inhibition following 5 mg single dose of vorapaxar sulfate is achieved by day 1. However, the time to reverse the platelet function to baseline may take relatively longer (~1 month for 20 to 40 mg single dose).

- Based on results from study P03450, it is expected that following repeat administration of clinically relevant dose of 2.5 mg vorapaxar sulfate, the onset for near maximal platelet inhibition will be achieved by end of day 2. The time for complete reversal of platelet inhibition upon cessation at steady state however may take about 6 to 8 weeks post-last dose.

Multiple Dose PK/PD		
Study report: P03450	**Study period:** 04/14/2004 - 11/24/2004	**EDR Link**[8]
OBJECTIVE		
To evaluate the pharmacokinetics, pharmacodynamics, safety and tolerability at multiple doses of vorapaxar sulfate – (i) 1, 3, and 5 mg once daily for 28 days, and (ii) loading dose of 10 or 20 mg followed by maintenance doses of 1 mg once daily for 28 days in healthy subjects		
STUDY DESIGN		
Randomized, single-blind, single center, placebo-controlled, parallel group, rising multiple-dose study Group 1: 1 mg QD for 28 days (N=12, vorapaxar: placebo = 2 : 1) Group 2: 3 mg QD for 28 days (N=12, vorapaxar : placebo = 2 : 1) Group 3: 5 mg QD for 28 days (N=12, vorapaxar : placebo = 2 : 1) Group 4: 10 mg or 20 mg loading dose on day 1 + 1 mg QD on days 2-7 (N = 12, 10 : 20 mg = 1 : 1) Escalation to the next dose level was based on satisfactory safety and tolerability results of the previously administered dose evaluated at least 2 weeks post-last dose (day 42). Subjects were confined at the study site for 2 days before the first dose, during dosing, and for 3 days after the last dose. Doses were administered in a fasted state.		
Population		
N = 48; (36 subjects in groups 1, 2 and 3; 12 subjects in group 4, 92% caucasians, 69% men) Healthy adult volunteers (age: 18-45 y; BMI: 19-29 kg/m^2) No formal estimation of sample size (exploratory)		
PK Sampling		
Plasma: For subjects in groups 1-3, blood samples for PK evaluation of vorapaxar were collected before dosing on days 1, 7, 14, 21, 26, 27, and 28; at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 16, and 24 h after dosing on days 1 and 28; and at 36, 48, and 72 h after the last dose. For subjects in group 4, blood samples were collected before dosing on days 1 to 7; at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 16, and 24 h after dosing on day 1; and at 36, 48, and 72 h after the last dose. Blood samples for metabolite profiling were collected for the 5 mg dose group before dosing and at 2 and 6 h after dosing on days 1, 14, and 28. Additional blood samples for PK evaluation were collected at weekly intervals corresponding to days 35, 42, 49 and 56 for groups 1-3 and days 14, 21, 28, and 35 for group 4.		
PD Sampling		
Platelet aggregation: For subjects in groups 1-3, blood samples for platelet aggregation induced by 15 μM TRAP[9] were collected before dosing on days 1, 7, 14, and 28, and at 1, 2, 4, 6, 12, and 24 h post-dose on days 1 and 28, and at 72 h after the last dose. For subjects in group 4, blood samples were collected before dosing on days 1 to 7, and at 0.5, 1, 2, 4, 6, 12, and 24 h post-dose on day 1. Additional blood samples for PD evaluation were collected at weekly intervals corresponding to days 35, 42, 49 and 56 for groups 1-3 and days 14, 21, 28, and 35 for group 4. Subjects whose platelet aggregation results indicated significant inhibition (>50%), were instructed to return for additional weekly visits. *Coagulation tests*: Blood samples for coagulation tests such as TT, PT, aPTT, ACT, and ECT were collected before dosing on day 1 for all groups, and at days 7, 14, 21, 28, 31, and 42 for groups 1-3 and		

[8] \\Cdsesub1\evsprod\NDA204886\0000\m5\53-clin-stud-rep\533-rep-human-pk-stud\5331-healthy-subj-pk-init-tol-stud-rep\p03450\p03450.pdf

[9] Inhibition of platelet aggregation in response to thrombin is measured using 'thrombin receptor activating peptide (TRAP) as the agonist. The clinical development program for vorapaxar used TRAP at a concentration of 15 μM which is in the concentration range typically used (5 to 20 μM).

at days 7, 10 and 21 for group 4.

Others: Blood samples for serum soluble P-selectin and CD40 ligand concentrations were measured before dosing on days 1, 7, 14, 21, and 28 for groups 1-3 only. Bleeding time was measured on day -1 for all groups, and before dosing on days 7, 14, 21, and 28 for groups 1-3, and day 7 for group 4.

Statistical method

PK: descriptive statistics; to assess dose-proportionality, GMR and 90% CIs for log-transformed, dose-normalized C_{max} and $AUC_{0\text{-}72\ h}$ was performed extracting effects due to dose. A repeated measures ANOVA was used to assess C_{min} data on days 21, 26, 27, and 28 for attainment of steady state.

PD: descriptive statistics; mean and 95% CI for treatment difference between vorapaxar and placebo in groups 1-3, and between 10 mg and 20 mg loading doses in group 4.

RESULTS

Bioanalysis assay method

	Vorapaxar
Method	**UPLC-MS/MS**
LLOQ (ng/mL)	0.1
Range (ng/mL)	0.1 to 50
QCs (ng/mL)	0.3, 7.5, 37.5

Comment: The analytical assay method is acceptable since the accuracy and precision for at least $2/3^{rds}$ of the QC and LLOQ samples are within the acceptable limits of ±15% and ± 20%, respectively, as specified in 'Guidance for Industry: Bioanalytical Method Validation'.

Pharmacokinetics

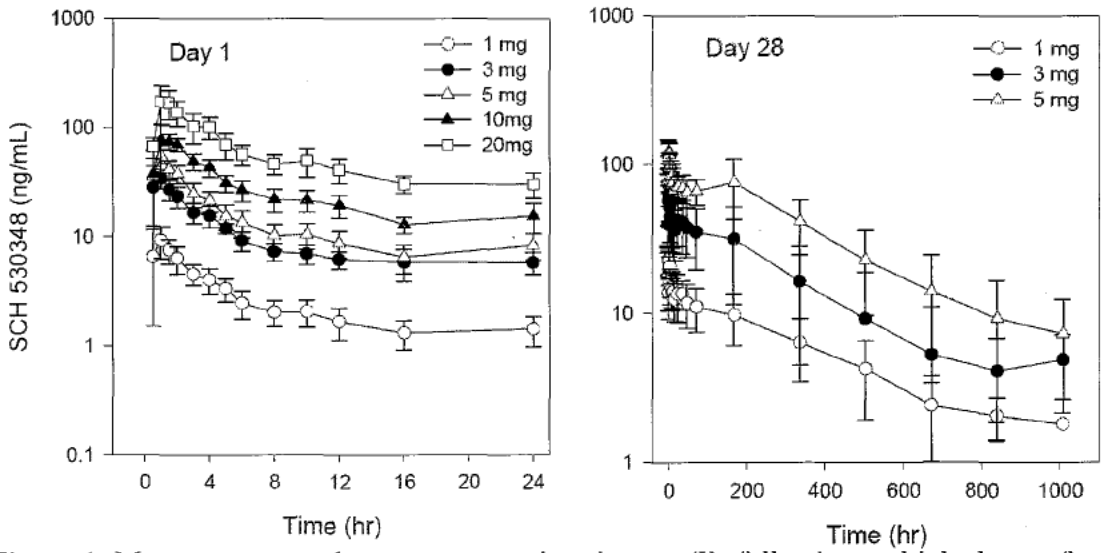

Figure 1: Mean vorapaxar plasma concentration-time profile following multiple doses of vorapaxar sulfate in healthy subjects – day 1 and day 28 [Source: CSR P03450, Figure 9, Page 94]

Table 1: Mean pharmacokinetic measures following multiple oral doses of vorapaxar sulfate [Source: CSR P03450, Table 24, Page 93]

Dose	Cmax (ng/mL) mean (CV[%])	Tmax (h) median (min-max)	$t_{½}$ (h) mean (CV[%])	AUC(0-24h) (ng•h/mL) mean (CV[%])	R mean (CV[%])
Day 1					
1 mg (n = 8)	9.78 (31)	1.00 (0.5-4.0)	NA	58.5 (24)	NA
3 mg (n = 8)	38.2 (25)	1.00 (0.5-1.0)	NA	225 (15)	NA
5 mg (n = 8)	56.4 (25)	1.00 (0.5-2.0)	NA	315 (21)	NA
10 mg (n = 6)	85.4 (24)	1.00 (1.0-2.0)	NA	592 (14)	NA
20 mg (n = 6)	188 (32)	1.50 (1.0-4.0)	NA	1280 (23)	NA
Day 28					
1 mg (n = 7)[a]	24.6 (24)	1.00 (0.5-2.0)	269 (30)	363 (24)	6.37 (18)
3 mg (n = 8)	65.8 (37)	1.00 (0.5-2.0)	173 (35)	1040 (34)	4.72 (33)
5 mg (n = 8)	131 (18)	1.00 (1.0-2.0)	217 (22)	1910 (17)	6.22 (20)

a: One subject excluded due to incomplete PK profile

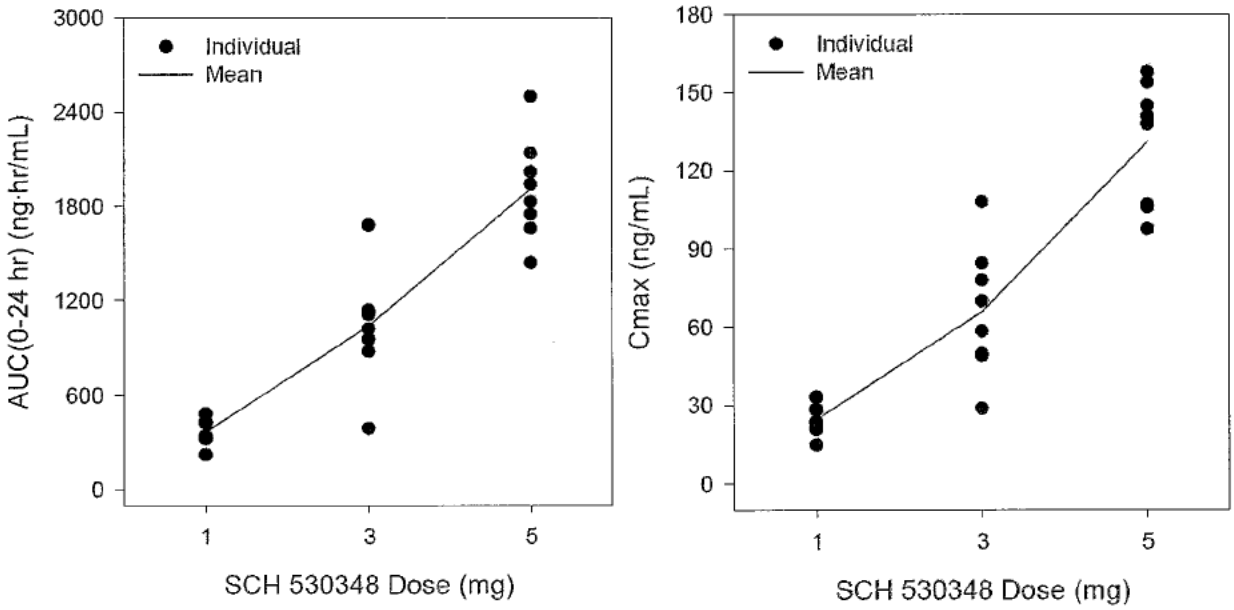

Figure 2: Assessment of dose-proportionality on C_{max} and $AUC_{0-\tau}$ on day 28 [Source: CSR P03450, Figure 10, Page 95]

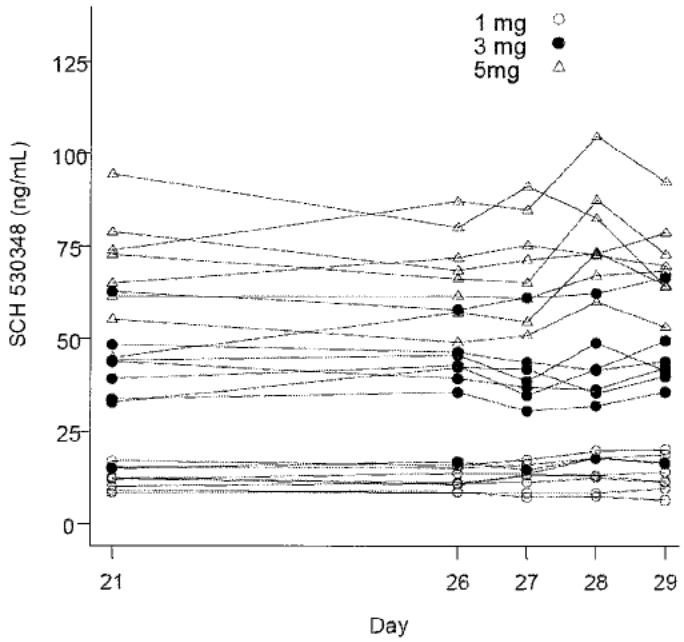

Figure 3: Individual plasma concentrations at the end of inter-dosing interval (C_{min}) upon multiple doses of vorapaxar sulfate in healthy volunteers [Source: CSR P03450, Figure 11, Page 96]

- Elimination of vorapaxar is slow with a mean terminal elimination half-life of 7-11 days. However, based on the accumulation ratios on day 28 which ranged from 4.7 to 6.4, the effective half-life can be calculated to be between 3-4 days.

- Inter-subject variability in PK measures of vorapaxar i.e., C_{max} and $AUC_{0-\tau}$ was < 35% (Table 1).

- PK measures of vorapaxar i.e., C_{max} and $AUC_{0-\tau}$ showed a dose-proportional increase on day 1 and day 28 (Fig. 2)

- Upon once daily multiple dosing, steady state exposures of vorapaxar are achieved by day 21. However, as there were no sampling time points between day 14 and 21, we may not know if the steady state could have been achieved earlier than day 21.

Metabolite profiling:

- Unchanged drug was the primary circulating moiety on days 1, 14, and 28. Amounts of the two mono-oxy metabolites (M20 and M21) were 2%-6.5% relative to the parent drug on days 14 and 28. No notable accumulation of metabolites was observed between days 14 and 28.

Pharmacodynamics

Platelet aggregation: Onset

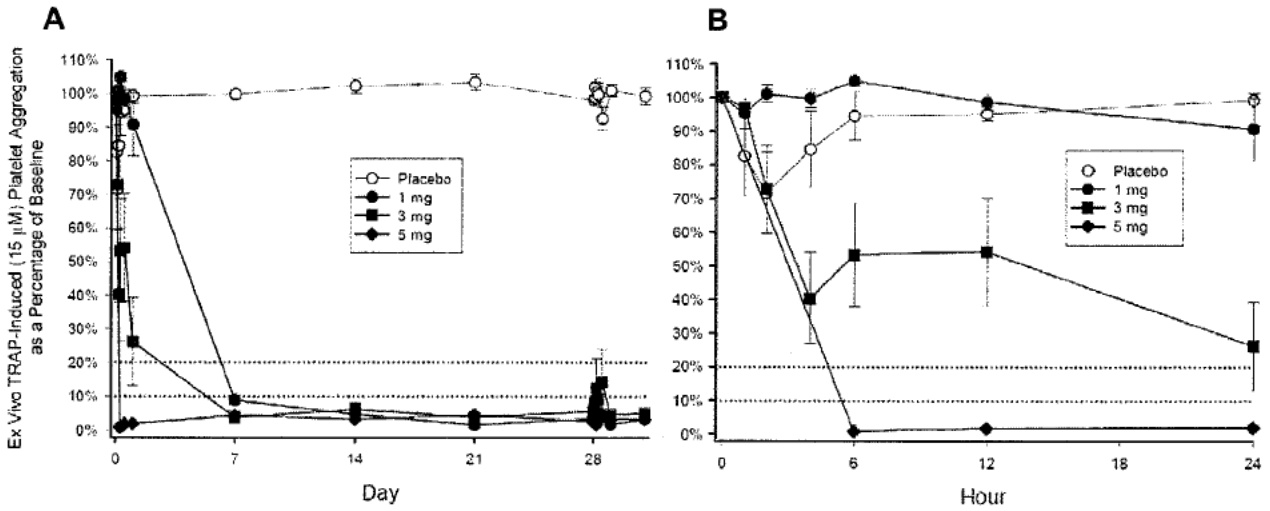

Figure 4: Time course of mean (±SE) % platelet aggregation in response to placebo and multiple doses of vorapaxar sulfate in healthy subjects – (A) day 1 and (B) day 28 [Source: CSR P03450, Figure 2, Page 80]

Platelet aggregation: Offset

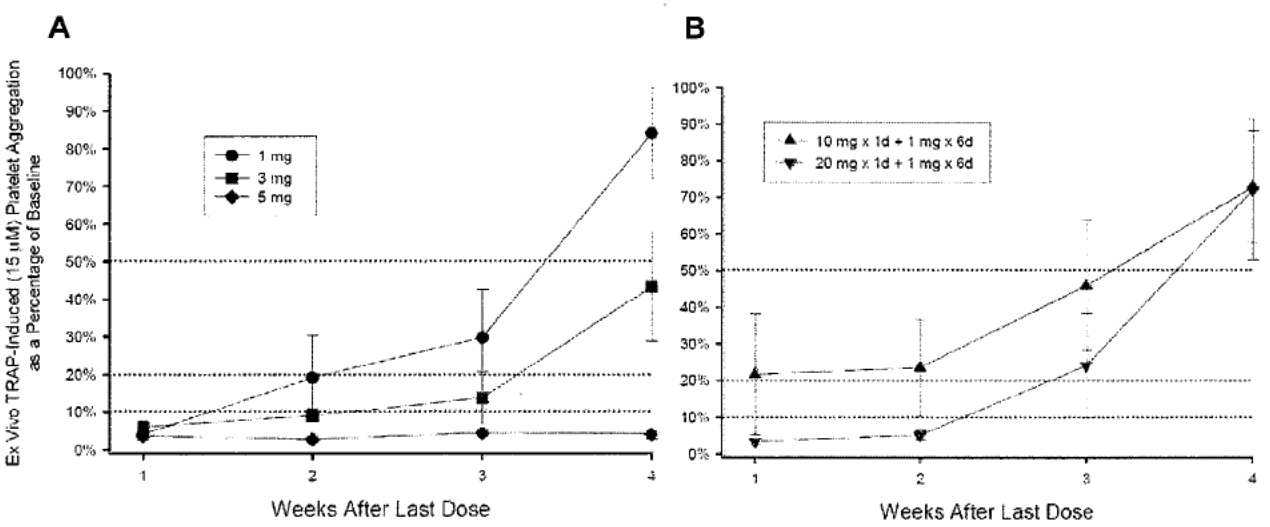

Figure 5: Time course of mean (±SE) % platelet aggregation recovery after the last dose of vorapaxar in groups (A) 1-3 and (B) 4 [Source: CSR P03450, Figure 4, Page 85]

- All dosing regimens inhibited platelet aggregation to <10%, but, the time to achieve maximum

inhibition was inversely related to dose.

- Following the first dose in groups 1-3, only 5 mg vorapaxar sulfate resulted in near maximal platelet inhibition by 24 h. The 3 mg dose group achieved 70-80% platelet inhibition by 24 h following the first dose. It is expected that the platelet inhibition would be >90% following the second dose (day 2). With 1 mg dose group, there was no appreciable platelet inhibition following the first dose, however, near maximal platelet inhibition was achieved by day 7. It may be possible that the maximal platelet inhibition is achieved prior to day 7 as there were no sampling time points between day 1 and day 7.
- Following the loading dose in group 4, both 10 mg and 20 mg vorapaxar sulfate produced near maximal platelet inhibition within 1-2 h of dosing. Once maximal platelet inhibition was achieved, the effects were sustained with repeat dosing in all the dose groups.
- Following once daily dosing for 28 days, complete recovery of platelet function was not achieved in any of the dose groups by week 4. At week 4, the mean % platelet aggregation relative to baseline was 84%, 43% and 4% in groups 1-3 and 72% in group 4.
- Subjects whose platelet aggregation values did not recover to at least 50% of baseline by week 4 were followed until the target was met. It took about 6 and 9 weeks for 90% of the subjects to recover at least 50% platelet function for the 3 and 5 mg dose groups, respectively.

Coagulation parameters, P-selectin, CD40:

There were no significant changes in coagulation parameters (TT, PT, aPTT, ACT, and ECT), soluble P-selectin and CD40 ligand levels between placebo and the vorapaxar sulfate dose groups (data not shown).

Bleeding time:

Based on results in Table 2, the applicant concludes that vorapaxar does not prolong bleeding time. However, no conclusions can be drawn based on these results for the reasons explained below.

Table 2: Mean bleeding time (seconds) following multiple doses of vorapaxar sulfate [Source: CSR P03450, Table 22, Page 90].

	Pooled Placebo			SCH 530348								
				1 mg			3 mg			5 mg		
	n	Mean	SE	n	Mean	SE	n	Mean	SE	n	Mean	SE
Baseline	12	45.8	3.7	8	47.6	4.7	8	54.9	6.6	8	39.0	2.2
Day 7	12	61.3	7.3	8	54.6	6.0	8	70.5	8.9	8	49.3	3.7
Day 14	12	69.8	11.6	8	66.0	9.6	8	59.5	7.4	8	57.3	5.4
Day 21	12	57.0	4.8	8	59.9	6.4	8	40.9	5.7	8	55.8	2.9
Day 28	12	61.5	6.7	8	68.0	10.0	8	72.0	6.9	8	75.0	8.0

Abbreviation: SE = standard error.

Typical bleeding times using a modified Ivy method ranges between 3 to 9 min. However, the baseline

bleeding times from this study were significantly lower, in the range of 40 to 80 sec. Following an information request, the applicant clarified that they used a commercially available spring-activated puncture device (Glucoject Duo®; Italy – a lancet used to obtain blood sample to measure blood glucose levels), to produce standardized incisions on the surface of the forearm. The applicant also mentioned that there were no literature reports in support of using this puncture device to measure bleeding times. Moreover, no positive controls were employed in this study to test the sensitivity of the puncture device in measuring bleeding times (e.g., aspirin, a known agent to prolong bleeding time). Therefore, no conclusions can be drawn on the impact of vorapaxar on bleeding times as the applicant did not use a validated assay.

Safety

All subjects received dosing as specified except one subject who discontinued daily treatment with 1 mg of vorapaxar sulfate after 24 days because of a chalazion developed on the eyelid. No intervention was required. The chalazion resolved and the subject completed required follow-up.

Adverse events tended to be reported without pattern and no more often with vorapaxar than with placebo, except for pain and hematoma at venipuncture sites. Hematoma at venipuncture sites was especially noticeable among subjects who received 5 mg of vorapaxar for 28 days, and was also reported in Group 4 (with loading dose). These events were all mild and transient, and none required intervention, but almost all were considered by the investigator as possibly related to treatment.

SUMMARY

- Upon repeat once daily dosing, there was a 4- to 6-fold accumulation in the systemic exposures to vorapaxar. Steady state levels are achieved by day 21. Exposure to vorapaxar at steady state is reasonably dose-proportional. Based on the accumulation at steady state, the effective half-life is about 3-4 days.
- All dosing regimens studied achieved >90% platelet inhibition, however, the time to achieve maximum platelet inhibition was inversely related to dose. Following a single dose of 3 mg vorapaxar sulfate, platelet aggregation was reduced to 20-30% of baseline by 24 h post-dose. Hence, it is expected that near maximal platelet inhibition would be attained with the second dose. Similar time course for the onset of PD effect is expected following the clinically relevant dose of 2.5 mg vorapaxar sulfate.
- As expected, time to recovery of platelet function is a function of dose and terminal elimination half-life. At 4 weeks after the last dose, the mean % platelet aggregation relative to baseline was 84%, 43% and 4% for dose groups 1, 3 and 5 mg, respectively. It took about 9 weeks for 90% of the subjects to recover at least 50% of platelet function in the 5 mg dose group.

Food Effect		
Study report: P07969	**Study period:** 02/08/2011 - 04/08/2011	**EDR Link**[10]

OBJECTIVE

To evaluate the effect of a standardized high-fat breakfast on the pharmacokinetics of 2.5 mg single oral dose of vorapaxar in healthy adult subjects

STUDY DESIGN

Randomized, open label, single center, two period, crossover study with a minimum wash-out interval of 6 weeks between periods.

Subjects on the fasted arm received 2.5 mg vorapaxar sulfate following an overnight fast of at least 10 h and continued to remain fasted for another 4 h post-dose. Subjects on the fed arm were given a FDA standardized high-fat breakfast to be eaten over 20 min, followed immediately by administration of 2.5 mg vorapaxar sulfate.

Population

N = 16; healthy adult volunteers (age: 18-50 y, BMI: 18-32 kg/m^2). All 16 subjects completed the study.

PK Sampling

Blood samples for pharmacokinetic evaluation of vorapaxar were collected pre-dose, and at 0.5, 1, 1.5, 2, 3, 4, 6, 12, 24, 48, and 72 h post-dose.

Comment: Considering the long terminal elimination half-life of vorapaxar (approx. 7-8 days), a truncated PK sampling scheme until 72 h is acceptable based on 'Guidance for Industry: Bioavailability and Bioequivalence Studies for Orally Administered Drug Products Submitted in New Drug Applications – General Considerations and Food Effect Assessment'

Statistical method

PK: descriptive statistics; geometric mean ratio and 90% CI for C_{max} and AUC between fed and fasted treatment arms using mixed-effect ANOVA model.

RESULTS

Bioanalysis assay method

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

	Vorapaxar
Method	**UPLC-MS/MS**
LLOQ (ng/mL)	1
Range (ng/mL)	1 to 1000
QCs (ng/mL)	3, 80, 800

Reviewer's comment: The analytical assay method is acceptable since the accuracy and precision for at least $2/3^{rds}$ of the QC and LLOQ samples are within the acceptable limits of ±15% and ± 20%, respectively, as specified in 'Guidance for Industry: Bioanalytical Method Validation'.

[10] \\Cdsesub1\evsprod\NDA204886\0000\m5\53-clin-stud-rep\531-rep-biopharm-stud\5311-ba-stud-rep\p07969\p07969.pdf

PK summary statistics

Table 1: Statistical analysis – Effect of food on the pharmacokinetics of vorapaxar [Source: CSR P07969, Table 11, Page 49]

Parameter	Treatment	n	LSMean [a]	90% CI	Comparison	GMR[b]	90% CI	STD[c]
$AUC_{(0\text{-}72h)}$ (ng*hr/mL)	A (Fasted)	16	314	284- 348	fed vs fast	96.9	92.2- 102	0.08
	B (Fed)	16	304	275- 337				
C_{max} (ng/mL)	A (Fasted)	16	23.4	20.7-26.4	fed vs fast	79.1	67.6-92.5	0.25
	B (Fed)	16	18.5	16.4-20.8				

a: Model-based (least squares) geometric mean: based on mixed effect model extracting the effect due to treatment, period and sequence as fixed effects and subject(sequence) as random effect

b: Model-based geometric mean ratio

c: Intra subject standard deviation on log scale

- Median T_{max} was delayed by 45 min in the fed treatment group (2.00 h) when compared to fasted treatment group (1.25 h)

SUMMARY

- This was a definitive relative bioavailability study evaluating the impact of a high fat meal on the pharmacokinetics of vorapaxar administered as 2.5 mg vorapaxar sulfate.

- There is no change in $AUC_{0\text{-}72\ h}$, and 21% decrease in the C_{max} of vorapaxar in the presence of a standardized high-fat breakfast when compared to vorapaxar administered in a fasted state. This decrease in C_{max} is not considered clinically significant, as vorapaxar is dosed for chronic use. Hence, vorapaxar can be administered without regards to a meal.

Race Effect PK/PD		
Study report: P03448	**Study period:** 07/22/2005 - 04/25/2005	**EDR Link**[11]
OBJECTIVE		
(i) To determine the influence of race/ethnic origin on the pharmacokinetics, pharmacodynamics, safety and tolerability of vorapaxar when administered as single doses of 0.5, 1, 2.5, 5, 10, 20 and 40 mg and as multiple once daily doses of 0.5, 1, 2.5 mg for 28 days. (ii) To evaluate the effect of food on the pharmacokinetics and pharmacodynamics of vorapaxar when administered as a single dose of 40 mg in Japanese and Caucasians.		
STUDY DESIGN		
Randomized, open label, parallel group study in healthy Japanese and Caucasian volunteers Group 1: 0.5 mg once daily for 28 days (N=12, vorapaxar: placebo = 2 : 1) Group 2: 1 mg once daily for 28 days (N=12, vorapaxar : placebo = 2 : 1) Group 3: 2.5 mg once daily for 28 days (N=12, vorapaxar : placebo = 2 : 1) Group 4: 5 mg single dose Group 5: 10 mg single dose Group 6: 20 mg single dose Group 7: 40 mg single dose in fed (A) or fasted (B) state Subjects in group 7 (B) were administered the study drug following a standardized high-fat breakfast; all other subjects were administered the study drug following an overnight fast on day 1 in groups 4 to 7 (A) and on days 1-28 in groups 1 to 3 (days 2-27 as outpatients).		
Population		
Planned: N = 108 (J:C = 1:1; 16 subjects/trt in groups 1-3, 12 subjects/trt in groups 4-6, 7A, 7B) *Enrolled*: N = 111 (J=56, C=55) *Completed*: N = 109 (J=54, C=55) Healthy adult volunteers (age: 18-65 y; BMI: 17-31 kg/m^2, matched for age, height and weight) Assuming an inter-subject variability of 24%, 8 subjects per race/ethnic group will have at least 80% power to detect a 36% difference between race/ethnic groups in C_{max} and AUC at an $\alpha = 0.05$		
PK Sampling		
Blood samples for pharmacokinetic evaluation of vorapaxar were collected pre-dose and at 0.5, 1, 1.5, 2, 4, 6, 12 and 24 h post-dose on day 1 (all subjects) and day 28 (groups 1 to 3). Samples were also collected on an outpatient basis on days 7, 14, 21, 26, 27, 35, 42, 49 and 56 (groups 1 to 3) or days 7, 14, 21 and 28 (groups 4 to 7). Samples were also obtained on days 35 and 42 (groups 4 to 7) or days 63 and 70 (groups 1 to 3) for subjects with significant (i.e., >50%) platelet inhibition during the previous visit.		
PD Sampling		
Blood samples for measurement of *ex vivo* TRAP-induced platelet aggregation were collected pre-dose and at 0.5, 1, 2, 4, 6, 12 and 24 h post-dose on day 1 (all subjects). Samples were also collected on days 7, 14, 21, 28, 35, 42, 49 and 56 (groups 1 to 3) or days 7, 14, 21 and 28 (groups 4 to 7). Samples were also obtained on days 35 and 42 (groups 4 to 7) or days 63 and 70 (groups 1 to 3) for subjects with significant (i.e., >50%) platelet inhibition during the previous visit.		
Statistical method		
PK: Descriptive statistics. The 90% CIs for the mean of the differences between matched Japanese and Caucasian subjects were calculated to assess the race/ethnic influence.		

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PD: Descriptive statistics. The matched difference between Japanese and Caucasian subjects was provided in terms of descriptive statistics and 95% CIs for % platelet inhibition.

RESULTS

Bioanalysis assay method

	Vorapaxar
Method	**UPLC-MS/MS**
LLOQ (ng/mL)	0.1
Range (ng/mL)	0.1 to 50
QCs (ng/mL)	0.3, 7.5, 37.5

Comment: The analytical assay method is acceptable since the accuracy and precision of 2/3^{rds} of the QC and LLOQ samples are within ±15% and ±20%, respectively.

Pharmacokinetics

Table 1: Statistical analysis of the differences in the pharmacokinetics of vorapaxar between Japanese and Caucasians following a single dose [Source: CSR P03448, Table 16, Page 89]

		Cmax		AUC(0-24 hr)		AUC(I)	
Dose (mg)	n(mp)[a]	Ratio[b] (%)	90% CI	Ratio[b] (%)	90% CI	Ratio[b] (%)	90% CI
Initial Doses of Multiple-Dose Regimens, Excluding 1-Hour Sample for Caucasian Subject 220[c]							
0.5	8	107	88-131	102	84-124	NC	NC
1	8	90	72-114	95	84-109	NC	NC
2.5[c]	8	102	84-124	103	96-111	NC	NC
Pooled	24	100	90-111	100	93-108	NC	NC
Single Doses							
5	6	110	91-133	113	95-134	125	95-165
10	7	121	74-198	113	94-135	114	96-136
20	6	119	96-148	94	76-116	97	63-147
40	6	92	76-111	93	79-110	102	83-125
Pooled	25	110	96-127	103	95-112	109	97-123
All Initial/Single Doses Pooled, Excluding 1-Hour Sample for Caucasian Subject 220[c]							
All	49	105	96-114	102	96-107	NC	NC

Abbreviations: AUC(0-24 hr) = area under the curve of plasma concentration versus time from time zero to 24 hours after dosing; AUC(I) = area under the curve of plasma concentration versus time from time zero to infinity; CI = confidence interval; Cmax = maximum observed plasma concentration; NC = not calculated (study design did not allow estimation of this parameter or calculation would be inappropriate).

a: Number of matched pairs.

b: Japanese/Caucasian.

c: The 1-hour sample for Caucasian Subject 220 was considered to be an "outlier", and was not included in the calculations.

Table 2: Statistical analysis of the differences in the pharmacokinetics of vorapaxar between Japanese and Caucasians following multiple doses at steady state [Source: CSR P03448, Table 18, Page 94]

		Cmax		AUC(0-24 hr)	
Dose (mg)	n(mp)[a]	Ratio[b] (%)	90% CI	Ratio[b] (%)	90% CI
0.5[c,d]	8	108	89-130	101	86-119
1	8	111	96-129	102	91-115
2.5	8	106	82-136	105	94-118
Pooled	24	108	98-120	103	96-110

Abbreviations: AUC(0-24 hr) = area under the curve of plasma concentration versus time from time zero to 24 hours after dosing; CI = confidence interval; Cmax = maximum observed plasma concentration.

a: Number of matched pairs.

b: Japanese/Caucasian.

c: Caucasian Subject 208 received 30 days of daily dosing. Samples collected after the last day of dosing were used for this analysis.

d: The 2-hour sample on Day 28 for Caucasian Subject 221 was considered to be an "outlier", and was not included in the calculations

Table 3: Statistical analysis of the effect of a standardized high-fat breakfast in the pharmacokinetics of vorapaxar in both Japanese and Caucasians [Source: CSR P03448, Table 21, Page 98]

			AUC(I) (ng·hr/mL)		Cmax (ng/mL)	
	Condition		Ratio		Ratio	
Subjects	Comparison	n	Estimate[a]	90% CI	Estimate[a]	90% CI
All	Fed / Fasted	12 / 12	94	81-110	72	60-85
Japanese	Fed / Fasted	6 / 6	97	78-121	65	50-85
Caucasian	Fed / Fasted	6 / 6	91	71-118	79	61-102

Abbreviations: AUC(I) = area under the curve of plasma concentration versus time from time zero to infinity; CI = confidence interval; Cmax = maximum observed plasma concentration.

a: Percent ratio of the log-transformed mean values.

- Pharmacokinetics of vorapaxar is similar between Japanese and Caucasians (Table 1 and 2). However, cross-study comparison of the pharmacokinetics between the current study (P03448) and multiple ascending dose study (03450) for the same doses shows that the exposures are 1.5-fold higher in the current study.
- Pharmacokinetic measures of vorapaxar are dose-dependent with a slight less than-proportional increase in exposure (data not shown). Terminal elimination half-life (7-11 days), time to attain steady-state (by day 21) and accumulation ratio at steady-state (5- to 6-fold) are in the range of what was observed in other studies (data not shown).
- Standardized high-fat breakfast decreased the peak concentration by 30%, however, there was no change in $AUC_{0\text{-}inf}$ to vorapaxar (Table 3).
- Inter-subject variability in PK measures of vorapaxar i.e., C_{max} and $AUC_{0\text{-}\tau}$ was <30% in Japanese healthy volunteers.

Pharmacodynamics

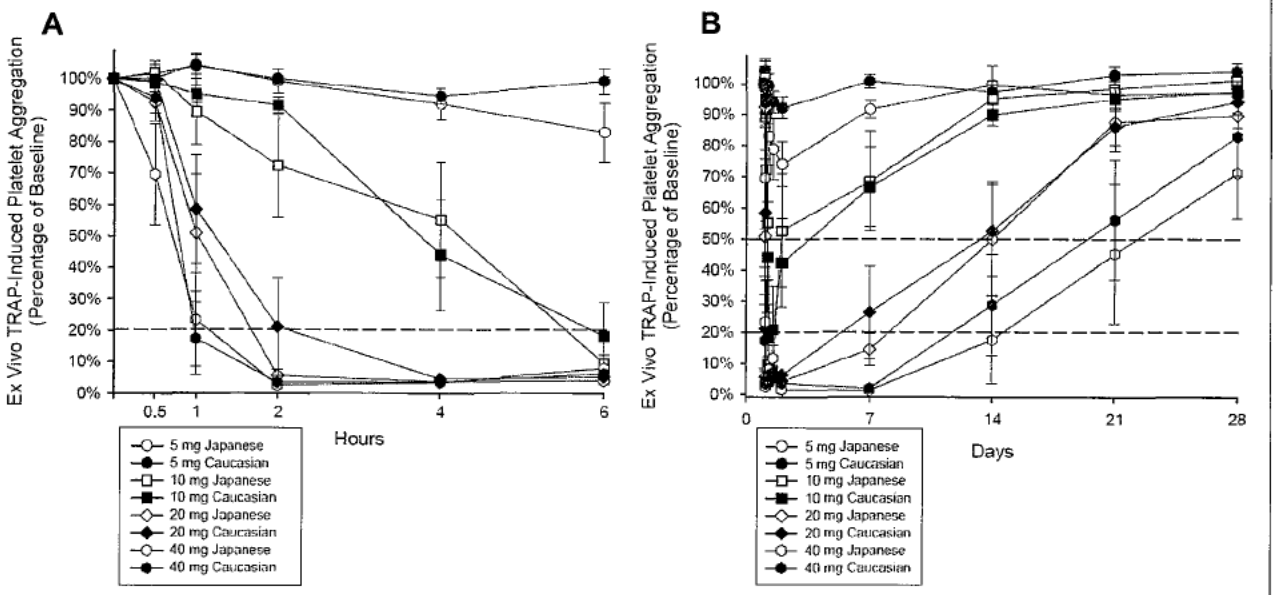


Figure 1: Time course of mean (±SE) % platelet aggregation (A) following a single dose through 6 h post-dose on day 1 and (B) recovery post single dose [Source: CSR P03448, Figure 8, Page 101]

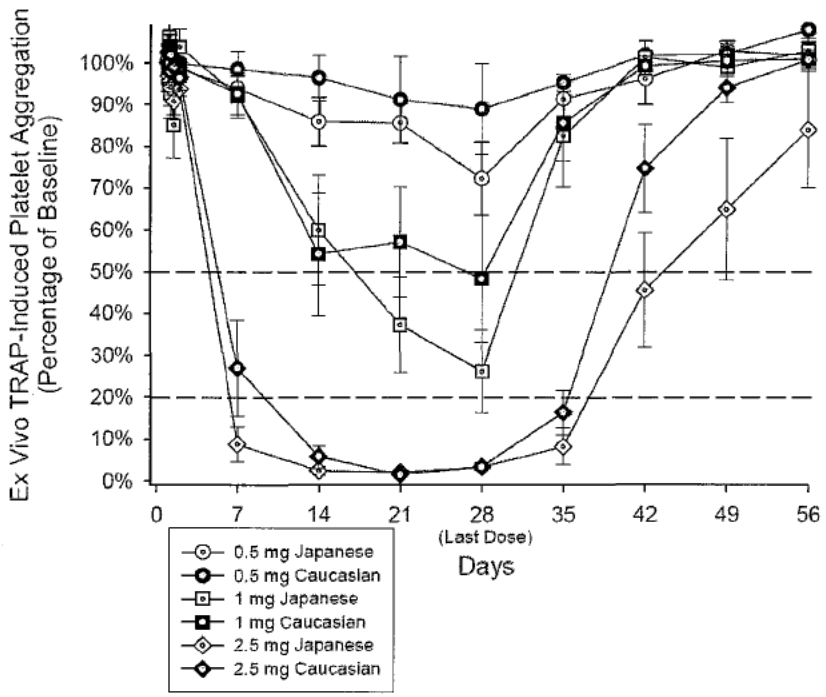


Figure 2: Time course of mean (±SE) % platelet aggregation following once daily 0.5, 1, 2.5 mg vorapaxar sulfate for 28 days in Japanese and Caucasians [CSR P03448, Figure 9, Page 102]

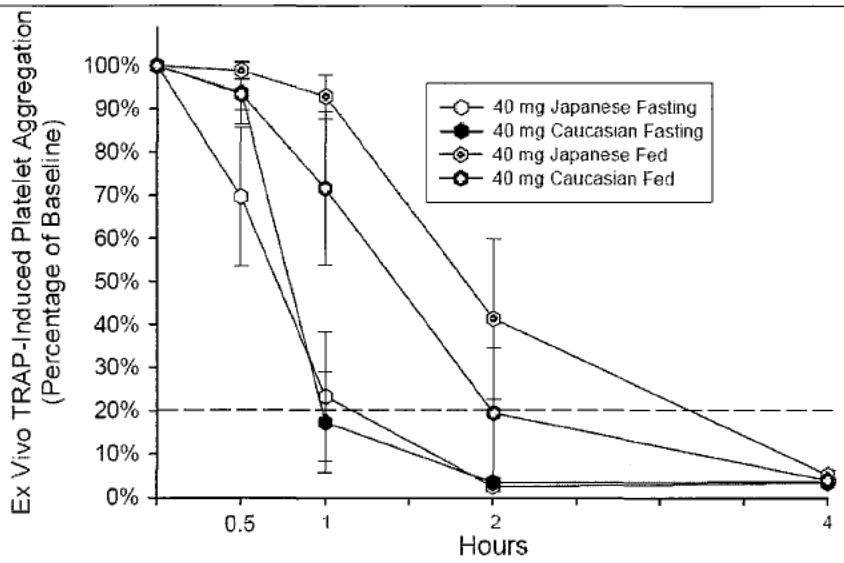


Figure 3: Time course of mean (±SE) % platelet aggregation following a single dose of 40 mg vorapaxar sulfate in Japanese and Caucasians between fed and fasted state [Source: CSR P03448, Figure 10, Page 103]

- The onset of platelet inhibition is not significantly different between Japanese and Caucasians in the current study (Fig. 1). However, a cross-study comparison with multiple ascending dose study (P03450) shows that the rate and extent of platelet inhibition achieved in the current study is significantly lower when compared to study P03450. For e.g., following a single dose of 5 mg, near maximal platelet inhibition is achieved by 6 h post-dose in study P03450 whereas to only about 10% in the current study. This difference in platelet inhibition between studies is not due to the pharmacokinetics of vorapaxar, as exposures are 1.5-fold higher in the current study when compared to study P03450.
- Similarly, with 2.5 mg once daily dosing regimen, the mean % platelet aggregation relative to baseline is 25% by day 7 (Fig. 2). However, in study P03450, following 3 mg once daily dosing regimen, <20% of % platelet aggregation relative to baseline is achieved by day 2 with maximal inhibition by day 7. As mentioned earlier pharmacokinetic differences do not explain the inconsistencies in platelet inhibition between the studies.
- A standardized high-fat meal decreased peak concentration by 30% and delayed T_{max} by 2-3 h. This is translated to a relatively faster time of onset i.e., time to reach <20% platelet aggregation relative to baseline, in the fasted state (Fig. 3).

Safety

There were no deaths or serious adverse event experienced in this study. Of the six subjects reported to have treatment emergent adverse events, five were considered mild and 1 subject experienced a generalized rash which appeared on the day of dosing and resolved two days later.

SUMMARY

Pharmacokinetics and pharmacodynamics of vorapaxar are similar between Japanese and Caucasians. However, a cross-study comparison with multiple ascending dose study (P03450) shows that the rate and extent of platelet inhibition achieved in this study is lower for the same doses. Differences in pharmacokinetics between the two studies do not account for the inconsistency in platelet inhibition results.

PK in Chinese Subjects

Study report: P06453	**Study period:** 07/23/2010 - 10/20/2010	**EDR Link**[12]

OBJECTIVE

To evaluate the safety, tolerability and pharmacokinetics of vorapaxar and metabolite M20 following a single dose of 40 mg and daily doses of 2.5 mg vorapaxar sulfate for 42 days in healthy Chinese subjects.

STUDY DESIGN

Single center, open label, two treatment, parallel group study in healthy Chinese adult volunteers

Treatment A: 40 mg (1 x 40 mg) vorapaxar sulfate administered as a single dose
Treatment B: 2.5 mg (1 x 2.5 mg) vorapaxar sulfate administered once daily for 42 days

All subjects were confined to the study center on day -1 and discharged the morning of day 2. Subjects in treatment B continued with dose administration in the morning on days 3 through 41 as outpatients and returned for confinement in the evening of day 41 and discharged the morning of day 43. At the study center, on days 1 and 42, vorapaxar sulfate was administered following an overnight fast.

Population

Enrolled: N = 28 (treatment A=14 subjects, treatment B=14 subjects)
Completed: N = 28 (treatment A=14 subjects, treatment B=14 subjects; 54% men)
Healthy adult volunteers (age: 18-45 y; BMI: 19-24 kg/m^2; body weight NLT 50 kg)
Sample size was calculated based on a prior estimate of the inter-subject variability on C_{max} and AUC of vorapaxar such that the 90% CIs around the geometric mean is NLT 17% and NMT 20%.

PK Sampling

Blood samples were collected pre-dose, 0.5, 1, 1.5, 2, 4, 6, 12 and 24 h post-dose on day 1 and day 42 (treatment B only), and on days 7, 14, 21, 28, 35, and 42.

Statistical method

PK: (i) Descriptive statistics, (ii) GMR and 90% CIs for accumulation ratio and metabolite/parent ratio, and (iii) In addition, log transformed C_{min} was analyzed using an ANOVA model extracting the effects due to day as a fixed effect and subject as a random effect. GMR and 90% CIs were calculated for each day *vs* the average of subsequent days. Steady state was claimed to be achieved on day X if the 90% confidence interval for day X *vs* the average of subsequent days fell within the 80-125% range.

RESULTS

Bioanalysis assay method

	Vorapaxar	**M20**
Method	**UPLC-MS/MS**	**UPLC-MS/MS**
LLOQ (ng/mL)	1	0.5
Range (ng/mL)	1 to 1000	0.5 to 500
QCs (ng/mL)	3, 80, 800	1.5, 40, 400

Comment: The analytical assay method is acceptable since the accuracy and precision of 2/3^{rds} of the QC and LLOQ samples are within ±15% and ±20%, respectively, as specified in the 'Guidance for Industry: Bioanalytical Method Validation'.

[12] \\Cdsesub1\evsprod\NDA204886\0000\m5\53-clin-stud-rep\533-rep-human-pk-stud\5333-intrin-factor-pk-stud-rep\p06453\p06453.pdf

Pharmacokinetics

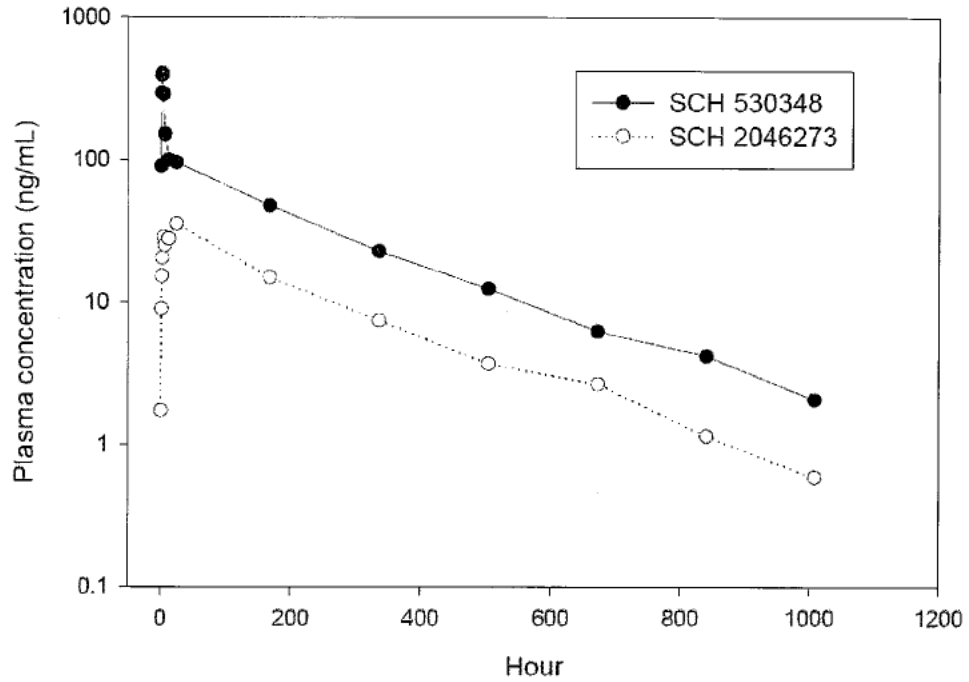


Figure 1: Mean plasma concentration of vorapaxar and metabolite M20 following a single oral dose of 40 mg vorapaxar sulfate in healthy Chinese adult volunteers [Source: CSR P06453, Figure 2, Page 54]

Table 1: Statistical analysis of C_{min} values for vorapaxar and metabolite M20 following daily doses of 2.5 mg vorapaxar sulfate for 42 days [Source: CSR P06453, Table 17, Page 57]

Analyte	Day	n	LS Mean (ng/mL) [a]	Comparison	Ratio (%)	90% CI	Intra CV (%) [b]
SCH 2046273	7	14	9.02	Day 7 vs. rest c	61	50, 75	0.42
	14	14	10.7	Day 14 vs. rest c	68	56, 83	
	21	14	13.9	Day 21 vs. rest c	86	70, 105	
	28	14	15.5	Day 28 vs. rest c	94	76, 117	
	35	14	18.3	Day 35 vs. rest c	118	94, 148	
	42	14	13.1	Day 42 vs. rest c	71	55, 92	
	43	14	18.4				
SCH 530348	7	14	27.9	Day 7 vs. rest c	54	49, 59	0.20
	14	14	43.1	Day 14 vs. rest c	80	73, 88	
	21	14	48.7	Day 21 vs. rest c	89	80, 98	
	28	14	52.6	Day 28 vs. rest c	94	85, 104	
	35	14	56.2	Day 35 vs. rest c	101	91, 113	
	42	14	50.8	Day 42 vs. rest c	84	74, 95	
	43	14	60.6				

a: Model-based (least squares) geometric mean: based on mixed effect model extracting the effect due to day as fixed effect and subject as random effect

b: Intra subject standard deviation on log scale

c: "rest"= the average of remaining days

Table 2: Mean PK parameters/measures following multiple oral dose of 2.5 mg vorapaxar sulfate for 42 days in healthy Chinese adult volunteers [Source: CSR P06453, Table 14, Page 56]

	SCH 530348				SCH 2046273			
	Day 1 (n=14)		Day 42 (n=14)		Day 1 (n=14)		Day 42 (n=14)	
PK Parameter	Mean	CV%	Mean	CV%	Mean	CV%	Mean	CV%
Cmax (ng/mL)	32.5	19	96.9	29	3.66	41	23.9	60
Tmax (hr)[a]	1.5	1-4	1.75	1-4	4	4.0-23.9	24	1.0-24
Cmin (ng/mL)	-	-	55.6	33	-	-	16.4	68
AUC24 (ng*hr/mL)	244	14	1470	31	68.6	42	444	60
M/P Ratio (%)[b]	-	-	-	-	28.2	41	31.7	53
t1/2eff (hr)	-	-	91.3	34	-	-	140	86
R_A[c]	-	-	6.00	31	-	-	8.50	85

a: Median (range)

b: M/P Ratio = $AUC24_{SCH\ 2046273}/AUC24_{SCH\ 530348}$ x100%

c: RA = $AUC24_{Day\ 42}/AUC24_{Day\ 1}$

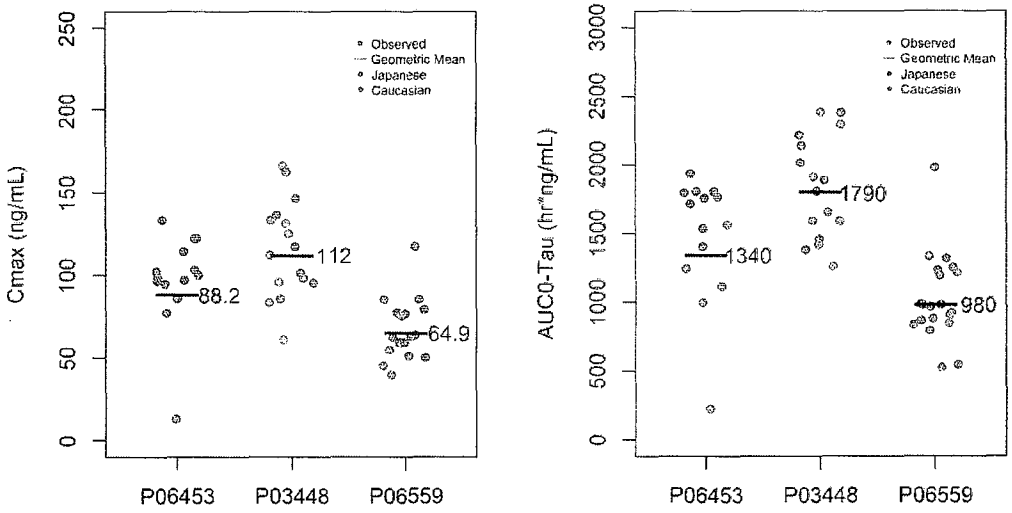
Table 3: GMR and 90% CIs for metabolite to parent ratio following multiple oral dose of 2.5 mg vorapaxar sulfate for 42 days in healthy Chinese adult volunteers [Source: CSR P06453, Table 15, Page 56]

Day	Analyte	n	AUC_{24} LS Mean (ng*hr/mL)[a]	90% CI (ng*hr/mL)	M/P Ratio	
					Ratio (%)	Ratio (%)
1	2046273	14	61.7[b]	51.4- 74.1	25.5	19.8-32.8
	530348	14	242[b]	202- 291		
42	2046273	14	360[b]	265- 490	26.9	19.7-36.8
	530348	14	1339[b]	984- 1822		

a: Model-based (least squares) geometric mean: based on mixed effect model extracting the effect due to Analyte as fixed effect and subject as random effect

b: Based on AUC24

Table 4: Cross-study comparison of the steady state PK measures of vorapaxar following daily doses of 2.5 mg vorapaxar sulfate



P06453=current study (Chinese); P03448=PK study (Japanese/Caucasians); P06559=PK study (Caucasians)

- Results of the cross study comparisons of pharmacokinetic measures in Chinese subjects *vs* Caucasians are inconsistent. When compared to study P06559, the exposures are 35% higher, but, 25% lower with respect to study P03448. This might be due to the inherent problems of comparing cross studies.

- M20 is a formation rate limiting metabolite as observed by similar terminal elimination half-life to that of vorapaxar, ~180 h (data not shown), and parallel slopes of elimination. This observation is consistent with study P06559 performed in Caucasian subjects.

- Metabolite-to-parent exposure ratio following single and multiple doses of 2.5 mg vorapaxar sulfate ranges from 25% to 27% (Table 3).

- Steady state exposures of vorapaxar are achieved by day 21. Statistical analysis for the comparison of day 21 C_{min} *vs* the average of remaining days show that the 90% CIs are contained within 80% to 125%, suggesting that steady state is achieved by day 21 (Table 1).

- Intra-subject CV% in C_{min} of vorapaxar is 20% (Table 1). Qualitatively, the variability in PK measures of metabolite M20 is higher when compared to vorapaxar.

Safety

There were no deaths or serious adverse events. The most frequent adverse event in treatment A was epistaxis (14%) and in treatment B was headache (49%).

SUMMARY

Results of the cross study comparisons of pharmacokinetic measures in Chinese subjects *vs* Caucasians are inconsistent. However, other pharmacokinetic aspects such as metabolite kinetics, accumulation ratio, metabolite-to-parent ratio, time to attain steady state are similar when compared to Caucasians.

Relative BA: Effect of Food, Age, Dosage Form and Antacid		
Study report: P03447	**Study period:** 10/14/2006 - 03/15/2007	**EDR Link**[13]
OBJECTIVE		
This study had multiple objectives to evaluate i.e., effect of meal, timing of the meal, age, antacid, and dosage form on the pharmacokinetics of vorapaxar following a single dose of vorapaxar sulfate 40 mg.		
STUDY DESIGN		
Randomized, open label, single center, two part, seven treatment, parallel arm, relative bioavailability study in healthy young adults and elderly subjects. *Treatment arms – Part 1*: A: vorapaxar sulfate (1 x 40 mg), fasted B: vorapaxar sulfate (2 x 20 mg), fasted* C: vorapaxar sulfate (4 x 10 mg), fasted * *Treatment arms – Part 2*: D: vorapaxar sulfate (1 x 40 mg), fasted, but, immediately after administration of 20 mL Gaviscon® E: vorapaxar sulfate (1 x 40 mg) within 5 min of completing a standardized high-fat breakfast F: vorapaxar sulfate (1 x 40 mg) within 1 h of completing a standardized high-fat breakfast G: vorapaxar sulfate (1 x 40 mg) within 2 h of completing a standardized high-fat breakfast In part 1 and 2, young adults were randomized to any one of the treatment arms. However, elderly subjects were assigned to receive treatment A only under part 1. * Results of the dosage strength proportionality are not discussed in this review as the strength studied is not relevant to the strength that is proposed to-be-marketed by the applicant.		
Population/Sample size		
Planned: N = 120 (young adults=100; elderly=20) Sample size by treatment: A (40 stratified by age), B (10), C (10), D (20), E (20), F (10), G (10) Enrolled: N = 123 (young adults=105; elderly=18) Young adults (age: 18-45 y, BMI: 19-32 kg/m^2); Elderly (age: > 65 y, BMI: 19-32 kg/m^2). *Power*: Assuming an inter-subject variability of 25% on C_{max} and AUC of vorapaxar, a sample size of 20 subjects per treatment group in a parallel design study will have 80% power to detect a 20% difference in exposure between two groups.		
PK Sampling		
Blood samples for pharmacokinetic evaluation of vorapaxar were collected pre-dose, and at 0.5, 1, 1.5, 2, 3, 4, 6, 12, 24, 48, and 72 h post-dose. Additional blood samples were collected on an outpatient basis on days 7, 14, 21, 28, 35 and 42 (± 1 day).		
Statistical method		
Effect of antacid, food and timing relative to food intake: Log-transformed C_{max} and AUC_{0-t} of vorapaxar was analyzed using ANOVA model extracting the effect due to treatment. The resulting geometric mean ratio and 90% CI were used to compare relative bioavailability of vorapaxar in the presence of food and timing relative to food intake i.e., treatments D, E, F, G *vs* A. *Effect of age*: Log-transformed C_{max} and AUC_{0-t} of vorapaxar was analyzed using ANOVA model extracting the effect due to age group. The resulting geometric mean ratio and 90% CI were used to compare relative bioavailability between young adults and elderly i.e., treatment A: young *vs* elderly.		

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RESULTS

Bioanalysis assay method

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

	Vorapaxar
Method	**UPLC-MS/MS**
LLOQ (ng/mL)	1
Range (ng/mL)	1 to 1000
QCs (ng/mL)	3, 80, 800

Reviewer's comment: The analytical assay method is acceptable since the accuracy and precision of 2/3[rds] of the QC and LLOQ samples are within ±15% and ±20%, respectively, as specified in 'Guidance for Industry: Bioanalytical Method Validation'.

PK summary statistics

Table 1: Statistical analysis – Effect of food and timing relative to food intake [Source: CSR P03447, Table 14, Page 71]

Parameter	Treatment Group	n	Least-Square Mean[a]	Ratio Estimate Fed vs Fasting	90% Confidence Interval
AUC(I)[b]	Fasting	19	18000	-	-
	Fed	18	25800	143	123-166
	1 hr after food	9	25800	143	119-172
	2 hr after food	9	22900	127	106-153
AUC(tf)	Fasting	21	16300	-	-
	Fed	20	21900	135	116-156
	1 hr after food	11	22400	137	115-164
	2 hr after food	10	21700	133	111-160
Cmax	Fasting	21	248	-	-
	Fed	20	325	131	108-159
	1 hr after food	11	290	117	93-147
	2 hr after food	10	339	137	107-174

a: Model-based (least squares) mean: ANOVA extracting the effects due to treatment.

b: AUC(I) cannot be determined for some subjects.

Table 2: Statistical analysis – Effect of age [Source: CSR P03447, Table 16, Page 73]

Parameter	Treatment Group[a]	n	Least-Square Mean[b]	Ratio Estimate: Elderly vs Young	90% Confidence Interval
AUC(I)[c]	Elderly	16	25400	141	124-161
	Young	19	18000		
AUC(tf)	Elderly	18	20100	123	105-144
	Young	21	16300		
Cmax	Elderly	18	320	129	102-162
	Young	21	248		

a: Both elderly and young subjects received Treatment A (SCH 530348 1 x 40 mg, fasting).

b: Model-based (least squares) mean: ANOVA extracting the effects due to age group (old or young).

c: AUC(I) cannot be determined for some subjects.

Table 3: Statistical analysis – Effect of antacid [Source: CSR 03447, Table 18, Page 75]

Parameter	Treatment Group	n	Least-Square Mean[a]	Ratio Estimate: SCH 530348 + Antacid vs SCH 530348	90% Confidence Interval
AUC(I)[b]	SCH 530348 Alone	19	18000	85	73- 99
	With Antacid	18	15300		
AUC(tf)	SCH 530348 Alone	21	16300	89	76-103
	With Antacid	20	14400		
Cmax	SCH 530348 Alone	21	248	62	51- 75
	With Antacid	20	154		

a: Model-based (least squares) mean: ANOVA extracting the effects due to treatment.

b: AUC(I) cannot be determined for some subjects.

Concentration-time profile

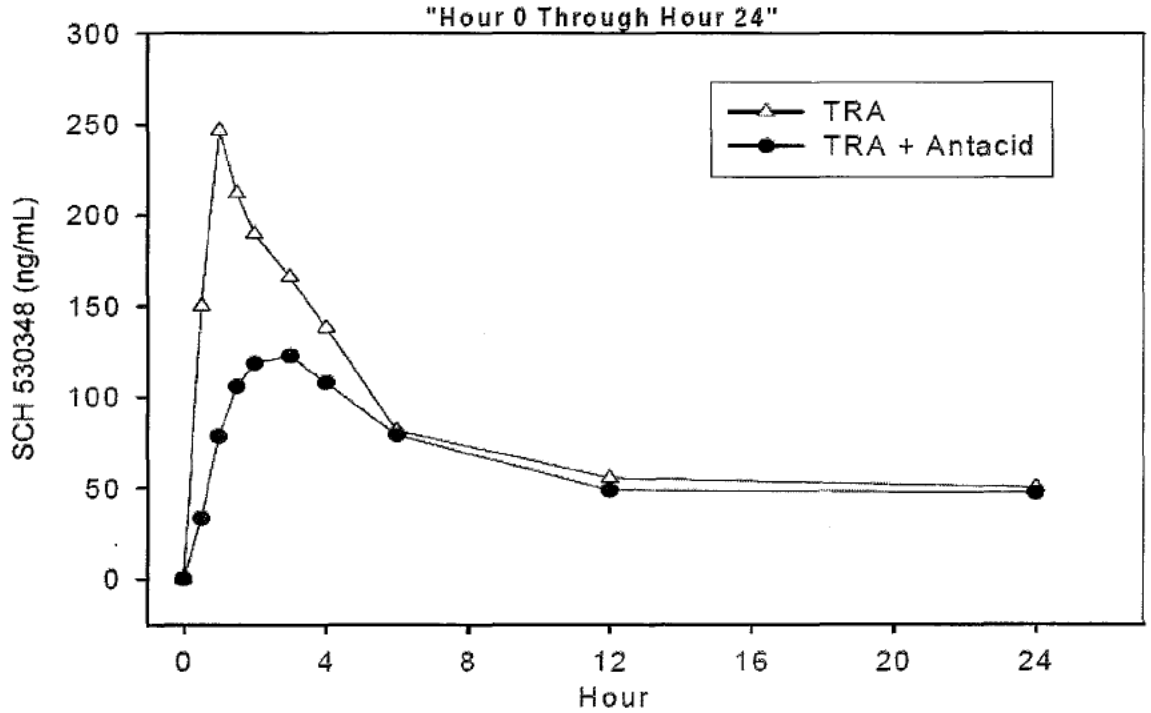

Figure 1: Mean vorapaxar plasma concentration-time profile following administration of single oral dose of vorapaxar sulfate 40 mg in the presence and absence of Gaviscon® 20 mL [Source: CSR 03447, Figure 5, Page 76]

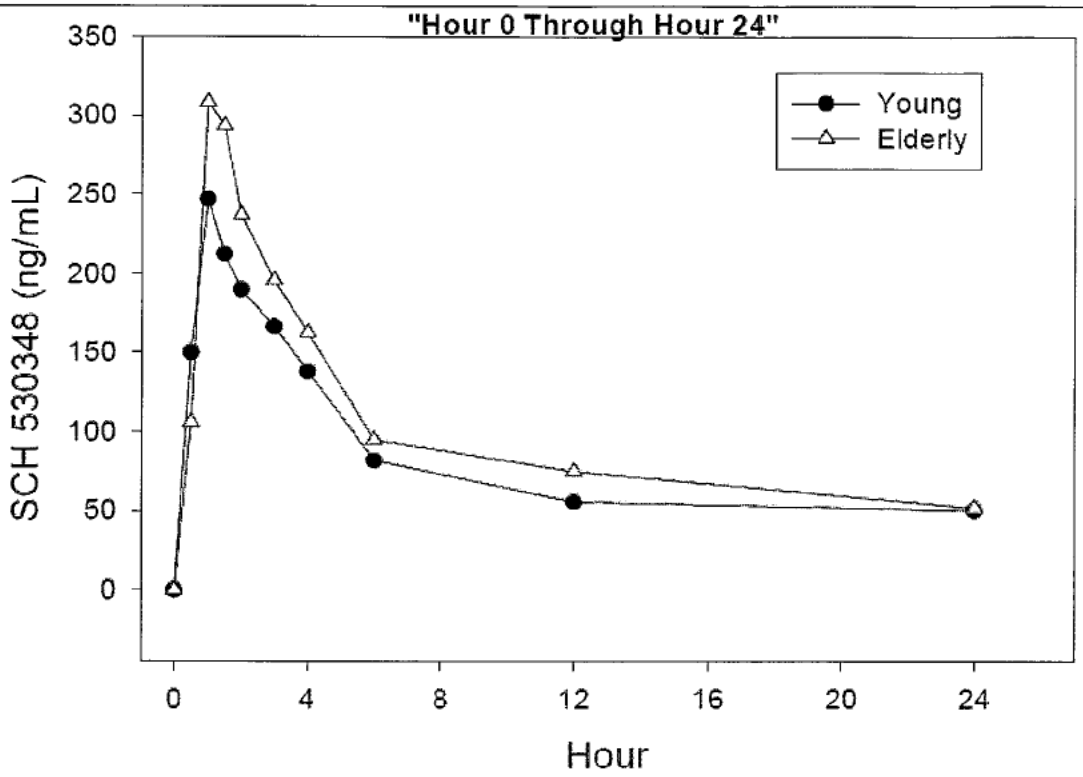

Figure 2: Mean vorapaxar plasma concentration-time profile following administration of single oral dose of vorapaxar sulfate 40 mg in healthy young adults and elderly subjects [Source: CSR P03447, Fugure 4, Page 74]

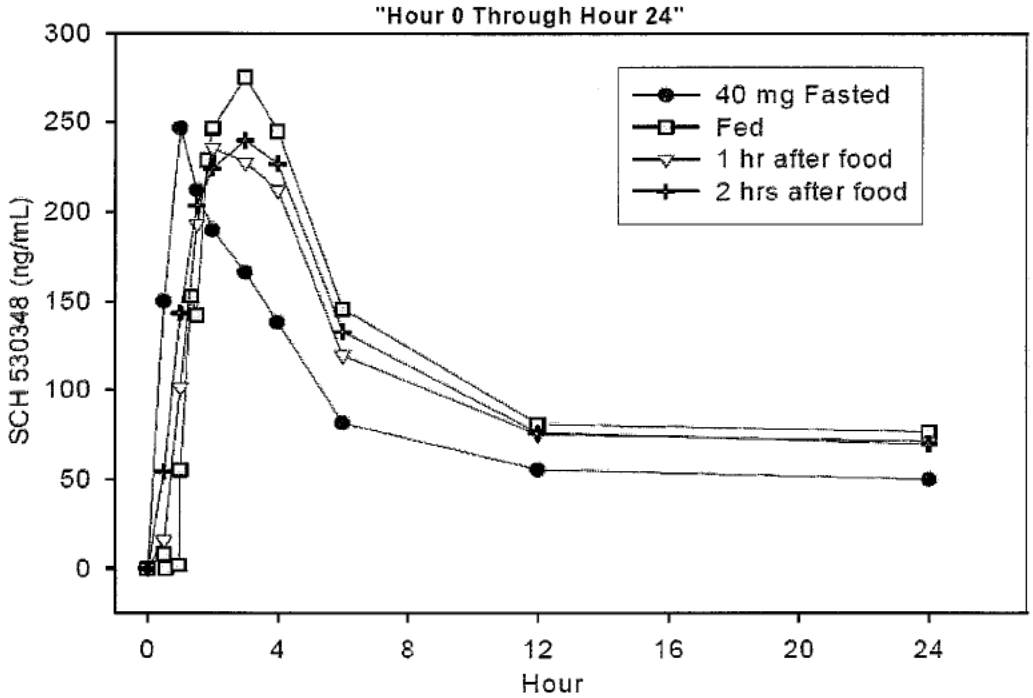

Figure 3: Mean vorapaxar plasma concentration-time profile following administration of single oral dose of vorapaxar sulfate 40 mg with and without co-administration of a high-fat breakfast [Source: CSR P03447, Figure 3, Page 72]

SUMMARY

- Food delayed T_{max} on an average by 2-3 h and increased exposure to vorapaxar by 30% (both C_{max} and AUC_{0-t}) irrespective of the time of food intake.

- Co-administration with an antacid delayed T_{max} of vorapaxar by 1 h and decreased C_{max} by 38% and AUC_{0-t} by 11%. This decrease in exposure is not clinically significant as vorapaxar is dosed for chronic use.

- There is a 20-30% increase in the exposure to vorapaxar in healthy elderly subjects compared to young adults.

- It should be noted that all inferences are made based on a parallel arm study and not a crossover design.

Relative BA: Effect of Free Base and PPI		
Study report: P06452	**Study period:** 11/03/2009 - 12/16/2009	**EDR Link**[14]
OBJECTIVE		
Part 1: To evaluate the relative bioavailability of vorapaxar sulfate 2.5 mg containing a range of free base – 27% (standard), 61% (low), 80% (intermediate) and 92% (high). *Part 2*: To evaluate the impact of a proton pump inhibitor on the relative bioavailability of vorapaxar sulfate 2.5 mg containing 27% and 80% free base.		
STUDY DESIGN		
Randomized, open label, single center, two part, parallel design, relative bioavailability study in healthy volunteers. *Treatment arms – Part 1*: A: vorapaxar sulfate 2.5 mg, standard free base content (27%) B: vorapaxar sulfate 2.5 mg, low free base content (61%) C: vorapaxar sulfate 2.5 mg, intermediate free base content (80%) D: vorapaxar sulfate 2.5 mg, high free base content (92%) *Treatment arms – Part 2*: E: pantoprazole 40 mg QD days 1-7, vorapaxar sulfate 2.5 mg standard free base (27%) on day 4 F: pantoprazole 40 mg QD days 1-7, vorapaxar sulfate 2.5 mg intermediate free base (80%) on day 4 G: placebo days 1-7, vorapaxar sulfate 2.5 mg standard free base (27%) on day 4		
Population/Sample size		
N = 126 (part 1=72 subjects, part 2=54 subjects, 18 subjects per treatment arm) Healthy adult volunteers (age: 18-65 y, BMI: 18-32 kg/m^2). *Power*: Assuming an inter-subject variability of 40% on C_{max} and 30% on AUC of vorapaxar, a sample size of 18 subjects per arm in a parallel design will have 80% power to detect the difference in bioavailability between 2 treatment arms if the mean AUC for one treatment arm is 22% lower or 29% higher compared to the other treatment arm.		
PK Sampling		
Blood samples for pharmacokinetic evaluation of vorapaxar were collected pre-dose, and at 0.5, 1, 1.5, 2, 3, 4, 6, 12, 24, 48, and 72 h post-dose. Pharmacokinetic evaluation of the active metabolite of vorapaxar (M20) was not performed. *Comment*: Considering the long terminal elimination half-life of vorapaxar (approx. 7-8 days), a truncated PK sampling scheme until 72 h is acceptable based on 'Guidance for Industry: Bioavailability and Bioequivalence Studies for Orally Administered Drug Products Submitted in New Drug Applications – General Considerations and Food Effect Assessment'.		
Statistical method		
Log-transformed C_{max} and $AUC_{0\text{-}72\ h}$ of vorapaxar was analyzed using ANOVA model extracting the effect due to treatment. The resulting geometric mean ratio and 90% CI were used to compare: *Part 1*: Relative bioavailability of low, intermediate and high free base products compared to standard free base product i.e., treatments B, C, D *vs* treatment A. *Part 2*: Relative bioavailability of vorapaxar (i) in the presence of pantoprazole i.e., treatment E *vs* treatment G and (ii) between 27% and 80% free base product in the presence of pantoprazole i.e., treatment F *vs* treatment E.		

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RESULTS

Bioanalysis assay method

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

	Vorapaxar
Method	**UPLC-MS/MS**
LLOQ (ng/mL)	0.835
Range (ng/mL)	0.835 to 835
QCs (ng/mL)	2.51, 66.8, 668

Reviewer's comment: The analytical assay method is acceptable since the accuracy and precision of 2/3^{rds} of the QC and LLOQ samples are within ±15% and ±20%, respectively, as specified in 'Guidance for Industry: Bioanalytical Method Validation'.

PK summary statistics

Table 1: Summary of pharmacokinetic measures for vorapaxar with varying free base content [Source: CSR P06452, Table 14, Page 71]

Treatment (Free Base Content)	Cmax (ng/mL)	Tmax (hr)[a]	AUC(0-72hr) (ng.hr/mL)
A (Standard)	28.2 (19)	1.50 (1.00 – 2.07)	417 (22)
B (Low)	26.9 (32)	1.50 (1.00 – 3.00)	379 (30)
C (Intermediate)	24.5 (27)	1.79 (1.00 – 3.00)	385 (35)
D (High[b])	24.3 (28)	1.50 (1.00 – 4.00)	375 (24)[c]

Note: For each treatment group, n = 18, except where noted.

Abbrevations: AUC (0-72hr) = area under the concentration-time curve from 0 to 72 hours; Cmax = maximum observed plasma concentration; CV = coefficient of variation, expressed as a percentage; hr = hours; Tmax = time of observed maximum plasma concentration

[a] Median (Range)

[b] Subject 1002 from high free base group had a pre-dose concentration of ~2 ng/mL (2 x LLOQ of 1 ng/mL); concentration was assumed to be zero for the analysis.

[c] n = 17. Subject 1019 had an AUC(0-24hr). Subject did not return for the 48- and 72-hour sample.

Table 2: Statistical analysis – Effect of varying free base content on the pharmacokinetics of vorapaxar [Source: CSR P06452, Table 15, Page 72]

PK Parameter	Treatment[a] (Free Base Content)	LS Mean[b]	90% CI	Treatment Comparison	GMR[c]	90% CI	Inter-CV (%)
AUC (0-72hr)	A (Standard; 27%)	408	366-454	-	-	-	27.5
	B (Low; 61%)	364	327- 405	B vs A	89.3	76.6- 104	
	C (Intermediate; 80%)	365	327- 406	C vs A	89.5	76.8- 104	
	D (High, 92%)[d,e]	365	326- 408	D vs A	89.5	76.7- 105	
Cmax	A (Standard; 27%)	27.8	24.5-31.5	-	-	-	31.8
	B (Low; 61%)	24.8	21.9-28.1	B vs A	89.3	74.8- 107	
	C (Intermediate; 80%)	23.6	20.8-26.7	C vs A	84.8	71.1- 101	
	D (High, 92%)	23.5	20.8-26.7	D vs A	84.6	70.9- 101	

Note: For each treatment group, n = 18, except where noted.

Abbreviations: ANOVA = analysis of variance; AUC(0-72hr) = area under the concentration-time curve from 0 to 72 hours; CI = confidence interval; Cmax = maximum observed plasma concentration; CV = coefficient of variation, expressed as a percentage; GMR = geometric mean ratio; hr = hour; LS = least squares; PK = pharmacokinetic.

[a] Treatment Description: A: SCH 530348 2.5-mg of standard free-base (27%); B: SCH 530348 of low free base (61%); C: SCH 530348 of 2.5-mg of intermediate free base (80%); D: SCH 530348 2.5-mg of high free-base (92%)

[b] Model – based (least squares mean): ANOVA extracting the effects due to the treatment

[c] Geometric mean ratios

[d] Subject 1019 from Treatment D only had AUC(0-24hr). This subject did not return for 48- and 72-hr samples.

[e] n=17

Table 3: Summary of pharmacokinetic measures for vorapaxar with in the presence of proton pump inhibitor [Source: CSR P06452, Table 16, Page 75]

Treatment (Free Base Content)	Cmax (ng/mL)	Tmax (hr)[a]	AUC(0-72hr) (ng.hr/mL)
E (Standard + PPI)[b]	22.9 (22)	1.50 (1.00 – 4.00)	363 (29)
F (Intermediate + PPI)	21.6 (38)	2.00 (1.00 – 4.00)	335 (22)
G (Standard + Placebo)	26.8 (21)	1.49 (1.00 – 2.00)	406 (29)

Note: For each treatment group, n = 18, except where noted.

Abbreviations: AUC(0-72hr) = area under the concentration-time curve from 0 to 72 hours; Cmax = maximum observed plasma concentration; CV = coefficient of variation, expressed as a percentage; Tmax = time of observed maximum plasma concentration

[a] Median (Range)

[b] n = 17. Subject 2011 did not have quantifiable PK samples.

Table 4: Statistical analysis – Effect of varying free base content on the pharmacokinetics of vorapaxar [Source: CSR P06452, Table 17, Page 75]

PK Parameter	Treatment[a] (Free Base Content)	LS Mean[b]	90 % CI	Treatment Comparison	GMR[c]	90% CI	Inter-CV (%)
AUC (0-72hr)	E[d,e] (Standard; 27%)+PPI	351	317-388	-	-	-	25
	F (Intermediate; 80%)+PPI	327	297-361	F Vs E	93.0	81-107	
	G (Standard; 27%)+placebo	391	355-432	E Vs G	90.0	78-103	
Cmax	E[d,e] (Standard; 27%)+PPI	22.4	20.0-25.1	-	-	-	28
	F (Intermediate; 80%)+PPI	20.2	18.1-22.5	F Vs E	90.0	77-105	
	G (Standard; 27%)+placebo	26.2	23.5-29.3	E Vs G	85.0	73-100	

Note: For each treatment group, n = 18, except where noted.

Abbreviations: ANOVA = analysis of variance; AUC(0-72hr) = area under the concentration-time curve from 0 to 72 hours; CI = confidence interval; Cmax = maximum observed plasma concentration; CV = coefficient of variation, expressed as a percentage; GMR = geometric mean ratio; hr = hour; LS = least squares; PK = pharmacokinetic

[a] Treatment Description: E: SCH 530348 2.5-mg tablet of standard free base (27%) + PPI; F: SCH 530348 2.5-mg tablet of intermediate free base (80%)+ PPI; G: SCH 530348 2.5-mg tablet of standard free base (27%)+ placebo

[b] Model – based (least squares mean): ANOVA extracting the effects due to the treatment

[c] Geometric mean ratios

[d] Subject 2011 did not have quantifiable PK samples

[e] n = 17

SUMMARY

- On an average, there is a 10% decrease in $AUC_{0\text{-}72\ h}$ and 10-15% decrease in C_{max} of vorapaxar with low (61%), intermediate (80%) and high (92%) free base products when compared to standard free base product (27%). The decrease in exposure was constant and not proportional to the increase in free base content. However, the results may not be of relevance as the to-be-marketed product of vorapaxar sulfate may only have free base content between 20% and 46%.
- A similar reduction in exposure i.e., 10% on $AUC_{0\text{-}72\ h}$ and 15% on C_{max} of vorapaxar is observed when vorapaxar sulfate 2.5 mg with 27% free base is co-administered with pantoprazole. This reduction in exposure with pantoprazole is not considered clinically significant as vorapaxar is dosed for chronic use.
- The decrease in exposure to vorapaxar in the presence of pantoprazole for a product with 80% free base when compared to standard free base product in the absence of pantoprazole was also 10%. This suggests that a higher free base product when co-administered with pantoprazole does not further reduce the exposure to vorapaxar when compared to either one change alone (higher free base or co-administration of pantoprazole.

INTRINSIC FACTOR STUDIES

Renal Impairment		
Study report: P03465	**Study period:** 12/18/2007 - 12/01/2008	**EDR Link**[15]
OBJECTIVE		
To evaluate the safety, tolerability, pharmacokinetics and pharmacodynamics following a single dose of 10 mg vorapaxar sulfate in subjects with chronic renal disease compared to matched subjects with normal renal function.		
STUDY DESIGN		
Single center, single dose, open label, parallel group study in subjects with end stage renal disease requiring hemodialysis *vs* matched healthy subjects. This was a reduced design renal impairment study because the results of mass balance studies showed that renal clearance of vorapaxar if anything at all is a very minor component. Other degrees of renal impaired subjects were planned to be enrolled only if the pharmacokinetic measures of vorapaxar i.e., either C_{max} or AUC in subjects with chronic renal disease was greater than 2-fold when compared to normal healthy controls. Healthy subjects matched with hepatic impairment subjects by gender, age (±5 years), height (±8 cm), and weight (±10 kg). *Group 1*: Matched subjects with normal renal function *Group 2*: End stage renal disease subjects requiring dialysis All subjects were confined to the study center on day -1 and received a single dose of 10 mg vorapaxar sulfate following an overnight fast on the morning of day 1. Hemodialysis was performed on day 2 for ESRD subjects with samples of dialysate collected every hour for vorapaxar pharmacokinetic evaluation. On day 3, last inpatient blood sample was obtained and then at weekly intervals relative to day 1 as outpatient visits.		
Population		
Planned: N = 16 (ESRD=8; normal healthy control=8) *Enrolled*: N = 15 (ESRD=8; normal healthy control=7) *Completed*: N = 15 (ESRD=8; normal healthy control=7) No formal statistical analysis for the calculation of sample size		
PK Sampling		
Blood samples for vorapaxar pharmacokinetic evaluation were collected pre-dose and at 0.5, 1, 2, 4, 6, 12 and 24 h post-dose on day 1. An additional blood sample was collected 2 h post-dose on day 1 for protein binding measurements. In ESRD subjects, additional blood samples were collected at the start, during, and at the end of dialysis, as well as 2, 6, and 16 into dialysis on day 2. Corresponding samples were also collected from matched normal controls. Samples were collected on an outpatient basis on days 7, 14, 21, 28, 35, and 42.		
PD Sampling		
Blood samples for platelet aggregometry assay were collected pre-dose and at 1, 2 and 24 h post-dose on day 1. In addition, samples were collected on days 7, 14, 21, 28, 35, and 42. Samples were also obtained on days 49 and 56 for subjects with significant (i.e., ≥50%) inhibition of TRAP-induced platelet aggregation at week 6.		
Statistical method		
PK: (i) Descriptive statistics, (ii) Log transformed C_{max} and AUC was analyzed using an ANOVA model extracting the effects due to renal function. GMR and 90% CIs were calculated for subjects with chronic renal disease *vs* subjects with normal renal function.		

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PD: Descriptive statistics. 95% CIs for the difference between renal impaired group vs normal healthy controls.

RESULTS

Bioanalysis assay method

	Vorapaxar
Method	**UPLC-MS/MS**
LLOQ (ng/mL)	0.1
Range (ng/mL)	0.1 to 50
QCs (ng/mL)	0.3, 7.5, 37.5

Comment: The analytical assay method is acceptable since the accuracy and precision for at least 2/3^{rds} of the QC and LLOQ samples are within the acceptable limits of ±15% and ± 20%, respectively, as specified in 'Guidance for Industry: Bioanalytical Method Validation'.

Pharmacokinetics

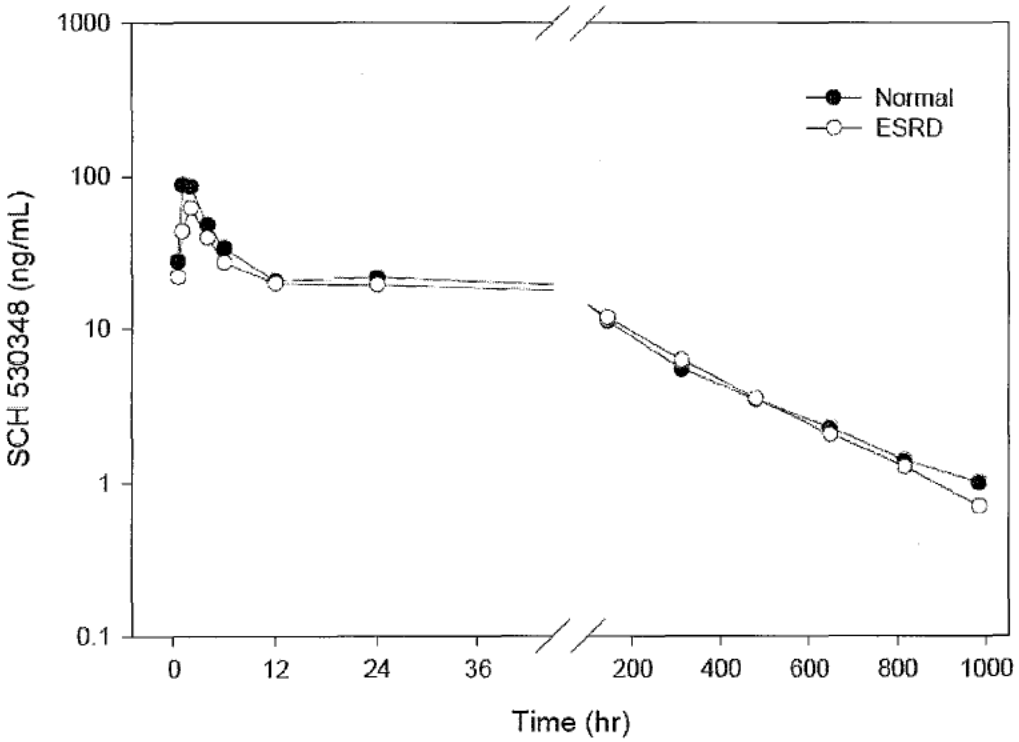

Figure 1: Mean plasma concentration of vorapaxar following a single oral dose of 10 mg vorapaxar sulfate in subjects with ESRD and matched normal renal function [Source: CSR P03464, Figure 2, Page 65]. *Note*: The drop is plasma concentrations between day 2 and 7 is an artifact of the break in x-axis and not an impact of hemodialysis.

Table 1: Statistical analysis of the PK measures of vorapaxar between subjects with ESRD and matched normal renal function [Source: CSR P03464, Table 14, Page 67]

	Mean[b]					
PK Parameter	ESRD[a]	Normal	Comparison	Sample Size	Ratio Estimate	90% Confidence Interval
AUC(tf)	5659	5767	ESRD/Normal	7/7	98	80 to 121
AUC(I)	5809	6189	ESRD/Normal	7/7	94	74 to 119
Cmax	72	95	ESRD/Normal	7/7	76	48 to 118

Abbreviations: AUC(tf) = area under the concentration vs. time curve to the final time point; AUC(I) = area under the plasma concentration vs. time curve from Time 0 to infinity; Cmax = maximum observed plasma concentration; ESRD = end stage renal disease; PK = pharmacokinetic.

a: As matched-pairs analysis was conducted, Subject 503 was excluded from statistical analysis due to no matching healthy volunteer.

b: Model-based (least square) means.

- The pharmacokinetics of vorapaxar is similar between ESRD subjects and matched normal renal function group (Table 2). Moreover, the pharmacokinetics is similar following a single dose of 10 mg vorapaxar sulfate between the current study and the single ascending dose study (P03449).
- The plasma concentration time course of vorapaxar during dialysis followed a decline which is consistent with the terminal elimination half-life of vorapaxar, suggesting that dialysis does not affect the pharmacokinetics of vorapaxar in ESRD subjects (Fig. 1).
- Protein binding was not estimated in this study.

Pharmacodynamics

Table 3: Mean platelet aggregation (relative to % baseline) following single oral dose of 10 mg vorapaxar sulfate in subjects with ESRD and normal renal function [Source: CSR P03464, Table 16, Page 72]

	Normal Renal Function Subjects (n=7)	ESRD Subjects (n=7)[b]	Difference (Normal – ESRD)	
Time Point	Mean	Mean	Point Estimate	95% CI
Day 1				
1 Hour	92.2	99.7	-7.5	-21.7 to 6.7
2 Hour[c]	64.7	88.3	-23.6	-64.9 to 17.8
24 Hour	38.9	69.2	-30.3	-81.4 to 20.7
Day 7	88.0	101.4	-13.4	-31.5 to 4.7
Day 14	94.7	94.2	0.5	-33.5 to 34.6
Day 21	95.8	91.9	3.8	-13.6 to 21.3
Day 28	99.7	99.7	-0.1	-21.9 to 21.8
Day 35	98.6	93.2	5.4	-14.2 to 24.9
Day 42[d]	98.7	101.9	-3.1	-14.5 to 8.2

Abbreviations: CI = confidence interval; ESRD = end stage renal disease; n = number of subjects; TRAP = thrombin-receptor agonist peptide.

a: Platelet aggregation based on sodium citrate anticoagulant and TRAP agonist (%).

b: Subject 503 was excluded from statistical analysis due to no matching healthy volunteer.

c: ESRD Subjects 505 and 506 and their respective matching, healthy subjects were excluded from the 2-hour time point statistical analysis because the ESRD subjects' 2-hour samples were collected outside of the acceptable sample-collection window.

d: ESRD Subject 501 and matching healthy subject, Subject 101, were excluded from the Day 42 time point statistical analysis because Subject 501's Day 42 measurement was not interpretable.

- A single dose of 10 mg vorapaxar sulfate did not produce % platelet aggregation <20% by 24 h post-dose in the matched normal renal function group. This is in contrast with the single ascending dose study (P03449) where near maximal platelet inhibition was observed at 2 h post-dose following a single dose of 10 mg vorapaxar sulfate.
- At 2 and 24 h post-dose, subjects with normal renal function had a lower % platelet aggregation relative to baseline when compared to ESRD subjects (baseline values were comparable between the two groups). As platelet function recovered near to baseline by day 7, there were no significant differences in platelet aggregation between the two groups.
- Due to the above inconsistencies, the PK/PD relationship of vorapaxar from this study cannot be characterized.

Safety

There were no deaths or serious adverse events reported in the study. Dizziness, reported by two ESRD subjects, was the most frequently reported adverse event.

SUMMARY

- The pharmacokinetics of vorapaxar is similar between ESRD and matched normal renal function groups. Hemodialysis does not affect the pharmacokinetics of vorapaxar in ESRD subjects.
- PK/PD relationship in ESRD subjects relative to matched normal renal function group cannot be characterized due to limited informative data from the current study.

Hepatic Impairment		
Study report: P03465	**Study period:** 12/18/2007 - 12/01/2008	**EDR Link**[16]
OBJECTIVE		
To evaluate the safety, tolerability and pharmacokinetics of vorapaxar in subjects with different degrees of hepatic impairment compared to matched-healthy subjects.		
STUDY DESIGN		
Single center, open label, parallel group study in subjects with varying degrees of hepatic impairment *vs* matched healthy subjects. Healthy subjects were matched with hepatic impairment subjects by gender, age (±5 years), height (±8 cm), and weight (±10 kg). Degrees of hepatic impairment were determined during screening by Child-Pugh class score. *Group 1*: Matched healthy subjects *Group 2*: Mild hepatic impairment subjects (C-P score: 5-6) *Group 3*: Moderate hepatic impairment subjects (C-P score: 7-9) *Group 4*: Severe hepatic impairment subjects (C-P score: 10-15) For safety purposes, 3 or more subjects in both the mild and moderate hepatic impairment groups and their matched healthy controls were to have completed the study and their safety and pharmacokinetic results have been evaluated, before patients with severe hepatic impairment were enrolled. All subjects were confined to the study center on day -1 and received a single dose of 40 mg vorapaxar sulfate following an overnight fast on the morning of day 1. Subjects were discharged on day 2, however, returned to the study center on days 7, 14, 21, 28, 35, 42, 49 and 56 as outpatients for blood sample withdrawals.		
Population		
Planned: N = 36 (6 each in groups 2, 3 and 4; 18 in group 1) *Enrolled*: N = 32 (6 each in groups 2 and 3; 4 in group 4; 16 in group 1) *Completed*: N = 32 (6 each in groups 2 and 3; 4 in group 4; 16 in group 1; 88% Hispanic or Latino) Sample size was calculated based on a prior estimate of the intra-subject variability on C_{max} and AUC of vorapaxar. A sample size of 6 subjects per group will detect about 42% and 92% mean difference in C_{max} and AUC between hepatic impaired group and normal hepatic function group with 80% power.		
PK Sampling		
Blood samples were collected pre-dose, 0.5, 1, 1.5, 2, 4, 6, 12 and 24 h post-dose on day 1. Additional samples will be drawn on an outpatient basis on days 7, 14, 21, 28, 35, 42, 49 and 56.		
Statistical method		
PK: (i) Descriptive statistics, (ii) Log transformed C_{max} and AUC was analyzed using an ANOVA model extracting the effects due to hepatic function. GMR and 90% CIs were calculated for hepatic impairment groups *vs* matched healthy subjects.		

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RESULTS

Bioanalysis assay method

	Vorapaxar	M20
Method	**UPLC-MS/MS**	**UPLC-MS/MS**
LLOQ (ng/mL)	1	0.5
Range (ng/mL)	1 to 1000	0.5 to 500
QCs (ng/mL)	3, 80, 800	1.5, 40, 400

Comment: The analytical assay method is acceptable since the accuracy and precision for at least $2/3^{rds}$ of the QC and LLOQ samples are within the acceptable limits of ±15% and ± 20%, respectively, as specified in 'Guidance for Industry: Bioanalytical Method Validation'.

Pharmacokinetics

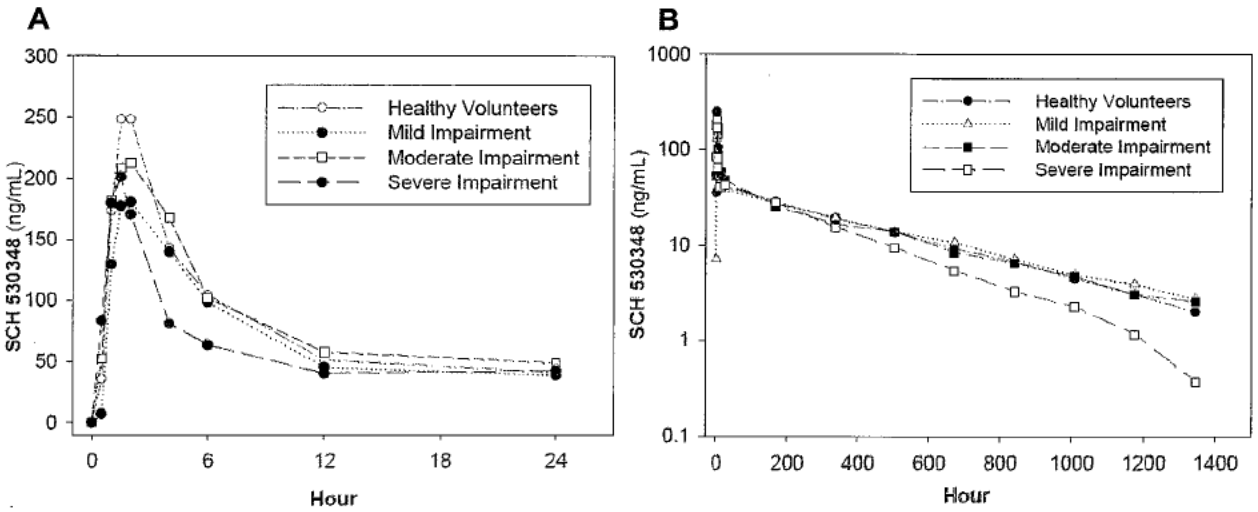

Figure 1: Mean plasma concentration of vorapaxar (A) through 24 h post-dose and (B) through day 59 post-dose following a single oral dose of 40 mg vorapaxar sulfate in subjects with varying degrees of hepatic impairment and matched healthy subjects [Source: CSR P03465, Figure 2, Page 70]

Table 1: Mean plasma PK measures of vorapaxar dose following a single oral dose of 40 mg vorapaxar sulfate in subjects with varying degrees of hepatic impairment and matched healthy subjects [Source: CSR P03465, Table 14, Page 70]

Hepatic Function Group	Cmax (ng/mL)	Tmax[a] (hr)	AUC(tf) (ng.hr/mL)	AUC(I) (ng.hr/mL)	t½ (hr)
Healthy Subjects (n=16)	279 (34)	1.50 (1-6)	18000 (38)	19100 (37)	298 (30)
Mild Impairment (n=6)	232 (35)	1.75 (1.5-6)	18200 (22)	19600 (27)[b]	366 (33)[b]
Moderate Impairment (n=6)	244 (53)	1.50 (1-4)	17900 (60)	19700 (61)	342 (37)
Severe Impairment (n=4)	206 (77)	1.00 (1-1.5)	14200 (40)	14800 (38)	298 (23)

Abbreviations: AUC(I) = area under the concentration-time curve from time 0 to infinity; AUC(tf) = area under the concentration-time curve from time 0 to the time of the final quantifiable sample; Cmax = maximum observed plasma concentration; CV =coefficient of variation; hr = hour; n = number; Tmax = time to maximum observed plasma concentration: t½ = terminal phase half-life.

a: Median (range)

b: n=5 (Subject 202 was excluded because the terminal phase could not be adequately characterized.)

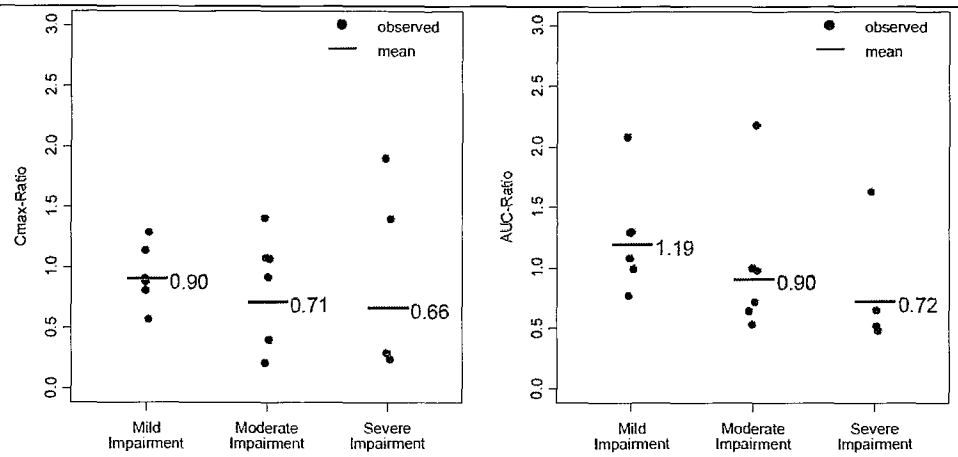

Figure 2: Statistical analysis of the PK measures of vorapaxar between varying degrees of hepatic impairment and matched healthy subjects [Source: CSR P03465, Figure 5, Page 74]

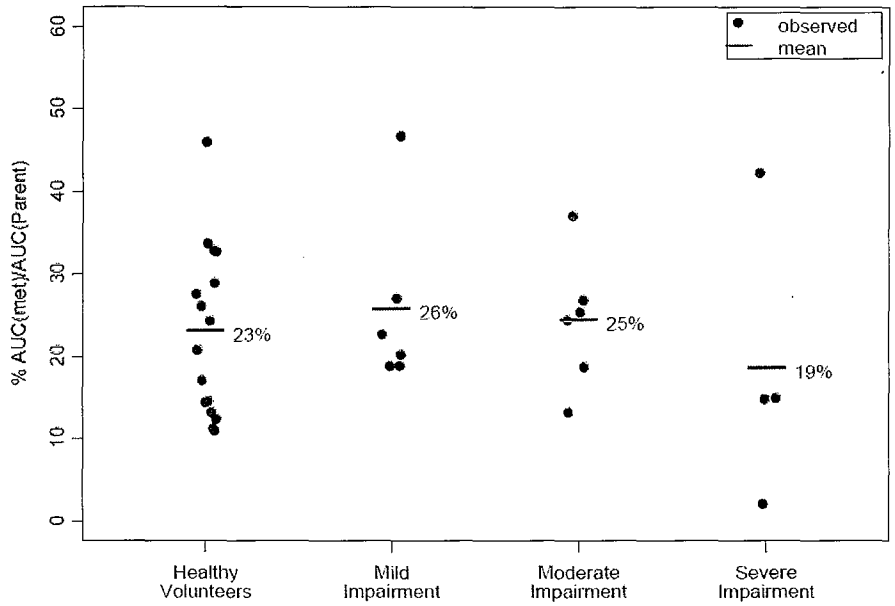

Figure 3: Metabolite-to-parent ratio in varying degrees of hepatic impairment and matched healthy subjects [Source: CSR P03465, Figure 12, Page 82]

- Enrollment in the severe hepatic impairment was stopped (at N=4) as one subject experienced severe gastrointestinal bleeding when administered with vorapaxar.
- Although there appears to be a trend towards lower exposures with increasing severity of hepatic impairment, the pharmacokinetics of vorapaxar is not significantly different between the hepatic impaired groups and matched healthy subjects. The slopes of the elimination phase in the completed groups i.e., mild and moderate hepatic impairment, are no different when compared to matched healthy control.
- The pharmacokinetics of the major metabolite M20 is no different between the hepatic impaired groups and matched healthy subjects as shown by the metabolite-to-parent ratio. The ratios observed

are in line with the range of values observed in other healthy volunteer studies. • Plasma protein binding across various degrees of hepatic function was not measured in this study.
Safety
Adverse events were reported in 3 subjects (9%) – 2 from group 1 and 1 from group 4. Two subjects in group 1 reported mild nasopharyngitis and both were considered unrelated to study drug. The group 4 subject (with severe hepatic impairment) experienced two treatment emergent adverse events: mild myalgia began on day 3, lasted for 1 day, and was considered unlikely related to study drug; while severe gastrointestinal hemorrhage began on day 4 and was considered a serious adverse event, with a possible relationship to study drug. It should be noted that the subject had hepatic cirrhosis complicated by portal hypertension as evidenced by the presence of esophageal varices, thereby at a pre-disposed higher risk of bleeding. Follow up fecal occult blood tests were performed on day 13 and 20 and both tested negative. The subject remained in the study, returning for scheduled weekly visits for PK sampling, and completed the final follow-up visit (day 56) without any further bleeding episode.
SUMMARY
Vorapaxar is a drug with low hepatic extraction ratio and high plasma protein binding. Intrinsic capacity of hepatic elimination and unbound fraction of the drug are primary determinants of plasma clearance. Though total vorapaxar plasma concentrations did not change significantly between hepatic impaired groups and matched healthy control, it is not known if the free fractions could have been significantly different as plasma protein binding was not measured in this study. Nevertheless, as subjects with severe hepatic impairment are predisposed at a higher risk of bleeding (evidenced by the serious adverse event in group 4), use of vorapaxar in this subgroup is not recommended.

EXTRINSIC FACTOR STUDIES

DDI with Ketoconazole and Rifampin		
Study report: P03629	**Study period:** 08/16/2010 - 11/02/2010	**EDR Link**[17]

OBJECTIVES

Mass balance and metabolism studies showed that vorapaxar is extensively metabolized by CYP3A4. As a result, this study was design with the following objectives:

- To determine whether the potent CYP3A4 enzyme inhibitor ketoconazole or inducer rifampin affect the pharmacokinetics and systemic exposure of vorapaxar in healthy volunteers.
- To assess the multiple-dose safety and tolerability of vorapaxar when Co-administered with ketoconazole or rifampin relative to monotherapy.

STUDY DESIGN

A randomized, open-label, parallel-groups, multiple-dose single-center study of the potential effect of ketoconazole (400 mg/day) or rifampin (600 mg/day) on the pharmacokinetics of vorapaxar (20 mg loading dose, 2.5-mg maintenance dose) in healthy volunteers. The study was planned to be conducted in 36 volunteers who upon meeting entry criteria were to receive randomized assignment to one of the following three treatment groups:

Treatment A:
Ketoconazole 400 mg (2 x 200 mg tablets) once-daily in the AM x 28 days (Study Days 1 to 28) and vorapaxar 20 mg (2 x10-mg tablets) as a single dose in the AM of Study Day 7 followed by Vorapaxar 2.5 mg (1 x 2.5-mg tablet) once-daily in the AM x 21 days (Study Days 8 to 28) (n=12).

Treatment B:
Placebo (2 tablets) once-daily in the AM x 28 days (Study Days 1 to 28) and vorapaxar 20 mg (2 x 10-mg tablets) as a single dose in the AM of Study Day 7 followed by vorapaxar 2.5 mg (1 x 2.5-mg tablet) once-daily in the AM x 21 days (Study Days 8 to 28) (n=12).

Treatment C:
Rifampin 600 mg (2 x 300 mg capsules) once-daily in the AM x 28 days (Study Days 1 to 28) and vorapaxar 20 mg (2 x 10-mg tablets) as a single dose in the AM of Study Day 7 followed by vorapaxar 2.5 mg (1 x 2.5-mg tablet) once-daily in the AM x 21 days (Study Days 8 to 28) (n=12).

Reviewer's comment:

- All subjects were pretreated with ketoconazole or rifampin (or placebo) for 6 days prior to the administration of vorapaxar to ensure adequate CYP3A enzyme inhibition or induction. Co-administration of ketoconazole or rifampin with vorapaxar for 3 weeks assured evaluating the effects of inhibition or induction, respectively, at steady-state. Subjects were administered a 20 mg loading dose of vorapaxar on Study Day 7 (vorapaxar Dosing Day 1) and then daily maintenance dosing of 2.5 mg from Study Days 8 to 28 (vorapaxar Dosing Days 2 to 22) to reach quickly, and maintain, steady-state plasma exposures of vorapaxar.

- It should be noted that ketoconazole will not be used as a strong inhibitor of CYP3A for such experiments anymore due to hepatotoxicity issues. Sponsors are recommended to use either clarithromycin (pre-treatment for at least 4 days at 500 mg twice daily) or itraconazole (pre-treatment for at least 4 days at 200 mg once daily) for CYP3A inhibition DDI study.

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PK Sampling
Blood sampling for vorapaxar PK will be collected pre-dose (0-hour), 0.5, 1, 1.5, 2, 4, 6, 12, and 24 hours post dose on Study Days 7 and 28 (vorapaxar Dosing Days 1 and 22). Additional blood samples for Vorapaxar PK will be taken on Study Days 14, 21, 26, and 27 (vorapaxar Dosing Days 8, 15, 20, and 21) corresponding to the pre-dose sampling time.
Statistical Method
The primary pharmacokinetic parameters for vorapaxar were the AUC and C_{max}. The log-transformed data were statistically analyzed using a one-way analysis of variance model extracting the effect of treatment. The primary comparisons of interest were the contrasts between vorapaxar Cmax and AUC in Treatment A (ketoconazole + vorapaxar) versus B (placebo + vorapaxar) and Treatment C (rifampin + vorapaxar) versus Treatment B (placebo + vorapaxar) for Study Day 28 (vorapaxar Dosing Day 22) data. The relative bioavailability for Treatment A versus B and Treatment C versus B on Study Day 7 and Study Day 28 (vorapaxar Dosing Days 1 and 22) was provided for AUC and Cmax along with associated 90% confidence intervals.
Population
38 healthy subjects, 24 men and 14 women aged 19 to 65 years of age, having a BMI between 19-29 (BMI = weight (kg)/height (m^2). Thirty five subjects completed the study. Two subjects discontinued due to reasons unrelated to the study and work conflict. The other subject was withdrawn due to protocol violation (was lost to follow-up).

RESULTS

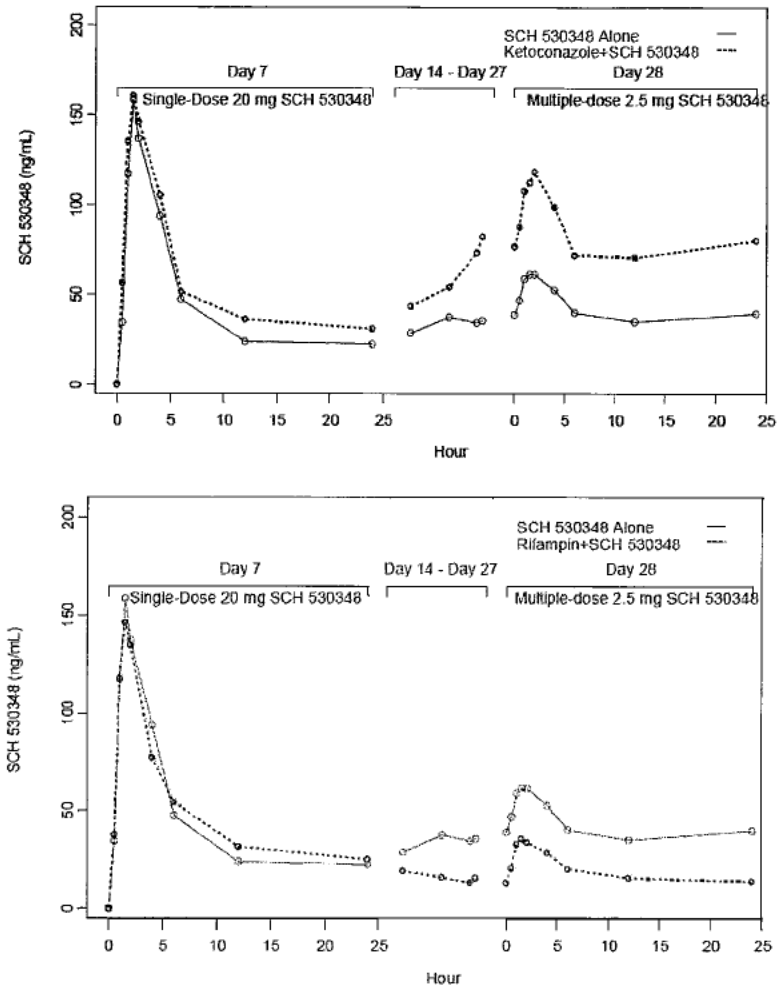

Figure 1. Mean Vorapaxar Plasma Concentrations Following Oral Administration of a Loading Dose of 20 mg Vorapaxar on Study Day 7, Followed by a Daily Maintenance Dose of 2.5 mg Vorapaxar for 21 Days With and Without 400 mg Ketoconazole or 600 mg Rifampin to Healthy Volunteers [Source: CSR P03629, Figure 3, Page 66]

Table 1: Relative Bioavailability of Vorapaxar Following Single and Multiple Dose Oral Administration of Vorapaxar With and Without 400 mg Ketoconazole to Healthy Volunteers

Parameter	**Units**	**Study Day (Vorapaxar Dosing Day)**	**Ketoconazole + Vorapaxar TMT A (n=13) (CV%)**	**Placebo + Vorapaxar TMT B (n=12) (CV%)**	**Ratio A/B**	**90% CI**
C_{max}	ng/ml	7 (1)	166 (31)	161 (21)	103	87-121
$AUC_{0\text{-}24\ h}$	ng·hr/mL	7 (1)	1260 (19)	1020 (23)	123	105-146

C_{max}	ng/ml	28 (22)	124 (18)	64.2 (30)	193	166-223
$AUC_{0-24\,h}$	ng·hr/mL	28 (22)	1900 (15)	969 (18)	196	173-222

Table 2. Relative Bioavailability of vorapaxar Following Single and Multiple Dose Oral Administration of vorapaxar With and Without 600 mg Rifampin to Healthy Volunteers

Parameter	**Units**	**Study Day (Day Vorapaxar dosing)**	**Rifampin +Vorapaxar TMT A (n=13)**	**Placebo+ Vorapaxar TMT B (n=12)**	**Ratio A/B**	**90% CI**
C_{max}	ng/ml	7 (1)	152 (23)	161 (21)	94.4	80-112
$AUC_{0-24\,h}$	ng·hr/mL	7 (1)	1110 (28)	1020 (23)	108	91-129
C_{max}	ng/ml	28 (22)	39.4 (16)	64.2 (30)	61.4	52-72
$AUC_{0-24\,h}$	ng·hr/mL	28 (22)	441 (21)	969 (18)	45.5	40-52

- Coadministration of ketoconazole had no effect on single-dose vorapaxar C_{max}, but increased single-dose vorapaxar $AUC_{0-24\,h}$ by 23%, compared with vorapaxar administered alone. The drug interaction is not that apparent following first dose (24 h) due to the long half-life of vorapaxar.

- Coadministration of rifampin had no effect on single-dose vorapaxar C_{max} and $AUC_{0-24\,h}$, compared with vorapaxar administered alone.

- Mean C_{min} in the ketoconazole coadministration group increased over time when compared to plateauing values with control. This showcases the fact that ketoconazole decreased vorapaxar's elimination, thereby delaying the attainment of steady state.

- Following repeated dosing of vorapaxar, coadministration of ketoconazole increased mean C_{max} and $AUC_{0-24\,h}$ of vorapaxar by ~2 fold on Study Day 28 (vorapaxar Dosing Day 22), compared with vorapaxar administered alone.

- Following repeated dosing of vorapaxar, coadministration of rifampin decreased mean C_{max} and $AUC_{0-24\,h}$ of vorapaxar by ~55% on Study Day 28 (vorapaxar Dosing Day 22), compared with vorapaxar administered alone.

Bioanalytical Assay Method

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

	Vorapaxar
Method	**LC-MS/MS**
LLOQ (ng/mL)	0.1
Range (ng/mL)	1 to 1000
QCs (ng/mL)	1,3, 80, 800

Comment: The analytical assay method is acceptable since the accuracy and precision for at least $2/3^{rds}$ of the QC and LLOQ samples are within the acceptable limits of ±15% and ± 20%, respectively, as specified in 'Guidance for Industry: Bioanalytical Method Validation'.

Safety

- Fifteen subjects (15/38 [39%]) reported AEs: 5/13 (38%) were in the placebo treatment group; 6/13 (46%) in the ketoconazole treatment group; and 4/12 (33%) in the rifampin treatment group (Page 71). Overall, headache was reported by more subjects than any other AE (8 of 38 subjects [21%]).

- The single AE that was reported as severe in intensity was recorded for Subject 25 on Study Day 27 (vorapaxar Dosing Day 21). These subjects reported a more severe myalgia than experienced 2 days prior. The subject took acetaminophen for severe aching, which resolved after approximately 5 hours and did not return despite dosing again on Study Day 28 (vorapaxar Dosing Day 22). The investigator considered the myalgia as unlikely to be related to investigational treatment.

SUMMARY

Upon repeat co-administration, ketoconazole, a strong CYP3A inhibitor, increases the systemic exposures to vorapaxar by 2-fold, while rifampin, a strong CYP3A inducer, decreases the systemic exposure to vorapaxar by 55%. The efficacy or bleeding risk for a change in exposure of this magnitude is not known due to the absence of concentration-outcome relationship. Further, concomitant administration of these drugs with vorapaxar was excluded in the phase 3 studies. Therefore, avoid use of vorapaxar with strong inhibitors or inducers of CYP3A.

DDI with Digoxin		
Study report: P03458	**Study period:** 05/30/2006 - 09/21/2006	**EDR Link**[18]
RATIONALE AND OBJECTIVES		
Rationale: Vorapaxar is not a substrate of P-glycoprotein (P-gp), but inhibited the transport of digoxin with an IC_{50} of 1.2 μM. The steady-state peak plasma concentration following a one daily administration of 2.5 mg vorapaxar sulfate is 0.11 μM. This suggests that vorapaxar can possibly act as a P-gp inhibitor at the intestinal level, but not systemically. Nevertheless, an *in vivo* drug interaction study with digoxin was conducted to validate the *in vitro* findings. *Objectives*: The objective of the study is to evaluate (1) the potential effects of vorapaxar on the pharmacokinetics and pharmacodynamics of digoxin in healthy adult volunteers, and (2) the safety and tolerability of the co-administration of vorapaxar and digoxin.		
STUDY DESIGN		
This is an open-label, fixed-sequence, two-period, two-treatment study in healthy adult volunteers. Subjects were to be screened within 3 weeks prior to initial dosing, and those who met the study entry criteria were to receive the following two treatments: *Treatment A*: Single 0.5 mg dose of digoxin on Day 1 of Period 1. *Treatment B*: Once daily 2.5 mg vorapaxar on Days 1 to 6 followed by a single 0.5 mg dose of digoxin and a single 40-mg dose of vorapaxar taken concurrently on Day 7 of Period 2. During Period 1, subjects were to be confined on Day -2, at least 12 h prior to the Day -1 Baseline electrocardiogram (ECG) recording. After an overnight fast, in the morning of Day 1, subjects were to receive digoxin 0.5 mg (Treatment A) as a single oral dose. In the afternoon of Day 2, subjects were to be discharged from the study center with instructions to return to the site daily in the morning from Days 3 to 5 for pharmacokinetic sampling. An outpatient washout period of 8 to 11 days followed. During Period 2, subjects were to return to the site on Day -1 for safety evaluations and drug screen. Subjects who continued to meet entry criteria were to return to the site on Days 1 to 6 for once-daily (morning) dosing of 2.5 mg vorapaxar. Subjects were to be confined again in the evening of Day 6, at least 12 h prior to Day 7 dosing. In the morning of Day 7, after an overnight fast, subjects were to receive digoxin 0.5 mg as a single dose concurrently with vorapaxar 40 mg. In the afternoon of Day 8, subjects were to be discharged from the study center with instructions to return to the site daily in the morning from Days 9 to 11 for pharmacokinetic sampling. End-of-study safety evaluation was to be performed on Day 11.		
PK Sampling		
During treatment and evaluation in Period 1 and Period 2, starting on Day 1 and Day 7 respectively, blood samples were collected for PK evaluation of digoxin at pre dose (0 h), and at 0.5, 1, 1.5, 2, 6, 8, 24, 36, 48, 72, and 96 h post dose.		
Statistical Method		
PK: Plasma digoxin concentrations and derived pharmacokinetic parameters were listed and summarized by treatment using mean, standard deviation (SD), and coefficient of variation (CV). The log transformed		

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pharmacokinetic parameters were statistically analyzed using an analysis of variance (ANOVA) model extracting the effects due to treatment and subject. The relative bioavailability of digoxin administered with vorapaxar versus administered alone was calculated along with the corresponding 90% confidence interval (CI). The observed and derived vorapaxar pharmacokinetic parameters were listed and summarized using mean, SD, and CV for Day 7 of Period 2 to confirm that subjects had adequate exposure to vorapaxar.

PD:
The primary comparison was between digoxin-alone treatment (Treatment A) on Day 1 of Period 1, and treatment with digoxin and vorapaxar (Treatment B) on Day 7 of Period 2. Summary statistics (means, standard errors, 95% CIs) were provided for the ECG parameters.

Population

- A total of 22 adult subjects (12 men and 10 women) between the ages of 19 and 54 years (mean 31.1 years) received treatment in Period 1, and 18 adult subjects (9 men and 9 women) between the ages of 19 and 54 years (mean 33.1 years) received treatment in Period 2.
- All 22 remaining subjects completed the digoxin-alone treatment (Period 1), and 18 finished the study as planned by completing the digoxin and vorapaxar treatment (Period 2). Four subjects were discontinued from Period 2 of the study; two subjects discontinued due to work related conflicts, One 20 years old white woman was discontinued after testing positive for digoxin or an excluded drug in urine, and one 27 years old native American/Caucasian man discontinued after period 1 dosing due to serious adverse event (see Safety).

Bio analysis assay method:

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

	Digoxin
Method	**LC-MS/MS**
LLOQ (ng/mL)	0.150 ng/mL
Range (ng/mL)	0.1 to 8
QCs (ng/mL)	0.45, 2, 4 ng/ml

Comment: The analytical assay method is acceptable since the accuracy and precision for at least 2/3^{rds} of the QC and LLOQ samples are within the acceptable limits of ±15% and ± 20%, respectively, as specified in 'Guidance for Industry: Bioanalytical Method Validation'.

RESULTS

Table 1: Effect of vorapaxar on digoxin pharmacokinetics [Report: P03458, Table 11, Page 63]

		Least Squares Mean[c]			
		Period 1	Period 2		
Parameter[a]	n[b]	Digoxin Alone	Digoxin With SCH 530348	Relative Bioavailability (%)[d]	90% CI[e]
Cmax	18	2.17	3.33	154	130 - 181
AUC(tf)	18	27.4	28.8	105	91.0 - 121

Note: In Period 1, 0.5 mg digoxin administered on Day 1. In Period 2, once-daily 2.5 mg SCH 530348 administered for 6 days followed by Day 7 coadministration of 0.5 mg digoxin and 40 mg SCH 530348.

Abbreviations: ANOVA = analysis of variance; AUC(tf) = area under the curve of plasma concentration versus time from time zero to final measurable sampling time; CI = confidence interval; Cmax = maximum observed plasma concentration; n = number of subjects.

a: AUC(I) was not presented because the extrapolated area under the curve was more than 25% of the defined (AUC(tf)) value.

b: Subjects 01, 06, 07, and 16 were excluded from the statistical analysis due to missing Period 2 data; these 4 subjects discontinued after Period 1.

c: Model-based (least squares) mean: ANOVA extracting the effects due to treatment and subject.

d: Percent ratio of the geometric mean value for digoxin with SCH 530348 (Period 2) to digoxin alone (Period 1).

e: Ninety percent CI based on log-transformed data, α=0.05, two-tailed.

Reviewer's comment:

- While 5 days repeat administration of vorapaxar is not enough to establish steady state plasma exposures following 2.5 mg dose, the 40 mg dose given on day seven will provide higher concentrations than the predicted steady state plasma exposures following 2.5 mg dose.

- Based on in vitro results, the DDI potential of vorapaxar (as a P-gp inhibitor) with digoxin (as a P-gp substrate), is not expected to be of clinical consequences 2.5 mg dose. The C_{max}/IC_{50} is 26/600=0.086 (less than 0.1). However C_{max}/IC_{50} at 40 mg dose is 451/600=0.75 (more than 0.1). This means that although there exists a potential for vorapaxar to affect the pharmacokinetics of digoxin at 40 mg dose (as seen clinically), it is unlikely to have an effect at the labeled 2.5 mg dose. In addition, there were no significant effects on ventricular heart rate or PR, QRS, QT, and QTc intervals following 40 mg vorapaxar sulfate.

Safety:

- The most frequently reported AE was headache. No subject died, and no serious AE was reported. No clinically significant change in physical examinations, blood chemistry and hematological parameters, or vital signs occurred. No QT or QTcF or QTcB > 500 msec was recorded.

- Two isolated instances of QTcF > 450 msec were reported for two male subjects in the digoxin plus vorapaxar treatment (Period 2); 1 observation was prior to dosing, and neither coincided with an AE.

- One SAE, non-sustained ventricular tachycardia, occurred prior to Period 1 dosing. The subject who experienced the SAE had no exposure to vorapaxar or to digoxin at the time of the event. The subject was discontinued after Period 1, upon discovery of the event by the central ECG lab, after having completed Period 1 procedures and measurements without incident or AEs.

Reviewer's comment:

There is a TQT study that has evaluated the effect of vorapaxar sulfate up to 200 mg single dose. There is no QT prolongation signal from that study (Study Report: P03462).

SUMMARY

Upon administration of 2.5 mg vorapaxar sulfate on days 1 to 6 and co-administration of digoxin 0.5 mg with vorapaxar sulfate 40 mg on day 7, showed that the C_{max} of digoxin increased by 50% with no change in AUC_{0-t}. However, the potential for vorapaxar to interact with digoxin or other P-gp substrates at the clinically labeled dose of 2.5 mg is expected to be lower.

DDI with Prasugrel		
Study report: P06560	**Study period:** 08/16/2010 - 11/02/2010	**EDR Link**[19]

RATIONALE AND OBJECTIVES

Rationale:
This drug interaction was evaluated as both vorapaxar and prasugrel share a common CYP450 (i.e., CYP3A4) metabolic pathway.

Objectives:
- To evaluate the potential for a pharmacokinetic drug-drug interaction between vorapaxar and prasugrel after multiple-dose administration.
- To evaluate the safety and tolerability of the co-administration of vorapaxar and prasugrel.

STUDY DESIGN

This is a randomized, open-label, multiple-dose study consisting of fixed arm crossover and parallel group design in healthy volunteers.

Subjects were randomized to either one of two treatment arm. Subjects in Arm 1 received Treatment A followed by Treatment B and subjects in Arm 2 received Treatment C.

Arm 1:
Treatment A: Prasugrel 60 mg orally on Day 1 followed by 10 mg orally once-daily on Days 2 to 7.
Treatment B: vorapaxar 40 mg and prasugrel 10 mg orally on Day 8, followed by vorapaxar 2.5 mg and prasugrel 10 mg orally once-daily on Days 9 to 28.

Arm 2:
Treatment C: vorapaxar 40 mg on Day 1 followed by 2.5 mg orally once-daily on Days 2 to 21.

PK Sampling

Blood samples for vorapaxar PK evaluation [PK1] were to be collected from subjects assigned to Treatment Arm1; pre-dose (0 h) on Days 1 and 28 and at 0.5, 1, 1.5, 2, 3, 4, 6, 12, and 24 h post last dose on dose Day 28.

Blood samples for vorapaxar PK evaluation [PK2] were to be collected from subjects assigned to Treatment Arm2; predose (0 h) on Days 1 and 21and at 0.5, 1, 1.5, 2, 3, 4, 6, 12, and 24 h post last dose on Day 21.

Blood samples for prasugrel active metabolite (R-138727) PK evaluation [PK3] were to be collected from subjects assigned to Treatment Arm 1; predose (0 h) on Days 1, 7 and 28 and at 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, and 24 h post last dose on Days 7 and 28.

Statistical Method

The plasma concentrations for vorapaxar and prasugrel's active metabolite R-138727 as well as the derived PK parameters were summarized by treatment. To assess the drug-drug interaction, the log transformed C_{max} and AUC for vorapaxar were analyzed using an ANOVA model extracting the effect due to treatment. The GMR along with the 90% CI was provided for B vs. C (Arm 1 Day 28/Arm 2 Day 21) for vorapaxar.

Log-transformed C_{max} and AUC for prasugrel's active metabolite R-138727 were analyzed using a

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linear mixed effects model extracting the effect due to treatment (fixed effect) and subject (random effect). The GMR as well as the 90% confidence interval for were calculated for treatment B vs. A (Arm 1 Day 28 vs. Arm 1 Day 7).

Population

A total of 54 subjects, 36 in Arm 1 and 18 in Arm 2, received randomized treatment assignment. Of the 36 subjects in Arm 1, 33 completed the study and 3 were discontinued due to non-compliance with protocol. Of the 18 subjects in Arm 2, 16 completed the study, one subject was discontinued due to noncompliance with protocol and another was discontinued for failure to meet eligibility criteria. Details of the discontinued subjects are as follows:

- Subject 001002, 001015, 001011, 001038 were discontinued due to non-compliance with protocol, the reason being a positive drug screen.
- Subject 001027 was discontinued due to non-compliance with protocol, for having missed 2 consecutive doses.

RESULTS

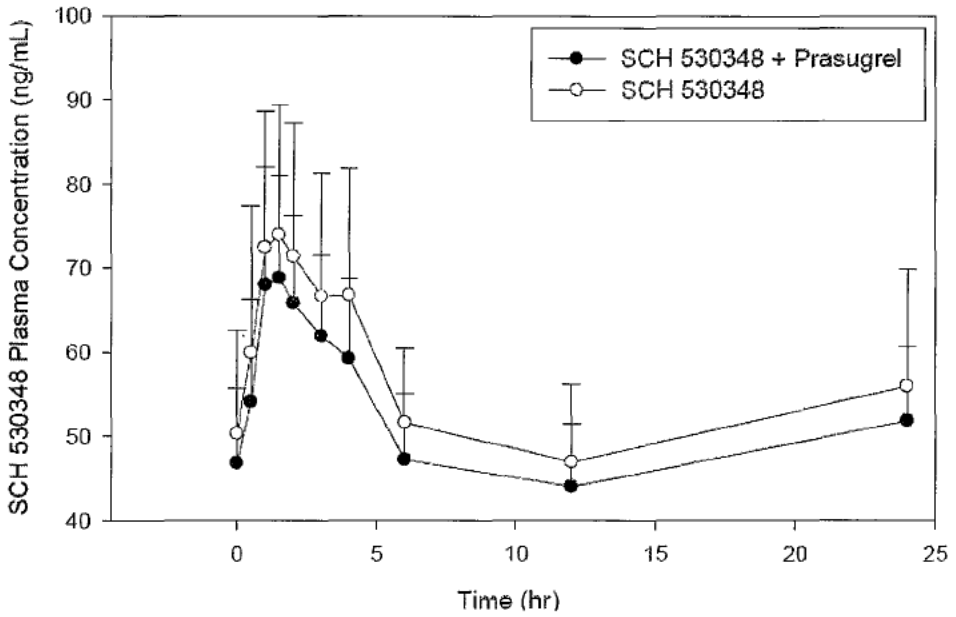

Figure 1: Mean + SD vorapaxar Plasma Concentration-Time Profiles after Administration of vorapaxar with Prasugrel and vorapaxar Alone in Healthy Adult Subjects . [Report: P06560, Figure 3, Page 60]

Table 1: Statistical Comparisons of Plasma Pharmacokinetic Parameters for Prasugrel's Active Metabolite R-138727 after Administration of Prasugrel with Vorapaxar and Prasugrel Alone in Healthy Adult Subjects. Source: [Report: P06560, Table 13, Page 62]

	SCH 530348 + Prasugrel			Prasugrel			(SCH 530348 + Prasugrel) / (Prasugrel)		
Pharmacokinetic Parameter	N	GM	(95% CI)	N	GM	(95% CI)	GMR	(90% CI)	rMSE ‡
AUC_{τ} (ng*hr/mL) †	33	45.2	(40.2, 50.8)	35	49.4	(44.0, 55.5)	0.91	(0.85, 0.99)	0.185
$AUC_{0\text{-}tf}$ (ng*hr/mL) †	33	44.0	(39.2, 49.5)	35	48.2	(42.9, 54.1)	0.91	(0.85, 0.99)	0.185
C_{max} (ng/mL) †	33	47.3	(40.4, 55.3)	35	46.2	(39.6, 53.8)	1.02	(0.89, 1.17)	0.327

† Back-transformed least squares mean and confidence interval from mixed effects model performed on natural log-transformed values.

‡ rMSE: Square root of conditional mean squared error (residual error) from the linear mixed effect model. rMSE*100% approximates the within-subject % CV on the raw scale.

GM = geometric mean; GMR = geometric mean ratio; CI = confidence interval

Table 2: Statistical Comparisons of Plasma Pharmacokinetic Parameters for Vorapaxar after Administration of vorapaxar with Prasugrel and Vorapaxar Alone in Healthy Adult Subjects. Source: [Report: P06560, Table 14, Page 62]

	SCH 530348 + Prasugrel			SCH 530348			(SCH 530348 + Prasugrel) / (SCH 530348)		
Pharmacokinetic Parameter	N	GM	(95% CI)	N	GM	(95% CI)	GMR	(90% CI)	rMSE ‡
AUC_{τ} (ng*hr/mL) †	33	1190	(1120, 1265)	16	1274	(1167, 1391)	0.93	(0.85, 1.02)	0.174
$AUC_{0\text{-}tf}$ (ng*hr/mL) †	33	1190	(1120, 1265)	16	1275	(1168, 1392)	0.93	(0.85, 1.02)	0.174
C_{max} (ng/mL) †	33	70.6	(66.1, 75.5)	16	74.3	(67.5, 81.8)	0.95	(0.86, 1.05)	0.190

† Back-transformed least squares mean and confidence interval from mixed effects model performed on natural log-transformed values.

‡ rMSE: Square root of conditional mean squared error (residual error) from the linear fixed effect model. rMSE*100% approximates the between-subject % CV on the raw scale.

GM = geometric mean; GMR = geometric mean ratio; CI = confidence interval

Bioanalytical Assay

	R-138727
Method	**UPLC-MS/MS**
LLOQ (pg/mL)	10
Range (pg/mL)	10 to 5120
QCs (pg/mL)	30, 1920, 3840

Comment: The analytical assay method is acceptable since the accuracy and precision for at least 2/3^{rds} of the QC and LLOQ samples are within the acceptable limits of ±15% and ± 20%, respectively, as specified in 'Guidance for Industry: Bioanalytical Method Validation'.

Safety

No adverse events reported following study drug administration were considered severe or life-threatening by the investigator.

SUMMARY

- The study results show no pharmacokinetic interaction between prasugrel and vorapaxar.
- The pharmacodynamic interaction potential was not assessed in this study. Though we know that vorapaxar does not affect platelet aggregation induced by ADP, PD information from this study would have been useful to evaluate the interaction potential of prasugrel on platelet aggregation induced by vorapaxar.

DDI with Warfarin		
Study report: P04132	**Study period:** 04/11/2006 - 06/20/2006	**EDR Link**[20]

OBJECTIVES

Rationale:
This *in vivo* drug interaction study with warfarin was performed because vorapaxar showed a modest potential to inhibit CYP2C9 *in vitro* [IC_{50}=30 μM].

Objectives:

- To evaluate the potential effects of vorapaxar on the pharmacokinetics and pharmacodynamics of warfarin in healthy male volunteers.

- To evaluate the safety and tolerability of the coadministration of vorapaxar and warfarin.

STUDY DESIGN

Open-label, single-center, fixed-sequence, two-period, two-treatment study in healthy male subjects.

Subjects were to be screened within 3 weeks of initial dosing and those who met the entry criteria were to receive the following two treatments:

Treatment A: Single 25 mg dose of warfarin on Day 1 of Period 1.

Treatment B: Once daily 2.5 mg vorapaxar sulfate on Days 1 to 6 followed by a single 25 mg dose of warfarin and a single 40 mg dose of vorapaxar sulfate taken concurrently on Day 7 of Period 2.

PK Sampling

Warfarin: During treatment and evaluation Periods 1 and 2, starting on Days 1 and 7, respectively, blood samples were collected for PK evaluation of R- and S-warfarin at predose (0 h) and at 2, 4, 6, 8, 10, 12, 16, 24, 36,48, 60, 72, 96, and 120 h after treatment administration.

Vorapaxar: On Day 7 of Period 2, blood samples were collected for PK evaluation of vorapaxar at predose (0 h), and at 0.5, 1, 1.5, 2, 4, 6, 12, and 24 h post-dose.

Statistical Method

PK:
The observed and derived warfarin pharmacokinetic parameters were summarized by treatment. Summary statistics were calculated for the plasma R- and S-warfarin concentration data at each time point and the derived pharmacokinetic parameters. The log-transformed pharmacokinetic parameters for R- and S-warfarin were separately analyzed. An analysis of variance (ANOVA) model was applied to the pharmacokinetic parameters extracting the effects due to subject and treatment. In addition, point estimates along with 90% confidence interval (CI) of the relative bioavailability were provided for Treatment B (warfarin plus vorapaxar, administered in Period 2) versus Treatment A (warfarin alone, administered in Period 1). The observed and derived SCH 530348 pharmacokinetic parameters were summarized for Day 7 of Period 2 to confirm that subjects had the anticipated exposure to SCH 530348.

PD:
The PT-ratio and INR-ratio were calculated as the ratio of the PT or INR after warfarin administration to the PT or INR measured just prior to warfarin administration. The pharmacodynamics parameters

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were statistically analyzed using an ANOVA model extracting the effects due to subject and treatment. Point estimates along with 95% CI for the difference in pharmacodynamic parameters between Treatment B (warfarin plus SCH 530348, administered in Period 2) and Treatment A (warfarin alone, administered in Period 1) were calculated.

Population

Healthy male subjects between the ages of 18 and 55 years, inclusive, and having a Body Mass Index (BMI) between 19 to 29 (BMI = weight (kg)/ height (m^2).

Clinical laboratory tests (CBC, blood chemistries, and urinalysis) were to be within normal limits (WNL) or clinically acceptable to the investigator/sponsor. PT, aPTT, INR, ALT, AST, and GGT were to be WNL at screening and on Day -1 of Period 1. Subjects with abnormal PT, aPTT, INR, ALT, AST, and GGT were not be re-screened.

RESULTS

Pharmacokinetics

Table 1: Effect of vorapaxar on pharmacokinetics of warfarin [Report: P04132, Table 11, Page 61]

			Least Squares Mean[b]			
Analyte	Parameter	n[a]	Period 1 Warfarin Alone	Period 2 Warfarin With SCH 530348	Relative Bioavailability (%)[c]	90% CI[d]
R-Warfarin	Cmax	12	1.34	1.41	105	99-111
	AUC(tf)	12	60.0	64.2	107	99-115
	AUC(I)	12	71.1	76.8	108	101-116
S-Warfarin	Cmax	12	1.32	1.39	105	99-112
	AUC(tf)	12	40.3	42.1	104	95-115
	AUC(I)	12	43.0	45.2	105	96-115

Note: In Period 1, 25 mg warfarin administered on Day 1. In Period 2, once-daily 2.5 mg SCH 530348 administered for 6 days followed by Day 7 coadministration of 25 mg warfarin and 40 mg SCH 530348

Abbreviations: ANOVA = analysis of variance; AUC(I) = area under the curve of plasma concentration versus time from time zero to infinity; AUC(tf) = area under the curve of plasma concentration versus time from time zero to final measurable sampling time; CI = confidence interval; Cmax = maximum observed plasma concentration; n = number of subjects.

a: Subjects 03 and 10 were excluded from the statistical analysis due to missing Period 2 data; both subjects discontinued after Period 1.

b: Model-based (least squares) mean: ANOVA extracting the effects due to treatment and subject.

c: Percent ratio of the geometric mean value for warfarin with SCH 530348 (Period 2) to warfarin-alone treatment (Period 1)

d: Ninety percent CI based on log-transformed data, $\alpha = 0.1$, two-tailed.

Pharmacodynamics

Table 2: Effect of vorapaxar on the pharmacodynamics of warfarin (INR) [Report: P04132, Table 14, Page 68]

		Least Squares Mean[b]			
Parameter	n[a]	Period 1 Warfarin Alone	Period 2 Warfarin With SCH 530348	Ratio Estimate (%)[c]	95% CI[d]
AUC(0-120 hr)$_{PT}$	12	1903	1839	97	95-98
AUC(0-120 hr)$_{PT\text{-}ratio}$	12	143	137	95	89-102
AUC(0-120 hr)$_{INR}$	12	149	143	96	94-98
AUC(0-120 hr)$_{INR\text{-}ratio}$	12	149	141	94	86-103

Note: In Period 1, 25 mg warfarin administered on Day 1. In Period 2, once-daily 2.5 mg SCH 530348 administered for 6 days followed by Day 7 coadministration of 25 mg warfarin and 40 mg SCH 530348.

Abbreviations: AUC(0-120 hr)PT = area under the PT-time curve from time 0 to 120 hours postdose; AUC(0-120 hr)PT-ratio = area under the PT-ratio-time curve from time 0 to 120 hours postdose; AUC(0-120 hr)INR = area under the INR-time curve from time 0 to 120 hours postdose; AUC(0-120 hr)INR-ratio = area under the INR-ratio-time curve from time 0 to 120 hours postdose; CI = confidence interval; hr = hour; n = number of subjects.

a: Subjects 03 and 10 were excluded from the statistical analysis due to missing Period 2 data; both subjects discontinued after Period 1.

b: Model-based (least squares) mean: ANOVA extracting the effects due to treatment and subject.

c: Percent ratio of the geometric mean value for warfarin with SCH 530348 (Period 2) to warfarin alone (Period 1).

d: Ninety-five percent CI based on log-transformed data, $\alpha = 0.05$, two-tailed.

Bioanalytical Assay Method			
	R-Warfarin	**S-Warfarin**	*Comment*: The analytical assay method is acceptable since the accuracy and precision for at least 2/3^{rds} of the QC and LLOQ samples are within the acceptable limits of ±15% and ± 20%, respectively, as specified in 'Guidance for Industry: Bioanalytical Method Validation'.
Method	**HPLC-MS/MS**		
LLOQ (ng/mL)	5	5	
Range (ng/mL)	5 to 1000	5 to 1000	
QCs (ng/mL)	10, 80, 250, 800	10, 80, 250, 800	

Safety

No treatment-related AE was reported. Results from laboratory tests and other safety evaluations did not indicate any identifiable potential adverse effect of the coadministration of vorapaxar and warfarin.

SUMMARY

Vorapaxar did not affect the pharmacokinetics or pharmacodynamics of warfarin. However, there is no clinical experience (to understand the risk for bleeding) with the use of vorapaxar in the background of warfarin or other anticoagulants. Therefore, avoid concomitant use of warfarin and vorapaxar.

DDI with Rosiglitazone		
Study report: P05361	**Study period:** 10/07/2008 - 12/16/2008	**EDR Link**[21]

RATIONALE AND OBJECTIVES

Rationale:
This *in vivo* drug interaction study with rosiglitazone was performed because vorapaxar showed a modest potential to inhibit CYP2C8 *in vitro* [IC_{50}=1.5 μM].

Objectives:
- To evaluate the drug interaction potential when vorapaxar is co-administered with rosiglitazone, a CYP2C8 substrate.
- To evaluate the pharmacodynamics, safety and tolerability of the coadministration of vorapaxar and rosiglitazone.

STUDY DESIGN

Open-label, fixed-sequence, two-period, two-treatment study of rosiglitazone administered alone and concurrently with vorapaxar in healthy volunteers.

Treatments:
A: Single 8 mg dose of rosiglitazone on Day 1 of Period 1.
B: Single 40 mg dose of vorapaxar on Day 1, once daily 7.5 mg vorapaxar on Days 2 to 6, and a single 8 mg dose of rosiglitazone and a 7.5 mg dose of vorapaxar taken concurrently on Day 7 of Period 2. There was a 5 days washout between the two periods.

Reviewer's comment: The rationale for using a dose of 7.5 mg vorapaxar sulfate is not clear. However, it represents a conservative scenario for evaluating the DDI potential.

PK Sampling

Blood samples were collected for pharmacokinetic evaluation of rosiglitazone and its metabolite N-desmethyl rosiglitazone at predose (0 h), and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16, and 24 h post dose.

Blood Glucose Concentrations
On Days -1 and 1 of Period 1 and Day 7 of Period 2, blood samples (2.5 mL each) for determination of glucose concentration were to be collected at the following nominal times corresponding to rosiglitazone dosing: predose (0 h), and at 0.5, 1, 1.5, 2, 4, and 24 h post dose.

Statistical Method

Plasma concentration-time data were used to determine the following pharmacokinetic parameters using Non-compartmental Pharmacokinetic Analyses: C_{max}, T_{max}, and $AUC_{0\text{-}24h}$. If the plasma concentration time data allowed, the following pharmacokinetic parameters were also to be determined: AUC∞, t½, CL/F, and Vd/F.

To determine the effect of vorapaxar on the pharmacodynamics (effects on plasma glucose) of rosiglitazone, the primary comparison was between Treatment A (rosiglitazone alone) and Treatment B (rosiglitazone plus vorapaxar). Summary statistics (means, standard deviations, 95% confidence intervals) were provided for plasma glucose. In addition, change from Baseline (Day -1 of Period 1) to Day 1 of Period 1 (rosiglitazone alone) was summarized.

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Population

A total of 18 healthy adult subjects, aged 18 to 51 years were enrolled. All 18 subjects received rosiglitazone-alone treatment (Treatment A) in Period 1. Sixteen subjects received treatment with rosiglitazone and vorapaxar (Treatment B) in Period 2, completing the study as planned. The two subjects who discontinued from the study had completed Period 1 study assessments. One subject discontinued because of a positive pregnancy test on Day -1 of Period 2, and the other after missing the Day 1 dose in Period 2.

RESULTS

Table 1: Statistical Analysis of Rosiglitazone Pharmacokinetic Parameters Following Single Dose Oral Administration of 8 mg Rosiglitazone With and Without Vorapaxar [Report P05361, Table 11, Page 62]

Parameter	Units	Least Squares Mean (90% CI)[a]		Treatment Comparison	GMR[a]	90% CI[a]
		Rosiglitazone (n=18)	Rosiglitazone + TRA (n=16)			
AUC(0-24 hr)[a]	ng.hr/mL	3086 (2831, 3365)	3171 (2904, 3462)	Rosi + TRA vs Rosi	103	98–108
Cmax[a]	ng/mL	652 (594, 715)	620 (563, 682)	Rosi + TRA vs Rosi	95	88–103

Note: In Period 1, 8 mg rosiglitazone administered on Day 1. In Period 2, 40 mg SCH 530348 administered on Day 1, once-daily 7.5 mg SCH 530348 on Days 2 to 6, followed by coadministration of 8 mg rosiglitazone and 7.5 mg SCH 530348 on Day 7.

Abbreviations: ANOVA = analysis of variance; AUC(0-24 hr) = area under the concentration-time curve from time 0 to 24 hours; CI = confidence interval; Cmax = maximum observed plasma concentration; GMR = ratio of geometric means; Rosi = rosiglitazone; TRA = SCH 530348; vs = versus.

a: Model based (least squares) geometric mean based on ANOVA model extracting the effects due to treatment and subject.

Table 2: Statistical Analysis of Desmethyl Rosiglitazone Pharmacokinetic Parameters Following Single Dose Oral Administration of 8 mg Rosiglitazone With and Without Vorapaxar [Report 05361, Table 13, Page 65]

Parameter	Units	Least Squares Mean (90% CI)[a]		Treatment Comparison	GMR[a]	90% CI[a]
		Rosiglitazone (n=18)	Rosiglitazone + TRA (n=16)			
AUC(0-24 hr)[a]	ng.hr/mL	2846 (2662, 3044)	2905 (2715, 3108)	Rosi + TRA vs Rosi	102	100–104
Cmax[a]	ng/mL	154 (144, 166)	157 (146, 169)	Rosi + TRA vs Rosi	102	99–104

Note: In Period 1, 8 mg rosiglitazone administered on Day 1. In Period 2, 40 mg SCH 530348 administered on Day 1, once-daily 7.5 mg SCH 530348 on Days 2 to 6, followed by coadministration of 8 mg rosiglitazone and 7.5 mg SCH 530348 on Day 7.

Abbreviations: ANOVA = analysis of variance; AUC(0-24 hr) = area under the concentration-time curve from time 0 to 24 hours; CI = confidence interval; Cmax = maximum observed plasma concentration; GMR = ratio of geometric means; Rosi = rosiglitazone; TRA = SCH 530348; vs = versus.

a: Model based (least squares) geometric mean based on ANOVA model extracting the effects due to treatment and subject.

Table 3: Summary Statistics for Rosiglitazone Pharmacodynamic Parameters Following Single Dose Oral Administration of 8 mg Rosiglitazone With and Without Vorapaxar (n=16). [Report 05361, Table 16, Page 69]

	Change in Plasma Glucose Concentrations (mmol/L)					
	Rosiglitazone[a] – Baseline[b]			(Rosiglitazone + TRA)[c]– Rosiglitazone[a]		
Hours Postdose	Mean	SD	95% CI	Mean	SD	95% CI
0	0.2	0.2	0.1 – 0.3	-0.4	0.4	-0.6 – -0.2
0.5	0.3	0.3	0.2 – 0.5	-0.2	0.5	-0.4 – 0
1	-0.1	0.3	-0.3 – 0	-0.2	0.5	-0.4 – 0.1
1.5	-0.1	0.3	-0.2 – 0.1	-0.1	0.4	-0.3 – 0.1
2	0	0.3	-0.1 – 0.2	-0.1	0.4	-0.4 – 0.1
4	0.2	0.4	-0 – 0.4	0.1	0.5	-0.2 – 0.4
24	0.2	0.2	0.1 – 0.3	0.1	0.2	0 – 0.3

Note: In Period 1, 8 mg rosiglitazone administered on Day 1. In Period 2, 40 mg SCH 530348 administered on Day 1, once-daily 7.5 mg SCH 530348 on Days 2 to 6, followed by coadministration of 8 mg rosiglitazone and 7.5 mg SCH 530348 on Day 7.

Abbreviations: CI = confidence interval; SD = standard deviation; TRA = SCH 530348.

a: Day 1 of Period 1.

b: Day -1 of Period 1.

c: Day 7 of Period 2.

Reviewer comment: As this study is conducted in healthy volunteers following a single dose of rosiglitazone as control (negligible effects on blood glucose as shown in Table 3), the potential for a pharmacodynamic interaction with vorapaxar may not be assessed. Nevertheless, the potential for a pharmacodynamic interaction seems low as vorapaxar did not significantly affect the pharmacokinetics of rosiglitazone and its metabolite.

Bio-analytical Assay

	Rosiglitazone
Method	**LC-MS/MS**
LLOQ (ng/mL)	1.0
Range (ng/mL)	1 to 500
QCs (ng/mL)	2.5, 6, 24,80

Comment: The analytical assay method is acceptable since the accuracy and precision for at least 2/3^{rds} of the QC and LLOQ samples are within the acceptable limits of ±15% and ± 20%, respectively, as specified in 'Guidance for Industry: Bioanalytical Method Validation'.

Safety
• A total of 9 subjects (9/18, 50%) reported at least one adverse event during the study: 5 subjects (5/18, 28%) after rosiglitazone-alone treatment (Period 1), and 7 subjects (7/16, 44%) after rosiglitazone and vorapaxar coadministration (Period 2). The most frequently reported adverse events were headache. • There was one bleeding-related adverse event, metrorrhagia reported during Period 2, which was considered by the investigator to be mild in intensity and unlikely related to treatment. No subject died, and no serious adverse event was reported following study treatment. No clinically significant change in blood chemistry, hematological parameters, or vital signs occurred.
SUMMARY
Vorapaxar does not affect the pharmacokinetics of rosiglitazone, a CYP2C8 substrate.

COMMENT ON OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REVIEW

OCP requested OSI to inspect the clinical and bioanalytical site pertaining to pivotal bioequivalence study (P06558) titled: "A study to determine the bioequivalence of vorapaxar sulfate 2.5 mg tablets containing high (46%) and low (23%) percentage of drug as the free base within the range used in the pivotal Phase 3 efficacy and safety trials". The final OSI review recommendations[22] were:

1. The results from the clinical portion and vorapaxar (SCH 530348) concentrations from the analytical portion of study P06558 are acceptable for Agency review.

2. The bioanalytical method for SCH 2046273 (metabolite, M20) was insufficiently sensitive to precisely describe the pharmacokinetic profile of this metabolite following dosing with vorapaxar, SCH 530348.

OCP comment:

Bioequivalence on the pharmacokinetic measures of vorapaxar (SCH 530348) was the primary objective of study P06558. Plasma concentrations of SCH 2046273 (metabolite M20) were also measured, but as an exploratory objective to evaluate the relative plasma exposures of metabolite M20 when compared to parent drug, vorapaxar. No statistical analysis was performed to establish bioequivalence on the pharmacokinetic measures of metabolite M20 nor was it a pre-specified objective of the study. Therefore, OSI review conclusion #2 does not affect the interpretation of study P06558, that vorapaxar sulfate 2.5 mg tablets with low (23%) and high (46%) free base content are bioequivalent with respect to the pharmacokinetic measures of vorapaxar.

[22] Reviewed by Dr. Biswas, NDA 204886, DARRTS date: 04/29/2014

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SUDHARSHAN HARIHARAN
05/10/2014

BILAL S ABU ASAL
05/10/2014

RAJANIKANTH MADABUSHI
05/10/2014

BIOPHARMACEUTICS REVIEW Office of New Drug Quality Assessment			
Application No.:	NDA 204-886 (000)	**Reviewer:** Okpo Eradiri, Ph.D.	
Division:	DCRP		
Applicant:	Merck, Sharp & Dohme	**Team Leader:** Angelica Dorantes, Ph.D.	
Trade Name:	Zontivity Tablets, 2.5 mg	Biopharmaceutics Supervisor: Richard Lostritto, Ph.D.	
Generic Name:	Vorapaxar Sulphate IR Tablets	**Date Assigned:**	May 13, 2013
Indication:	Reduction of atherothrombotic events in patients with history of myocardial infarction, MI, but no history of stroke or transient ischemic attack, TIA.	**Date of Review:**	January 9, 2014
Formulation/strength	Immediate Release Tablets/2.5 mg		
Route of Administration	Oral		

SUBMISSIONS REVIEWED IN THIS DOCUMENT		
Submission Dates May 10, 2013.	**Date of informal/Formal Consult**	**PDUFA DATE**
		Feb 3, 2014
Type of Submission:	505(b)(1)	
Key review points	1. Dissolution method; 2. Dissolution acceptance criterion and its justification; 3. Data supporting the bridging of the to-be-marketed (TBM) tablets to the clinical trial batch.	

TABLE OF CONTENTS

I) SUMMARY OF BIOPHARMACEUTICS FINDINGS

Vorapaxar Sulphate is an NME and a first-in-class selective protease-activated receptor-1 (PAR 1) antagonist. The drug was shown by the Applicant to block thrombin-mediated platelet aggregation, which is essential in reducing the risk of atherothrombotic complications of coronary disease.

The intended commercial dosage form is a 2.5 mg immediate-release tablet for once-daily administration. The formulation contains commonly used excipients that meet USP and Ph. Eur standards and does not contain novel excipients. The proposed manufacturing process is also (b) (4) The clinical trial formulation (CTM) is a white, round tablet while the proposed commercial (TBM) (b) (4) otherwise the same excipients, (b) (4) and manufacturing process are applicable to both products. The TBM tablet was bridged to the CTM tablet through in-vitro dissolution using the proposed method.

Vorapaxar is highly soluble in acidic pH below 4 but has low solubility in aqueous media between pH 4 – 7.5. In addition, the results from a permeability study showed that the drug has high permeability across Caco-2 cells. The Applicant therefore classifies Vorapaxar Sulphate as a BCS Class 2 compound.

Vorapaxar Sulphate partially converts to the free base during the manufacturing process; the free base (b) (4). The formation of vorapaxar base in the tablet is monitored by FT-Raman Spectroscopy at release and during stability. The Applicant has also performed two BA/BE studies on the drug product across a range of free base levels, demonstrating a decrease in bioavailability of the drug; the Applicant concludes that the decrease in bioavailability attributable to the base formation is unlikely to be clinically significant. The free base formation issue has been exhaustively discussed with the CMC Reviewer, Dr. Thomas Wong, and the Clinical Pharmacology Reviewer, Dr. Sudharshan Hariharan; further details on the free base are covered in the CMC and Clinical Pharmacology reviews.

This review focuses on the evaluation and acceptability of the following:

1) Adequacy of the proposed dissolution method;
2) Adequacy of the proposed dissolution acceptance criterion and its justification;
3) Adequacy of data supporting the bridging of the to-be-marketed (TBM) tablets to the clinical trial batch.

1) Acceptability of the Dissolution Method:

The Applicant's investigation of the dissolution parameters indicates that the method is suitable for QC testing and release of the proposed product. (b) (4)

(b) (4)

Overall, the provided data support the proposed dissolution method and is deemed acceptable.

The Applicant's response can be found at the following link:
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2) Dissolution Acceptance Criterion and Justification

The Applicant used a statistical simulation approach in predicting failure rates of future commercial batches at (b) (4) minutes as the basis for the proposed acceptance criterion; a Stage 1 failure rate of (b) (4) was deemed by the Applicant as reasonable. Details of the simulation analyses are not provided in the NDA and room temperature stability data were not used in the statistical analyses. However, the two clinical and two primary stability batches release more than (b) (4) of the label claim by 30 min. In addition, long-term stability data for 3 registration batches over 12 months showed vorapaxar release higher than (b) (4) at 30 min except in one vessel at the 12-month time point where (b) (4) was released. The acceptance criterion was therefore recommended to be tightened to Q = (b) (4) at 30 min in the October 4, 2013 IR letter.

In the response (to the IR comments) dated November 7, 2013, the Applicant reiterated the validity of the simulation results as follows: "*After evaluation of the simulation results, we believe a control for dissolution rate with an acceptance criterion of Q =* (b) (4) *at 30 minutes will result in overly high batch rejection rate*". Furthermore, the Applicant concluded that "*Based on our process and product understanding and the discriminatory capability of the dissolution method, we believe an acceptance criterion of Q =* (b) (4) *minutes represents an appropriate quality control for vorapaxar sulfate tablets, 2.5 mg*".

This Reviewer disagrees with the Applicant's above conclusion for the following reasons:

i) As stated earlier, no details on the simulation or process capability determination are provided;
ii) All but two of the excipient- and (b) (4)-DOE batches would pass the recommended acceptance criterion of Q = (b) (4) at 30 min. The two failed batches were made with (b) (4), indicating the dissolution method's discriminating ability for these two (b) (4) parameters;

iii) The long-term stability data for 3 registration batches over 12 months showed vorapaxar release greater than (b) (4) at 30 min except in one vessel at the 12-month time point where (b) (4) was released.

During a teleconference held on January 9, 2014, between the Applicant and FDA, the information/data supporting FDA's recommended limit of Q = (b) (4) at 30 min for the dissolution acceptance criterion of the proposed product and the Applicant's concerns for the dissolution method's overall capability, particularly with respect to variability due to changes in the API particle size were discussed. At the end of the teleconference the Applicant agreed to implement the FDA's recommended dissolution criterion of Q = (b) (4) at 30 min (Please see Ms. Yvonne Knight's DARRTS entry on January 9, 2014).

3) Acceptability of Data Supporting Bridging of the To-Be-Marketed Tablets to the Clinical Trial Material (CTM)

The Phase 3 clinical trial formulation (CTM) is a white, round tablet while the proposed commercial (TBM) tablet (b) (4); the main differences between the CTM and TBM tablets are therefore (b) (4) The Applicant bridged the TBM tablet to the CTM tablet through in-vitro dissolution using the proposed method (USP 2, 50 rpm) with 3 different media: 500 mL 0.1N HCl, 900 mL pH 4.5 acetate buffer, and 900 mL pH 6.8 phosphate buffer. (b) (4) The bridging of the TBM to the CTM is acceptable.

II) RECOMMENDATION

ONDQA-Biopharmaceutics has reviewed NDA 204-886 for Vorapaxar immediate-release tablets, 2.5 mg. The following dissolution method and acceptance criterion for Vorapaxar Tablets are agreed upon and are acceptable for release and stability.

USP Apparatus	Paddle Speed Rotation	Medium Volume	Temperature	Medium	Acceptance Criterion
II	50 rpm	900mL	37 ± 0.5 °C	41 mM Na2HPO4, 1.5% Citric Acid, pH 3.0 ± 0.5	Q = (b) (4) at 30 min

We find the provided information/data acceptable and therefore, from a Biopharmaceutics perspective, recommend APPROVAL of NDA 204-886.

Okpo Eradiri, Ph. D.
Biopharmaceutics Reviewer
Office of New Drug Quality Assessment

Angelica Dorantes, Ph.D.
Biopharmaceutics Team Leader
Office of New Drug Quality Assessment

III) QUESTION BASED REVIEW – BIOPHARMACEUTICS EVALUATION

A) GENERAL ATTRIBUTES

1 What are the highlights of the chemistry and physico-chemical properties of the drug substance (e.g. solubility) and formulation of the drug product?

Drug Substance

Vorapaxar Sulphate is a white to off-white, slightly hygroscopic powder. The drug is practically insoluble in hexane as well as in aqueous solvents at pH values above 3.0. The pKa of Vorapaxar Sulphate is 4.7 and the highest aqueous solubility of the drug substance at ambient temperature (25 ˚C) was found to be 3.76 mg/mL at pH 1.0; the least solubility obtained experimentally was 0.0256 mg/mL at pH 6.4. In general, the solubility at 37 ˚C was found to be lower than at ambient temperature, presumably due to the formation of free base. Interestingly, solubility experiments with simulated biological media at 37 ˚C showed the highest solubility at pH 1.4 (Table 1). The drug substance has 7 chiral centers.

Table 1: Solubility of Vorapaxar Sulphate in simulated biological media.

Conditions	Media	Solubility (mg/mL) at 37°C
Gastric fasted condition (pH ~1.4)	0.0484 N HCl, 8.84 mM Sodium dodecyl sulfate, 0.034 M NaCl in water	0.63
Small intestine fasted condition (pH~ 6.7)	0.029 M KH_2PO_4, 4.93 mM Sodium taurocholate, 1.71 mM Lecithin, and 0.222 M KCl in water. pH adjusted with NaOH to 6.71	0.065
Duodenum fed condition (pH ~ 5.0)	0.144 M Acetic acid, 14.95 mM sodium taurocholate, 3.81 M Lecithin, 0.19 M KCl in water and pH adjusted with NaOH	0.085

The solubility of vorapaxar sulphate and the free base in potential (acidic) dissolution media between pH 1.3 – 3 are displayed in Table 2.

Table 2: Solubility of Vorapaxar Sulphate and free base under ambient conditions.

	Solubility (µg/mL)	
Solution (approximate pH)	Vorapaxar Sulfate	Vorapaxar Free Base
0.05 N HCl (pH 1.3)	1871	852
0.01 N HCl (pH 2)	447	258
0.001 N HCl (pH 3)	158	21
Experiment conducted by dissolving vorapaxar sulfate or free base in the specified solution by periodic vortexing at ambient laboratory conditions for (b) (4)		

The solubility of the sulphate salt is approximately 7-fold that of the free base in 0.001 N HCl (pH 3).

Drug Product

The intended commercial drug product is an immediate-release, yellow, oval, film-coated 2.5 mg tablet for once-daily oral administration. The proposed manufacturing process is (b) (4) The components and composition of Vorapaxar Sulphate Tablets are summarized in Table 3.

Table 3. Composition of Vorapaxar Sulphate IR Tablets, 2.5 mg.

Ingredient	Quality Standard	Function	Amount (mg/tablet)
Vorapaxar Sulfate	In-house	Active	(b) (4)
Lactose Monohydrate	NF or Ph. Eur.	(b) (4)	
Microcrystalline Cellulose	NF or Ph. Eur.		
Croscarmellose Sodium	NF or Ph. Eur.		
Povidone[a]	USP or Ph. Eur.		
Magnesium Stearate	NF or Ph. Eur.		
(b) (4)	USP or Ph. Eur.		
Theoretical Tablet Core Weight			
(b) (4)	In-house	(b) (4)	
	USP or Ph. Eur.		
Theoretical Coated Tablet Weight[e]			**104**

a: (b) (4)
b:
c (b) (4) contains lactose monohydrate, (b) (4) hypromellose (b) (4) titanium dioxide, triacetin/glycerol triacetate, and iron oxide yellow
d: (b) (4)
e:

2 Is there any information on BCS classification? What claim did the applicant make based on BCS classification? What data are available to support this claim?

Vorapaxar drug substance is reported as a Biopharmaceutics Classification System (BCS) Class II compound (low solubility/high permeability).

The Applicant's CACO-2 permeability study showed vorapaxar to be a highly permeable drug (Section 3.2.S.1.3, sub-section 1.12) compared to a standard, pindolol (Table 4).

Table 4: Permeability data for Vorapaxar and Pindolol.

Vorapaxar (μM)	Vorapaxar $P_{app\_AP\ oBL}$ ($\times 10^{-6}$ cm/sec)	Pindolol $P_{app\_AP\ oBL}$ ($\times 10^{-6}$ cm/sec)	p Value[a]
0.1	28.4 ± 2.8	10.4 ± 0.3	0.004
1	34.0 ± 2.7	9.9 ± 1.6	0.001
10	27.9 ± 3.2	11.8 ± 0.2	0.006
a: t-Test: Paired two sample for means, one tail (significant level <0.05)			

Although not claimed by the Applicant in the NDA, the results from this study indicate that Vorapaxar Sulphate is a highly permeable drug. However, note that this information is not complete and additional permeability data as described in the BCS guidance are needed to support an official highly permeable classification for this drug.

B.1. DISSOLUTION INFORMATION

3 What is the proposed dissolution method?

The dissolution method proposed for the quality control of Vorapaxar Sulphate IR Tablets, 2.5 mg, is summarized below:

USP Apparatus	Spindle Rotation	Medium Volume	Temperature	Medium
II	50 rpm	900mL	37 ± 0.5 ˚C	41 mM Na2HPO4, 1.5% Citric Acid, pH 3.0 ± 0.5

The HPLC chromatographic conditions are:

Mobile Phase: 0.1% v/v trifluoroacetic acid in water:acetonitrile - 3:2
Column: Octadecylsilane chemically bonded to (b) (4), (b) (4) particle size or equivalent.
Column Temperature: 30°C
Flow Rate: 1.5 mL/minute
Detection: UV absorbance at 320 nm
Injection Volume: 90 µL
Run Time: 5 minutes

4 What data are provided to support the adequacy of the proposed dissolution method (e.g medium, apparatus selection, etc.)?

The Applicant initially developed a dissolution method (USP Apparatus 1) for the drug product which was used as one of the QC tools for release of the clinical batches. While the definitive Phase III study and the stability program were ongoing, it was discovered that the drug substance in the formulation was converting to the free base; in fact, it was later discovered that immediately after manufacture, the drug product contained (b) (4) of the labeled amount as free base. The dissolution method was therefore modified (b) (4) (b) (4) The Applicant will be using the more recently developed dissolution method for QC release and stability testing of commercial batches of the drug product; only the said method (referred to as "Diss-2 by the Applicant) will therefore be evaluated in this review.

(b) (4)

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(b) (4)

7 Is the proposed method acceptable? If not, what are the deficiencies?

The Applicant adequately investigated the dissolution parameters, validated the method along with the associated HPLC method for quantifying Vorapaxar concentrations and investigated the discriminating power of the method. Therefore, the overall dissolution information/data support the proposed dissolution method and is acceptable.

B.2. ACCEPTANCE CRITERION

8 What is the proposed dissolution acceptance criterion for this product?

The Applicant's proposed acceptance criterion for QC and release of vorapaxar tablets was Q (b) (4). In the Applicant's IR response dated Nov 7, 2013, the proposed acceptance criterion was revised to:

Dissolution Acceptance criterion
Q= (b) (4)

9 What data are available to support it?

The Applicant used a statistical simulation approach in predicting failure rates of future commercial batches at (b) (4) as the basis for the proposed acceptance criterion (Stage 1 failure rate of (b) (4) Table 7). Details of the simulation analyses are not provided in the NDA and room temperature stability data were not used in the statistical analyses. Expanded statistical simulation computations were submitted in the Nov 7, 2013 response by including API median particle size range as well as (b) (4) In discussions in a teleconference on Jan 9, 2014, the Applicant was informed that use of intermediate stability data precludes acceptance of the simulation results.

Table 7: Predicted dissolution test failure rates with Q = (b) (4) at 30˚C/75 % RH for 24 months.

(b) (4)

10 Is the acceptance criterion acceptable? If not, what is the recommended criterion? Is the setting of the dissolution acceptance criterion based on data from clinical and registration batches?

The proposed dissolution acceptance criterion is not supported by the provided data and therefore is **not** acceptable.

The individual vessel release dissolution data for the two clinical batches (K-H09802, K-H08778) and two primary stability batches (K-H11411, K-H11413) provided by the Applicant on September 9, 2013, in response to our IR comments, are presented graphically in Figure 5.

Figure 5: Composite dissolution profiles of clinical and primary stability batches of Vorapaxar Tablets, 2.5 mg (USP 2, 50 rpm, 900 mL pH 3 buffer)

As shown in Figure 5, all batches release more than (b) (4) of the label claim by 30 minutes; therefore, the newly proposed (b) (4) time point is not adequate.

In addition, long-term stability data over 12 months were also evaluated for the following stability batches (\\cdsesub1\evsprod\nda204886\0000\m3\32-body-data\32p-drug-prod\vorapaxar-sulfate-tablet\32p8-stab\stability-data.pdf):

- K-H11411_002 (Table 26), 30-ct
- K-H11412_002 (Table 28), 30-ct
- K-H11413_002 (Table 30), 30-ct
- K-H11411_003 (Table 32), 90-ct
- K-H11412_003 (Table 34), 90-count – at 12 months, [redacted], pg 34
- K-H11413_003 (Table 36), 90-count

The lowest percentage of vorapaxar dissolved value at 30 minutes [redacted] lot K-H11412-003, 90-ct bottle) was observed in only one vessel, indicative that this batch will also pass Stage 2 testing at the 30-minute time point.

In conclusion, the overall dissolution data supports an acceptance criterion of **Q = [redacted] at 30 min.** Therefore, it is recommended that this criterion be implemented for the dissolution test of vorapaxar tablets for batch release and stability testing.

The dissolution acceptance criterion was discussed with the Applicant in a teleconference held on Thursday January 9, 2014. The Applicant's concerns about the dissolution method's overall capability, particularly with respect to variability due to changes in the API particle size were also discussed, but a specification of Q = [redacted] at 30 min was deemed appropriate for the product. The Applicant agreed to implement the recommended specification of Q = [redacted] at 30 min for batch release and stability testing of the proposed product (Please see Ms. Yvonne Knight's DARRTS entry on January 9, 2014).

C) DRUG PRODUCT FORMULATION DEVELOPMENT AND BRIDGING ACROSS PHASES

11 What are the highlights of the drug product formulation development?

The intended manufacturing process is [redacted]

Details of the formulation development are summarized in section 3.2.P.2 (\\cdsesub1\evsprod\nda204886\0000\m3\32-body-data\32p-drug-prod\vorapaxar-sulfate-tablet\32p2-pharm-dev\pharmaceutical-development.pdf).

12 Are there any manufacturing changes implemented (e.g. formulation changes, process changes, site change, etc.) to the clinical trial formulation? What information is available to support these changes?

The Phase 3 clinical trial formulation (CTM) is a white, round tablet while the proposed commercial (TBM) tablet is [redacted] otherwise the same excipients,

(b) (4) and manufacturing process are applicable to both products. The main differences between the CTM and TBM tablets are therefore (b) (4) The Applicant bridged the TBM tablet to the CTM tablet through in-vitro dissolution using the proposed method (USP 2, 50 rpm) with 3 different media:

- 500 mL 0.1N HCl;
- 900 mL pH 4.5 acetate buffer
- 900 mL pH 6.8 phosphate buffer

The results of the six experimental runs are presented in Figure 6. The calculated f_2 similarity factors in pH 4.5 and 6.8 buffered media were 94 and 95, respectively. The intended commercial product formulation therefore exhibits similar in-vitro vorapaxar release characteristics as the Phase 3 CTM.

Figure 6: Comparison of Phase 3 CTM and TBM tablets in 3 different media using the proposed dissolution method.

Reviewer's Comments

The CTM and TBM tablets are similar in their in-vitro drug release performance as demonstrated in the comparative dissolution data in three media; therefore, these data support the bridging and is acceptable. Note that the Applicant did not use the proposed regulatory dissolution medium in the experiments.

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/s/

OKPONANABOFA ERADIRI
01/09/2014

ANGELICA DORANTES
01/09/2014

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA	204886
Submission Date	May 10, 2013
Submission Type	Original, NME – Standard Review
Brand Name	ZONTIVITY®
Generic Name	Vorapaxar Sulfate
Sponsor	Merck, Sharp and Dohme Corp.
Therapeutic Class	Protease Activated Receptor-1 [PAR-1] antagonist [anti-platelet]
Formulation	Oral immediate release tablet
[Strengths]	[2.5 mg]
Dosing Regimen	2.5 mg once-daily
Proposed Indication	Reduction of atherothrombotic events in patients with a history of myocardial infarction [MI] and no prior history of stroke or transient ischemic attack [TIA]
OCP Division	Division of Clinical Pharmacology I
OND Division	Division of Cardiovascular and Renal Products
Primary Reviewers	Sudharshan Hariharan, Ph.D. AbuAsal Bilal, Ph.D. Fang Li, Ph.D.
Team Leaders	Rajanikanth Madabushi, Ph.D. Yaning Wang, Ph.D.

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1. EXECUTIVE SUMMARY

Merck Sharp and Dohme Corp. is seeking approval of vorapaxar sulfate [NDA 204886] for use in reduction of atherothrombotic events in patients with a history of MI and no history of stroke or TIA. Vorapaxar is a first-in-class, selective, competitive and reversible antagonist of protease activated receptor-1 [PAR-1], the receptor that mediates the downstream effects of thrombin on human platelets. Aspirin and clopidogrel are the other two approved drugs for the secondary prevention of thrombotic events in patients with MI.

The efficacy and safety of vorapaxar was evaluated in two independent, large, multi-center, outcome studies - TRACER[1] and TRA2°P - TIMI 50[2], designed to support acute coronary syndrome [ACS] and secondary prevention post MI indications, respectively. The applicant identified a subgroup of patients post MI with no prior history of stroke or TIA, which does not have an excess of intracranial hemorrhage [ICH] risk in TRA2°P - TIMI 50 and is seeking approval for this population. The applicant does not seek approval of vorapaxar for treatment of ACS.

The clinical pharmacology program consists of 19 *in vivo* studies designed to characterize mass balance, relative bioavailability/bioequivalence, pharmacokinetics [PK], pharmacodynamics [PD], and impact of intrinsic factors and extrinsic factors on vorapaxar PK and/or PD. In addition, 15 *in vitro* studies were conducted to characterize protein binding, and identify the role of metabolizing enzymes/transporters in the disposition of vorapaxar and its monohydroxy metabolite, M20.

1.1. Recommendations

The Office of Clinical Pharmacology [OCP] has reviewed the clinical pharmacology and biopharmaceutics information submitted to this NDA and recommends approval pending agreement with the applicant on labeling.

Based on the review, OCP has the following labeling recommendation: Avoid use of vorapaxar in patients with body weight < 60 kg due to unfavorable benefit-risk.

1.2. Phase 4 Commitments

No specific post-marketing commitments or requirements are proposed at this point of time.

[1] Thrombin Receptor Antagonist for Clinical Event Reduction in Acute Coronary Syndrome
[2] Thrombin Receptor Antagonist in Secondary Prevention of Atherothrombotic Ischemic Events

1.3. Summary of Important Clinical Pharmacology and Biopharmaceutics Findings

The key findings are listed below.

Pharmacokinetics:

- Following oral administration, median T_{max} for vorapaxar is 1 to 2 h. The disposition is biphasic, characterized by a relatively faster distribution and slow terminal elimination [$t_{1/2}$ = 7 to 11 days]. The absolute bioavailability as estimated by a microdosing study is ~ 100%.

- The steady state is attained by day 21 [earliest available PK] following repeat once-daily dosing regimen. The accumulation at steady state for vorapaxar is 5- to 6-fold. The effective half-life based on accumulation at steady state is 3 to 4 days.

- The monohydroxy metabolite M20, is active as shown by inhibition of calcium efflux in human coronary artery smooth muscle cells with similar potency to that of vorapaxar. Exposure of M20 was in the range of 8% to 29% of vorapaxar across Phase 1 studies. The concentration-time course of M20 generally mirrors that of vorapaxar, suggesting M20 is formation rate-limited.

- Vorapaxar is extensively metabolized followed by excretion in urine and feces. Based on a mass balance study, <2% of vorapaxar is excreted unchanged in feces and none in urine.

Pharmacodynamics:

- Vorapaxar inhibits platelet aggregation induced by thrombin receptor activating peptide [TRAP]. Following repeat oral doses of 2.5 mg once-daily, the onset of platelet inhibition [i.e., <10% aggregation relative to baseline] is projected to be achieved by day 2. Time to offset platelet inhibition is relatively slow with ~50% of platelet function recovered by 4 weeks post-last dose.

PK/PD:

- Vorapaxar demonstrates a steep exposure-platelet inhibition relationship. Over a narrow range of vorapaxar concentration [~1 to 5 ng/mL], the TRAP-induced platelet aggregation changes from non-effect to maximal inhibition.

- Based on population PK and PK//PD data from Phase 1, 2 and 3 studies, 2.5 mg vorapaxar sulfate administered once-daily is predicted to achieve the target engagement i.e., ≥ 80% platelet inhibition in almost all patients by day 7.

Impact of intrinsic factors:

- Based on an increased risk of bleeding [hazard ratio (HR) = 1.87; GUSTO severe or moderate bleeding events] and potential lack of benefit [HR = 1.28; primary efficacy MACE endpoint] for vorapaxar in patients with body weight < 60 kg, the use of vorapaxar should be avoided in this subgroup.

- Though vorapaxar is extensively metabolized, the results of a dedicated hepatic impairment study showed that the pharmacokinetics of vorapaxar was not significantly impacted. It should be noted that one subject from the severe hepatic impairment group in the dedicated study experienced severe gastrointestinal hemorrhage secondary to esophageal varices. As severe hepatic impaired subjects are predisposed to a higher risk of bleeding due to compromised coagulatory state, the use of vorapaxar should be avoided in this subgroup.

- Renal impairment does not affect the pharmacokinetics of vorapaxar. No dose-adjustment is proposed in patients with renal impairment.

Impact of extrinsic factors:

- Vorapaxar is metabolized by CYP3A4 and CYP2J2. Inhibition or induction of these enzymes may affect the systemic exposures to vorapaxar.

- Upon repeat co-administration, ketoconazole, a strong CYP3A inhibitor, increases the systemic exposures to vorapaxar by 2-fold, while rifampin, a strong CYP3A inducer, decreases the systemic exposure to vorapaxar by 55%. The efficacy or bleeding risk for a change in exposure of this magnitude is not known due to the absence of concentration-outcome relationship. Further, concomitant administration of these drugs with vorapaxar was excluded in the phase 3 studies. Therefore, avoid use of vorapaxar with strong inhibitors or inducers of CYP3A.

- The phase 3 trial allowed the use of mild and moderate CYP3A inhibitors. The bleeding risk of vorapaxar in the patients concomitantly receiving these drugs was similar to the control group. No dose adjustments are required when used with mild or moderate CYP3A inhibitors.

- The role of vorapaxar as a perpetrator is low. There is no PK or PD interaction between vorapaxar and digoxin, warfarin, and rosiglitazone.

- Co-administration with a high fat meal, or an antacid, or a proton pump inhibitor [PPI], has a modest impact on the rate of absorption of vorapaxar, but does not significantly alter the extent of absorption. No dose-adjustments are required.

Biopharmaceutics:

- Vorapaxar sulfate converts partially to the amorphous free base upon manufacturing and storage. A pivotal bioequivalence study was performed to evaluate the impact of the base content in the batches used in Phase 3 trial on PK. The low base product [23%] and high base product [46%] were bioequivalent in the presence of a PPI [worst case scenario].

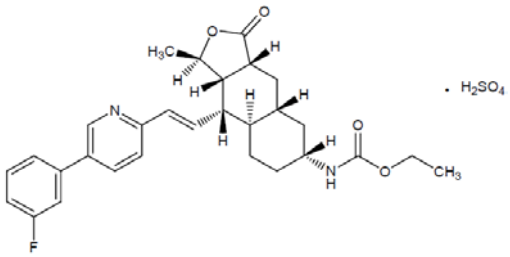
2. QUESTION BASED REVIEW

2.1. General Attributes of the Drug

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?

Drug substance: The physicochemical characteristics of vorapaxar sulfate are summarized in Table 1.

Table 1: Physicochemical properties of vorapaxar sulfate

Appearance	White to off-white crystalline powder
Chemical name	Ethyl[(1R,3aR,4aR,6R,8aR,9S,9aS)-9-{(1E)-2-[5-(3-fluorophenyl) pyridin-2-yl]ethen-1-yl}-1-methyl-3-oxododecahydronaphtho[2,3-c] furan-6-yl]carbamate sulfate
Molecular formula	$C_{29}H_{33}FN_2O_4 \bullet H_2SO_4$
Molecular weight	590.7
Structural formula	
Solubility	pH dependent • fasted conditions, stomach [pH 1.4] = 0.65 mg/mL • fasted conditions, small intestine [pH 6.7] = 0.065 mg/mL • pH 7.5 = 0.001 mg/mL
pKa	4.7
Partition coefficient	Log P = 5.1
Stability	Vorapaxar sulfate salt converts partially to the amorphous free base upon manufacturing and storage
Hygroscopicity	Slightly hygroscopic, adsorbs 1% wt at 85% RH

Drug product: Vorapaxar sulfate is formulated as an immediate release, yellow, oval, film-coated tablet. The formulation does not contain any excipients that impact the release of the drug substance.

2.1.2. What are the proposed mechanism(s) of action and therapeutic indication(s)?

Vorapaxar is a selective, competitive and reversible antagonist of PAR-1, the receptor that mediates the downstream effects of thrombin on human platelets. The EC_{50} of vorapaxar is 15 nM, as shown *in vitro* by the effects on human platelet aggregation induced by thrombin receptor activating peptide [TRAP]. The monohydroxy metabolite of vorapaxar M20, is also reported to be active in an activity assay involving inhibition of calcium efflux induced by a specific PAR-1 agonist in human coronary artery smooth muscle cells. Based on this assay, M20 [EC_{50} = 3.4 nM] and vorapaxar are equipotent [EC_{50} = 4.5 nM].

The proposed indication for vorapaxar in the current submission is for the reduction of atherothrombotic events in patients with a history of MI and no prior history of stroke or TIA.

2.1.3. What are the proposed dosage(s) and route(s) of administration?

The proposed dosage form is an immediate release tablet for oral use to be administered once-daily without regards to food. The dosage form is available at a single strength of 2.5 mg.

2.1.4. What are the current treatments available for the proposed indications?

Aspirin [80-325 mg once daily] and clopidogrel [75 mg once daily] are the other approved treatment options available to reduce the rate of thrombotic cardiovascular events in patients with a prior history of MI.

2.2. General Clinical Pharmacology

2.2.1. What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

The clinical pharmacology program for vorapaxar comprised of 19 *in vivo* studies which are listed in Table 2. The submission also included 15 *in vitro* studies which characterized plasma protein binding and the enzymes/transporters responsible for metabolism/transport of vorapaxar and M20.

Table 2: List of *in vivo* clinical pharmacology studies

Relative bioavailability/Bioequivalence studies	
P03445	Pilot effect of food on vorapaxar PK administered as a 1 mg tablet Relative BA of tablet *vs* capsule
P03447	Effect of food and antacid on PK Relative BA of different dose strengths of vorapaxar
P06452	Relative BA of vorapaxar sulfate salt *vs* free base
P06558	BE study of vorapaxar sulfate 2.5 mg tablets containing high and low percentage of drug as the free base within the range used in Phase 3 trials
P07045	Absolute BA and mass balance of vorapaxar using a microdosing technique
P07969	Effect of food on vorapaxar PK administered as a 2.5 mg tablet
Healthy volunteer PK and PD studies	
P03449	Rising single dose safety, tolerability, PK and PD
P03450	Rising multiple dose safety, tolerability, PK and PD
P03454	^{14}C-vorapaxar absorption, metabolism, excretion
P06559	PK of vorapaxar and M20 in healthy volunteers (Caucasians)
Intrinsic factor studies	
P03448	Effect of race and food on vorapaxar PK, PD and safety (Japanese *vs* Caucasians)
P03464	Effect of renal impairment on vorapaxar PK and PD
P03465	Effect of hepatic impairment on vorapaxar PK
P06453	PK of vorapaxar and M20 in healthy volunteers (Chinese)
Extrinsic factor studies	
P03458	Effect of vorapaxar on digoxin PK and PD
P03629	Effect of ketoconazole and rifampin on vorapaxar PK
P04132	Effect of vorapaxar on warfarin PK and PD
P05361	Effect of vorapaxar on rosiglitazone PK and PD
P06560	Evaluation of PK drug interaction between vorapaxar and prasugrel

The clinical development program comprised of a Phase 2 study [P03573, N = 1030] aimed to establish proof-of-concept, evaluating a range of loading and maintenance doses in patients eligible for non-emergent percutaneous coronary intervention [PCI]. Two other Phase 2 studies with smaller sample size were conducted in Japanese patients.

In Phase 3, the efficacy and/or safety of vorapaxar to reduce the rate of atherothrombotic cardiovascular events in two different at-risk populations was explored in two independent multi-center trials. TRACER and TRA2°P - TIMI 50 were long-term, large-scale, outcome studies designed to support different indications of ACS and secondary prevention post MI, post stroke or peripheral artery disease [PAD], respectively. TRACER enrolled subjects in the midst of an acute episode during hospitalization while TRA2°P - TIMI 50 enrolled clinically stable subjects, 2 weeks- to 1 year-post the index event. The results of TRACER showed an excess of ICH in the vorapaxar group. Hence, the applicant is not pursuing approval of vorapaxar in ACS patients.

A similar finding was also observed in the TRA2°P - TIMI 50 trial. The applicant identified a subgroup of patients with a prior history of stroke, to have a higher risk of ICH on vorapaxar.

The protocol was amended to discontinue vorapaxar in patients with a prior history of stroke for the remainder of the trial. Upon trial completion and data analysis, the applicant has further identified specific patient population in whom the benefit may outweigh the risk and is seeking approval only in patients post MI with no history of stroke or TIA.

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

Inhibition of platelet aggregation induced by TRAP was used as a target engagement biomarker for dose-selection. The primary efficacy endpoint in TRA2°P - TIMI 50 was a composite of cardiovascular death, MI, stroke and urgent coronary revascularization [UCR]. Safety assessments included primarily pre-specified bleeding endpoints defined by GUSTO and TIMI categories and reported individual bleeding events.

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

Vorapaxar and M20 are the active moieties in plasma. These were appropriately identified and measured to permit adequate assessment of the pharmacokinetics in Phase 1 studies. Systemic exposures of vorapaxar and M20 was not measured in TRA2°P - TIMI 50 and available only from a small subset of patients [N=95] in TRACER, thus limiting a direct evaluation of concentration-outcome relationship.

2.3. Exposure-Response

2.3.1. What was the basis of dose selection for Phase 3 trial and is the rationale acceptable?

Exposure-TRAP induced platelet aggregation relationship from Phase 1 and 2 studies was utilized for selection of dose in TRA2°P - TIMI 50. The selected dose was 2.5 mg vorapaxar sulfate administered once-daily.

TRAP induced platelet aggregation was measured in 4 Phase 1 [P03449, P03448, P03450, P03464], 3 PK sub studies from Phase 2 [P3573, P04772, P05005] and a PK/PD sub study of TRACER [P04736] trial. Based on preclinical and clinical experience, achievement of ≥80% inhibition of TRAP-induced platelet aggregation by high proportion of patients on day 7 was considered as the target engagement for vorapaxar to show clinical efficacy. It should be noted that the type and nature of the relationship between platelet inhibition and prevention of atherothrombotic ischemic events is not known.

Vorapaxar demonstrated a steep exposure-platelet inhibition relationship [Fig. 1]. In a narrow range of vorapaxar concentration, the TRAP-induced platelet aggregation can switch from a low to a high inhibition; however, there existed large variations in EC_{50} value among studies. While most Phase 1 to 3 studies demonstrated comparable EC_{50}, two Phase 1 studies [P03448 and P03464] showed exceptionally high EC_{50}, as demonstrated in Figure 1. There is no

pharmacogenomic basis to account for the differences in EC_{50} values in studies P03448 and P03464. Further, there were no identifiable methodological differences between these studies and the rest which could explain a shift in EC_{50} value.

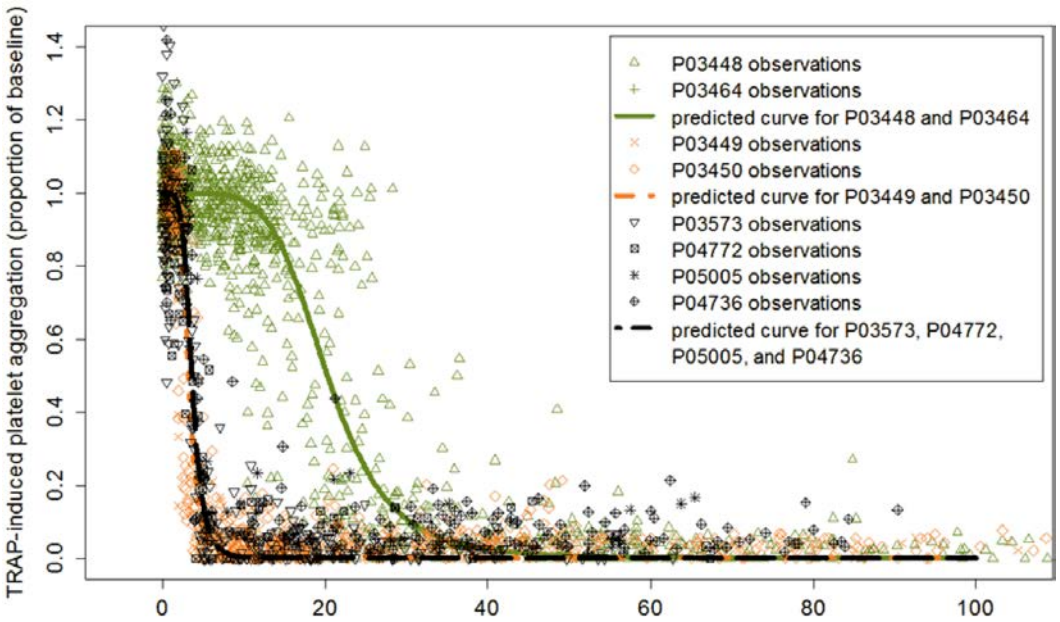


Figure 1: TRAP-induced platelet aggregation data versus effective concentration

[Source: Figure 9 on page 47 of applicant's Summary of Clinical Pharmacology Studies]

The applicant used the combined population PK and PK/PD models to simulate the percentage of patients achieving ≥ 80% inhibition of TRAP-induced platelet aggregation on day 7 and 28 [Fig. 2]. In patients representative of low EC_{50} value, 2.5 mg dose once-daily would achieve maximum platelet inhibition in almost all patients by day 7. In patients representative of high EC_{50} value, 80% of patients are projected to achieve ≥ 80% inhibition by day 28 following 2.5 mg dose once-daily.

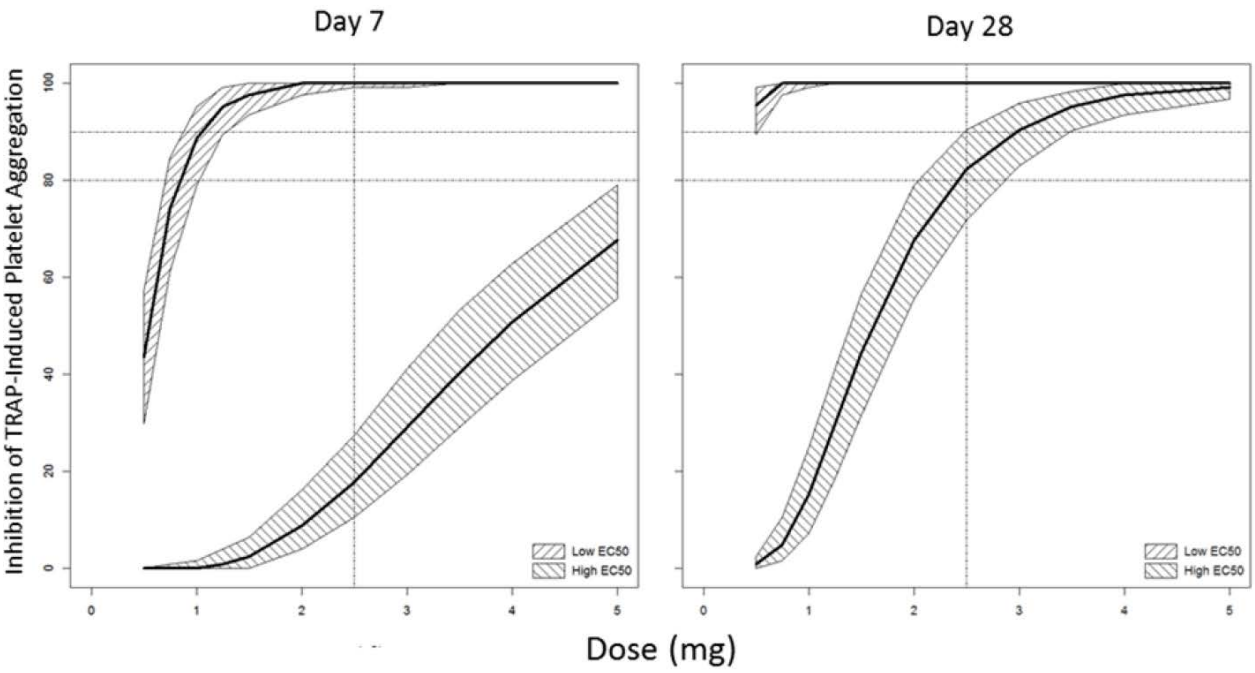


Figure 2: Proportion of subjects achieving at least 80% inhibition of TRAP-induced platelet aggregation after 7 days (left) and 28 days (right) of treatment

[Source: Figure 19 on page 62 of applicant's Population PK and PK/PD report]

In the absence of a plausible explanation for the differences in EC_{50}, discussion on the choice of 2.5 mg once-daily as the selected Phase 3 dose can be made in light of low and high EC_{50} values. If the high EC_{50} subgroup is a spurious finding [given the lack of plausible explanation], then a lower dose of 1 mg once daily can also achieve the desired target engagement. On the other hand, if there truly exists a subgroup with the high EC_{50} and that this subgroup cannot be identified prior to treatment, the selected dose of 2.5 mg once day is not optimal. As the target engagement is not achieved until 4 weeks post-dosing, a regimen with loading dose would be more appropriate in this scenario.

Hence, based on the applicant's choice of defined target engagement for vorapaxar, a 2.5 mg once-daily dose may not be optimal. As stated earlier, the relationship between TRAP-induced platelet aggregation and clinical outcomes is not known. Also, based on the results of the phase 2 study, there was no dose response for bleeding risk at 0.5 mg, 1 mg or 2.5 mg doses, when administered concomitantly with aspirin and clopidogrel.

2.3.2. What are the characteristics of the exposure-response relationship for efficacy?

No PK sampling was included in the pivotal study. Therefore, it was not possible to estimate individual patient-level vorapaxar exposure to allow for a direct evaluation of exposure-response relationships for the primary efficacy endpoint [composite of cardiovascular death, MI, stroke, and UCR]. The applicant conducted an exploratory exposure-efficacy analysis based on population PK model-predicted average exposure data for subgroups of patients. No obvious exposure-efficacy relationship was identified. The reviewer agrees with the limitations of this

analysis outlined by the applicant, i.e., the lack of individual exposure and the assumption of balanced distribution of other risk factors among the subgroups. This highlights the fact that the population PK model from Phase 1 and 2 studies cannot entirely alleviate the need for sparse PK sample collection in Phase 3, for the evaluation of exposure-response relationship.

2.3.3. What are the characteristics of the exposure-response relationship for safety?

The applicant conducted an exploratory exposure-bleeding analysis based on a similar approach described under [Q. 2.3.2]. An upward trend was observed in the overall population, suggesting higher bleeding risk was associated with higher drug exposure. Despite the limitations of this analysis as outlined by the applicant [the lack of individual exposure and the assumption of balanced distribution of other risk factors among the subgroups], such a relationship is considered reasonable and is consistent with other drugs with similar mechanism of action. This relationship may be partially responsible for the observed higher risk of bleeding in the subgroup of patients with body weight < 60 kg [HR = 1.87 in patients with body weight < 60 kg versus 1.48 in patients with body weight ≥ 60kg, ITT population] because higher drug exposure was observed in patients with lower body weight.

2.3.4. Does this drug prolong the QT or QTc interval?

No, vorapaxar does not appear to prolong QTc interval. Please refer to the QT-IRT review [DARRTS date: 11/29/2010].

2.4. Pharmacokinetics

2.4.1. What are the single- and multiple-dose PK parameters?

The pharmacokinetics of vorapaxar was evaluated following a single dose range of 0.25 to 120 mg as well as following once daily repeat administration of 1 to 5 mg up to 28 days in healthy volunteers. Upon oral administration, the median T_{max} of vorapaxar was 1 to 2 h. This was followed by a relatively faster distribution and a slow terminal elimination phase. The mean apparent clearance [CL/F] and volume of distribution [V_d/F] of vorapaxar is 2.2 L/h [CV%=32] and 634 L [CV%=43], respectively. The mean terminal elimination half-life of vorapaxar is about 7 to 11 days across Phase 1 studies. However, based on the accumulation ratios at steady state which ranged from 4.7 to 6.4, the effective half-life can be estimated to be about 3 to 4 days. Upon once-daily dosing, steady state exposures of vorapaxar are achieved by day 21 [earliest available PK].

Pharmacokinetics of M20 was evaluated following a single dose of 120 mg and repeat doses of 2.5 mg vorapaxar sulfate [once-daily, 42 days]. The median time to reach peak concentration was 4 h post-dose with the elimination phase of the concentration-time course mirroring that of the parent drug, vorapaxar [Fig. 3]. This suggests that M20 is a formation rate-limited metabolite, where the rate of elimination of the metabolite is faster than the rate at which it is formed. Across Phase 1 studies where M20 was quantified, the exposure to M20 was in the range of 8% to 29% to that of vorapaxar.

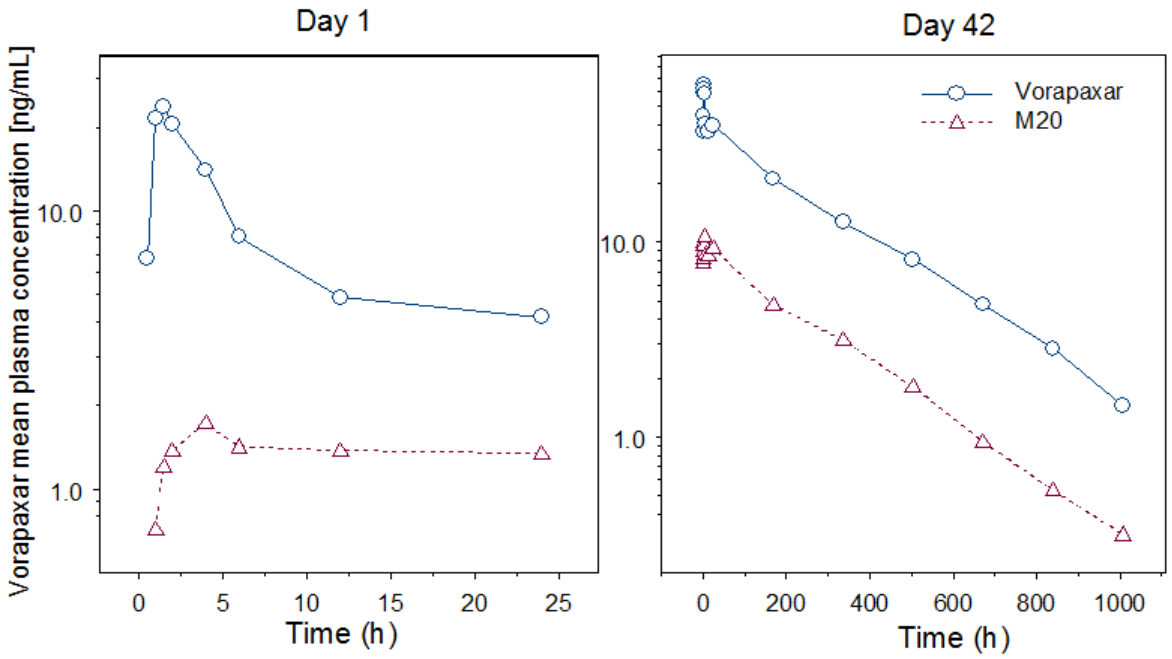


Figure 3: Plot of vorapaxar and M20 plasma concentration-time profile following repeat doses of 2.5 mg vorapaxar sulfate on day 1 and day 42

2.4.2. How does the PK in healthy volunteers compare to that in patients?

A population PK analyses was conducted to evaluate the influence of disease on the PK of vorapaxar. The results show that there is a 9% reduction in bioavailability and 82% increase in Vc/F in patients relative to healthy subjects. This translated to a 14% decrease in steady state exposures to vorapaxar [$AUC_{0-\tau}$], which may not be clinically meaningful [Fig. 4].

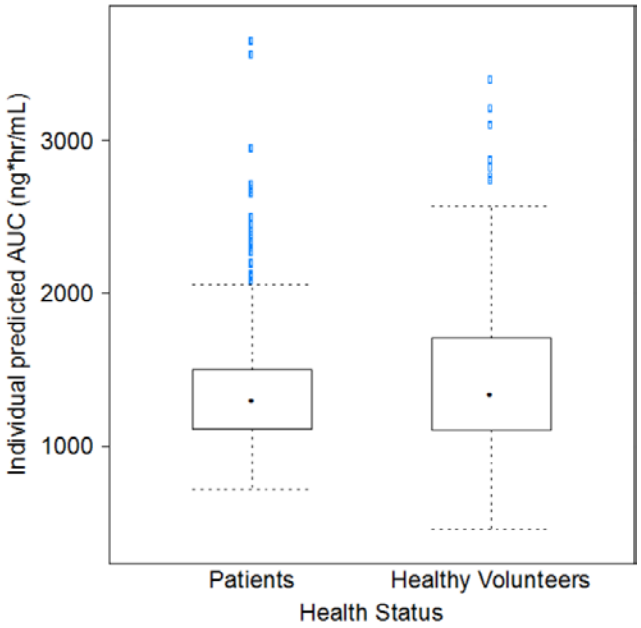


Figure 4: Box-plot of individual vorapaxar exposure [$AUC_{0-\tau}$] determined using population PK model in healthy volunteers versus patients

[Source: Figure 16 on page 59 of applicant's Summary of Clinical Pharmacology Studies]

2.4.3. What are the characteristics of drug absorption?

The absolute oral bioavailability of vorapaxar evaluated using a microdosing technique is ~ 100%. Co-administration with a high fat meal, or an antacid, or a proton pump inhibitor, has a modest impact on the rate of absorption of vorapaxar, but does not significantly alter the extent of absorption [Table 3].

Table 3: Impact of a high fat meal, an antacid and proton pump inhibitor on the PK measures of vorapaxar

	C_{max}	$AUC_{0\text{-}72\ h}$	T_{max}
Standardized high fat meal	↓21%	↓3%	delayed by 45 min
20 mL Gaviscon®	↓38%	↓11%[a]	delayed by 60 min
40 mg Pantoprazole[b]	↓15%	↓10%	No change

[a] $AUC_{0\text{-}t}$

[b] 7 day pretreatment with pantoprazole before vorapaxar administration

2.4.4. What are the characteristics of drug distribution?

Vorapaxar is widely distributed with a volume of distribution of 379 L. The protein binding [predominantly to serum albumin] of vorapaxar and M20 as determined using equilibrium dialysis is high [≥ 99%]. The binding of vorapaxar to plasma proteins is not concentration dependent in the range 40 to 10,000 ng/mL. The mean blood-to-plasma ratio of vorapaxar is 0.60, indicating limited partitioning into red blood cells.

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

Vorapaxar is eliminated mainly by metabolism followed by excretion in urine and feces. Following oral administration of ^{14}C-vorapaxar sulfate solution, only 39.2% [35% in feces, 4.2% in urine] of the administered dose was recovered in 7 days. Metabolite profiling showed that vorapaxar and M20 are the primary circulating moieties in plasma. Vorapaxar was not detected unchanged in urine in the 7 day collection period, suggesting that renal clearance of vorapaxar is low. Vorapaxar appears to be extensively metabolized followed by excretion of vorapaxar [minor, < 2%] and the metabolites [major] predominantly in feces [Table 4]. When the radioactivity recovery period was extended to 6 weeks, 83.5% [58.4% in feces, 25.1% in urine] of administered dose was recovered, however, metabolite profiling was not performed in this study [P07045].

Table 4: LC-MS/FSA[3] characterized drug derived material in 0-168 h post-dose pooled urine and 0-168 h, days 13-14 and 20-21 post-dose pooled feces following a single dose of 9.3 mg (100 µCi) ^{14}C-vorapaxar sulfate administered as oral solution

Metabolite label	Metabolite name	m/z	% dose in urine	% dose in feces
NA	Unknown	--	0.11	--
M8	Monohydroxy-vorapaxar-gluc	685[a]	0.42	ND
M10	Monohydroxy-vorapaxar-gluc	685[a]	0.31	ND
M13	Monohydroxy-vorapaxar-sulfate	589[b]	0.11	ND
M14	Monohydroxy-vorapaxar-sulfate	589[b]	0.05	ND
M15	Monohydroxy-vorapaxar	509	0.21	ND
M16	Carboxylic acid metabolite	523	0.41	2.30
M17	M+34	527	1.40	0.87
M17a	Dihydroxy-vorapaxar	525[c]	ND	0.88
M17b/c	Dihydroxy-vorapaxar	525[c]	ND	2.30
NA	Unknown	--	--	1.08
NA	Unknown	--	--	1.15
M19	Amine metabolite	421	1.21	18.4
M19a	Monohydroxy-vorapaxar	509[d]	ND	3.51
M20	Monohydroxy-vorapaxar	509[d]	ND	0.68
M20b	Monohydroxy-vorapaxar	509[d]	ND	2.44
M21	Monohydroxy-vorapaxar	509[d]	ND	6.96
Parent	Vorapaxar	493	ND	1.59
Cumulative recovery (% of dose)			**4.23**	**42.2**

ND Not detected
[a] Retention times for M8 and M10 are 18.4 and 18.9 min, respectively
[b] Retention times for M13 and M14 are 21.6 and 22.7, respectively
[c] Retention times for M17a and M17b/c are 24.0 and 26.2 min, respectively
[d] Retention times for M19a, M20, M20b and M21 are 30.0, 30.7, 31.5 and 31.9 min, respectively

2.4.6. What are the characteristics of drug metabolism?

Vorapaxar is extensively metabolized by the liver. The major route of metabolism is carbamate hydrolysis leading to the amine metabolite [M19], the predominant metabolite [44%] in excreta. In addition, vorapaxar undergoes oxidation at one or more sites resulting in numerous monohydroxy [M15, M19a, M20, M20b, M21] and dihydroxy [M17a/b/c] metabolites as shown

[3] Flow Scintillation Analysis

in Figure 5. Monohydroxy metabolites are also excreted as glucuronide [M8, M10] or sulfate [M13, M14] conjugates. All characterized human metabolites were also observed in the preclinical species used in toxicity and carcinogenicity studies.

The role of various cytochrome [CYP] P450 enzymes in the biotransformation of vorapaxar was studied *in vitro*. CYP3A4 and CYP2J2 are the predominant enzymes involved in the formation of M19 and M20.

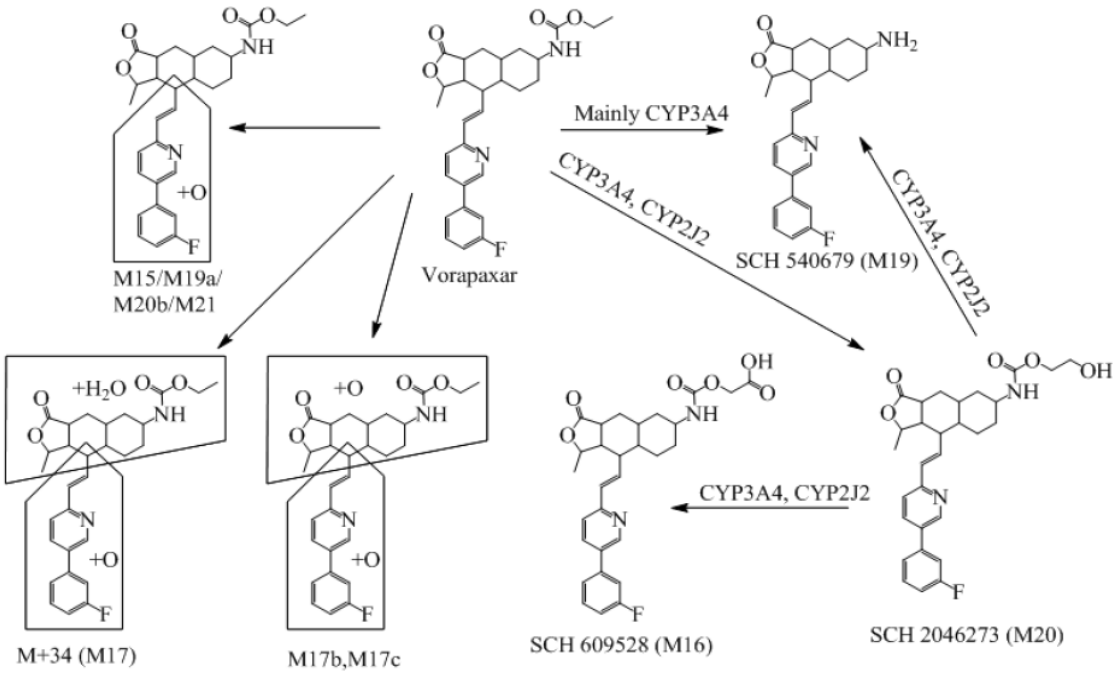


Figure 5: Proposed in vitro and in vivo biotransformation pathway for vorapaxar. Boxed region represent probable region of metabolism.

[Source: Figure 1 on page 19 of applicant's Summary of Clinical Pharmacology Studies]

2.4.7. What are the characteristics of drug elimination?

Vorapaxar is eliminated mainly by metabolism followed by excretion in urine and feces. Based on the mass balance study [P03454], a small fraction [< 2%] of vorapaxar as unchanged drug is excreted in feces [Table 4].

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

The PK measures of vorapaxar in the dose range 2.5 mg to 40 mg are dose-related with a slight less than-proportional increase in exposure.

2.4.9. What is the inter- and intra-subject variability of PK parameters in healthy volunteers and patients, and what are the major causes of variability?

The between subject variability in the PK measures i.e., C_{max} and $AUC_{0-\tau}$ as observed across individual Phase 1 healthy volunteer studies is in the range of 15% to 40% for vorapaxar and 30% to 50% for M20, expressed as percent coefficient of variation. The between subject variability in the PK parameters of vorapaxar i.e., CL/F, Vc/F and Vp/F based on the final population PK model is 30%, 45% and 42%, respectively. Based on the results of a bioequivalence study [P06558] which employed a crossover design, the within subject variability of vorapaxar is estimated to be 6% and 14% for AUC_{0-72h} and C_{max}, respectively.

2.5. Pharmacodynamics

2.5.1. What are the PD characteristics of the drug?

Inhibition of platelet aggregation induced by 15 µM TRAP was the primary pharmacodynamic measure in the vorapaxar development program. Vorapaxar was shown not to inhibit platelet aggregation in response to adenosine diphosphate [ADP]. The PD characteristics of vorapaxar were evaluated in a dedicated study following repeat doses of 1, 3 and 5 mg once-daily for 28 days. A dose dependent inhibition in platelet aggregation was observed at 24 hours following the first dose. The 3 mg dose group showed 70 to 80% platelet inhibition by 24 h post-dose [Fig. 6]. On the next available sampling time point i.e., day 7, all the dose groups including 1 mg showed <10% platelet aggregation relative to baseline and continued at maximal inhibition through vorapaxar dosing period. Based on this data, following 2.5 mg once-daily, >90% inhibition of platelet aggregation can be expected 48 hours after the start of the treatment.

Relative to the onset of pharmacodynamic effect, complete recovery of the platelet function upon drug discontinuation takes a long time. In the same study [P03450], after 28 days of stopping treatment, complete recovery of platelet function was not achieved in any of the dose groups by week 4. The mean % platelet aggregation relative to baseline was 84%, 43% and 4% for the dose groups 1, 3 and 5 mg, respectively at week 4 post-drug discontinuation [Fig. 6]. It took about 6 weeks for 90% of the subjects to recover to at least 50% platelet function at baseline for the 3 mg dose group and ~9 weeks for the 5 mg dose group.

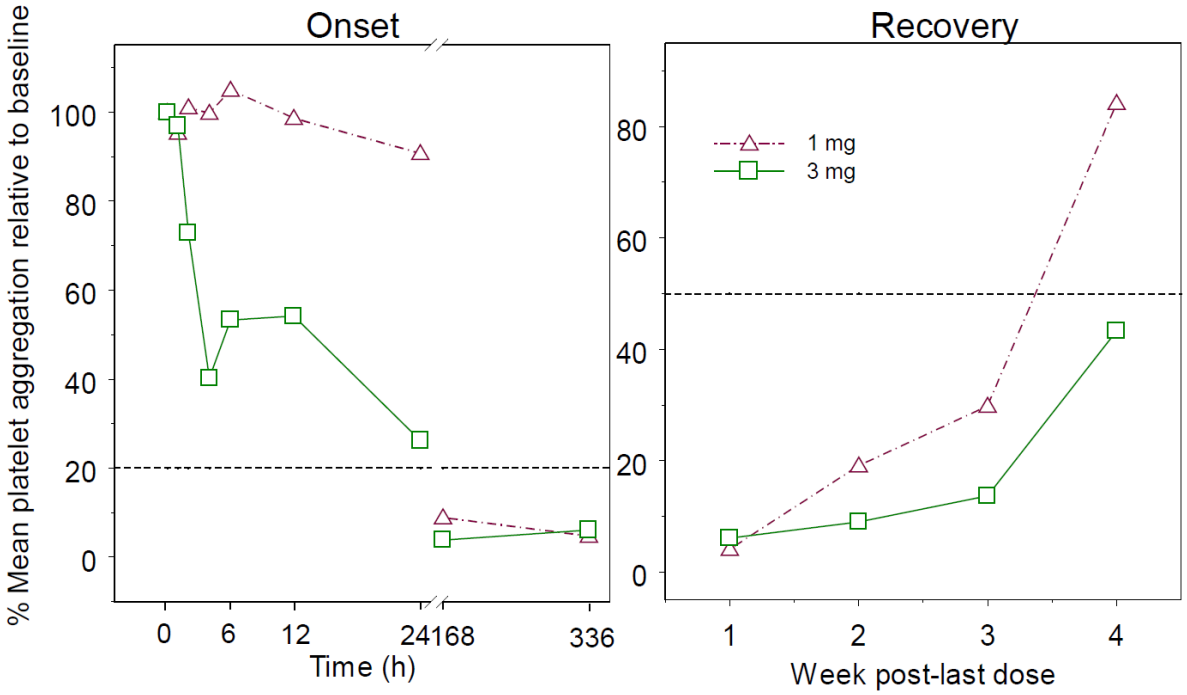


Figure 6: Onset and offset of pharmacodynamic effect following repeat doses of 1 and 3 mg vorapaxar sulfate [once-daily, 28 days] in healthy volunteers

2.6. Intrinsic Factors

2.6.1. What intrinsic factors influence exposure and/or response, and what is the impact of any differences in exposure on efficacy or safety responses?

Vorapaxar is extensively metabolized, thus suggesting that impairment in hepatic function might impact the pharmacokinetics of vorapaxar.

Hepatic impairment: The effect of hepatic impairment on the PK of vorapaxar was assessed following administration of a single dose of 40 mg vorapaxar sulfate in subjects with mild [Child-Pugh A], moderate [Child-Pugh B] and severe [Child-Pugh C] hepatic impairment versus matched healthy volunteers. The results appeared to show a trend towards lower systemic exposures with increasing severity of hepatic impairment [Fig. 7]. The modest decrease in extent of absorption is driven by decrease in peak concentration, while the elimination half-life was similar [data not shown]. The pharmacokinetics of M20 was not affected by impairment in hepatic function. The metabolite-to-parent ratio across all groups of hepatic impairment and the matched healthy volunteers was similar [19 to 26%]. Pharmacodynamics or protein binding was not measured in this study.

One subject from the severe hepatic impairment group experienced severe gastrointestinal hemorrhage secondary to esophageal varices, which was considered a serious adverse event with possible relationship to vorapaxar administration. Patients with severe hepatic impairment are

predisposed at a higher risk for bleeding events due to reduced synthesis of coagulation proteins. In the phase 3 program, patients with clinically significant hepatobiliary disease or an ALT/AST > 3 times ULN were excluded. Hence, use of vorapaxar should be avoided in patients with severe impairment of hepatic function.

Renal impairment: As the expectation for renal impairment to have a significant impact on the pharmacokinetics of vorapaxar was negligible, the applicant conducted a reduced design study in subjects with end stage renal disease [ESRD] requiring hemodialysis versus matched normal renal function subjects. The results show that the pharmacokinetics of vorapaxar is similar between ESRD and matched normal renal function subjects [Fig. 7]. The PK/PD relationship in ESRD subjects relative to matched normal renal function group could not be characterized as the data were limited.

Population PK analyses showed that creatinine clearance [CrCl] was a significant predictor of vorapaxar CL/F. The estimated increase in systemic exposure to vorapaxar is 17% and 34% for mild and moderate renal impairment groups, respectively. However, the mass balance study indicates minimal excretion via renal route. Hence, this finding may be confounded with body weight, as subjects with impaired renal function usually have lower body weights. A subgroup analysis from TRA2°P - TIMI 50 for GUSTO severe or moderate bleeding events in subjects with CrCl < 60 mL/min [N=1510] when compared to CrCl ≥ 60 mL/min [N=15131] did not show any increase in bleeding risk. Integrating all these results, a dose-adjustment in patients with impairment of renal function is not required.

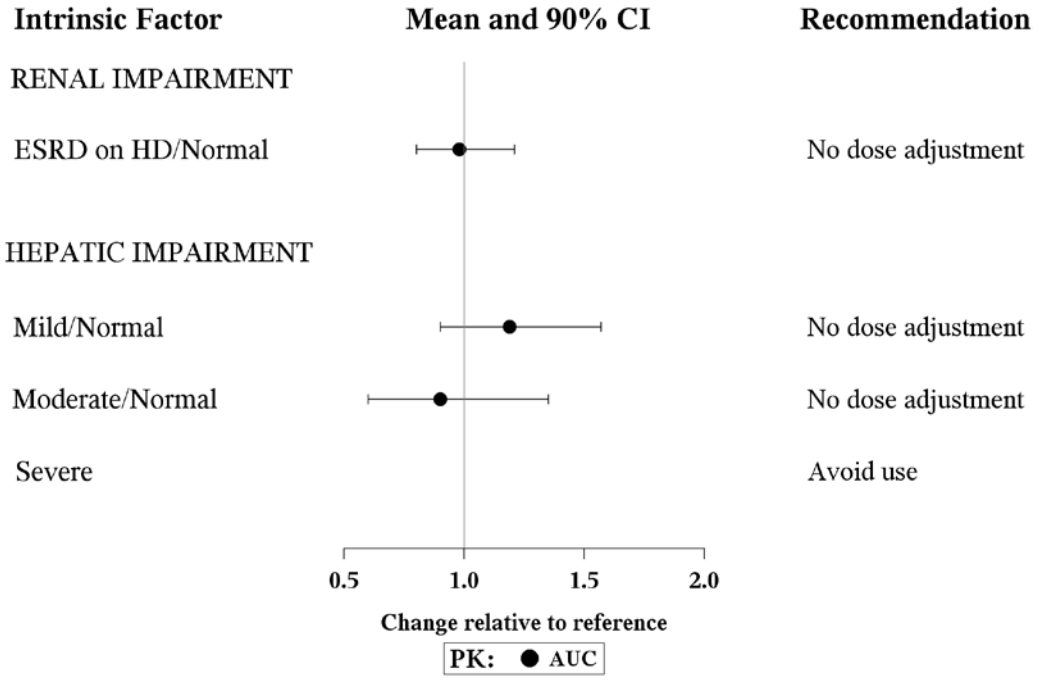


Figure 7: Impact of renal and hepatic impairment on the PK measures of vorapaxar

Age, Gender, Race:

The applicant conducted a population PK study that characterized the PK profile of vorapaxar in healthy volunteers and patients. Effect of covariates such as health status [healthy versus patients], body weight, age, sex, race, and creatinine clearance on key PK parameters was also explored [Fig. 8].

Results demonstrated that health status [healthy versus patients], gender, race and renal function had modest effects on vorapaxar exposure. But due to the high correlation among these demographic covariates, body weight may be the underlying driver for other covariates. Low body weight [< 60 kg] and high body weight [> 100 kg] patients have 33% [90% CI: 28% - 38%] higher and 19% [90% CI: 16% - 22%] lower steady state AUC, respectively, than typical patients weighing 60 to 100 kg. Since females and Asians tend to have lower body weight compared to male and White patients, exposures in females were estimated to be 32% [90% CI: 26% - 40%] higher than those in male patients and exposures were estimated to be 22% [90% CI: 16% - 30%] higher in Asian patients and 19% [90% CI: 13% - 24%] lower in Black patients relative to exposures in White patients. Patients were estimated to have 14% [90% CI: 10% - 17%] lower steady state AUC compared to healthy volunteers. Except body weight [which is discussed further] no other covariates require dose-adjustments.

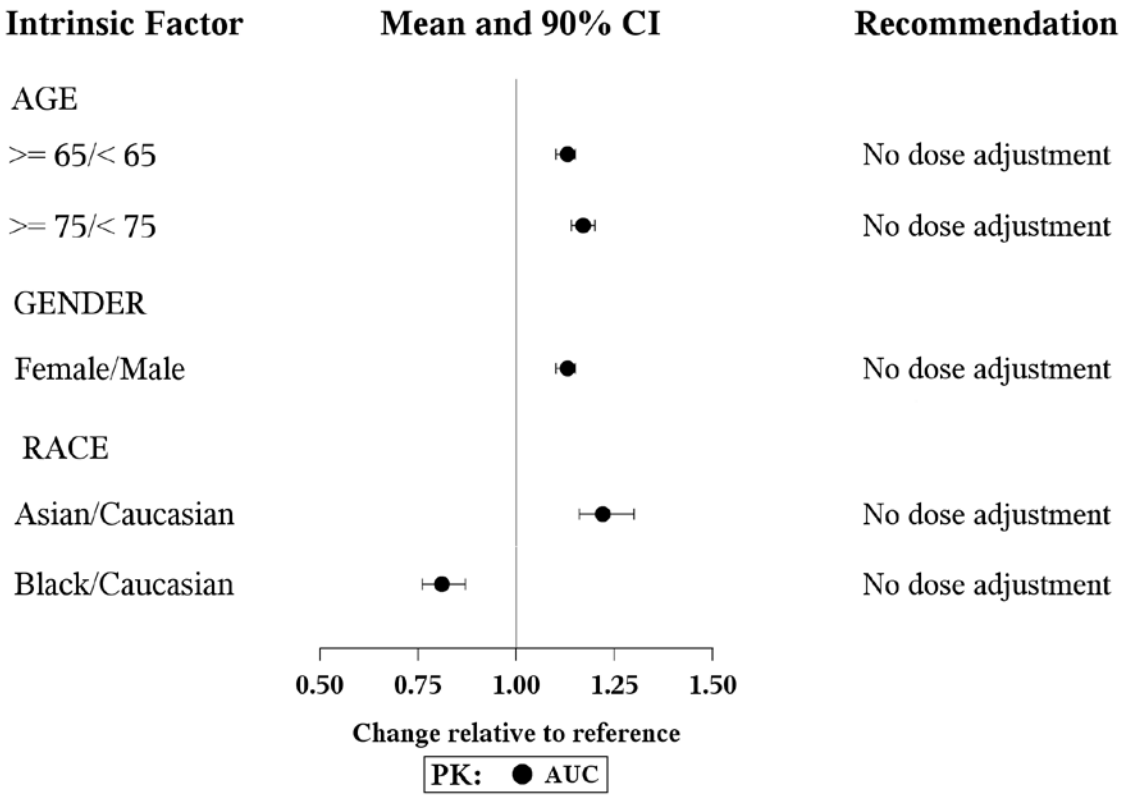


Figure 8: Impact of intrinsic factors on the PK measures of vorapaxar estimated using population PK model

Body weight:

The increased drug exposure in lighter patients and the exposure-bleeding relationship provided a clear pharmacological justification to look into the safety subgroup analysis based on body weight. A subgroup analysis of the overall population from TRA2°P - TIMI 50 for GUSTO severe or moderate bleeding events showed that the hazard ratio between vorapaxar and placebo was 1.87 [95% CI: 1.19-2.94] in patients with body weight < 60 kg while it was estimated to be 1.48 [95% CI: 1.28-1.73] in patients with body weight ≥ 60 kg patients. The larger point estimate of HR for the lighter patients suggested that the increased bleeding risk of vorapaxar relative to placebo was even higher [87%] in lighter patients when the hazard of bleeding was already 48% higher for vorapaxar relative to placebo in heavier patients.

Individual steady state AUC was calculated based on the population PK model for vorapaxar. The median steady state AUC of vorapaxar in patients with body weight < 60 kg was 48% higher than that in patients with body weight ≥ 60 kg. In addition, the lighter patients included more elderly and female patients [Table 5]. Therefore, higher vorapaxar exposure, older age, and higher percentage of female patients all contributed to the higher bleeding risk of vorapaxar relative to placebo in patients with body weight < 60 kg. Exclusion of patients with prior history of stroke/TIA reduced the percentage of patients with body weight < 60 kg [Table 5]. However, the higher bleeding risk in patients with body weight < 60 kg was still evident as indicated by the HR of 1.78 [95% CI: 0.85-3.74] for GUSTO severe or moderate bleeding events even within the proposed label population. The wide confidence interval was due to the small sample size in this subgroup [N=857]. The median steady state AUC of vorapaxar in patients with body weight < 60 kg was 49% higher than that in patients with body weight ≥ 60 kg in the proposed label population.

Table 5: The distribution of elderly and female patients in weight based subgroups: overall and proposed label population

Weight Group [kg]	**Age > 65**		**Age > 75**		**Female**		**Overall**	
	Plc	Vor	Plc	Vor	Plc	Vor	Plc	Vor
	Overall population							
<60	53%	56%	23%	24%	68%	68%	7%	7%
≥60	36%	37%	11%	10%	21%	21%	93%	93%
	Proposed label population							
<60	40%	46%	15%	16%	68%	66%	5%	5%
≥60	28%	29%	7%	7%	17%	18%	95%	95%

Plc = Placebo; Vor = Vorapaxar

Given the increased risk of bleeding in patients with body weight < 60 kg, a reasonable benefit on the efficacy endpoint should be demonstrated to justify the increased bleeding risk from a risk/benefit perspective. However, the weight based subgroup analysis for the efficacy endpoint showed that vorapaxar was almost statistically worse than placebo with a HR of 1.28 [95% CI: 0.95-1.73] in the overall population.

To explore whether the results for the weight based subgroup analyses were due to chance, a resampling procedure was used to randomly select 1852 patients from the overall population of

26449 [ITT population] with a randomization allocation of 1:1 between placebo and vorapaxar arms [926 per arm]. The hazard ratio of the randomly selected subgroups [vorapaxar relative to placebo] was calculated. Such a procedure was repeated 100,000 times to evaluate the chance of estimating a hazard ratio of 1.28 or larger when the hazard ratio was 0.88 between the two arms in the overall population. The random chance of generating a subgroup [N=1852] with a hazard ratio of 1.28 or larger was estimated to be 0.0057, suggesting the results for the weight based subgroup analyses were unlikely due to random chance.

The applicant's supplementary secondary analysis for efficacy [Table 6] showed that the numerically worse efficacy result for vorapaxar was mainly driven by hemorrhagic stroke with 10 events [1.1%] in vorapaxar arm and 1 event [0.1%] in placebo arm. This observation is consistent with the increased bleeding risk in this subgroup. Exclusion of patients with prior history of stroke/TIA mitigated the body weight effect to a certain degree as demonstrated by a HR of 1.07 [95% CI: 0.69-1.66] for patients with body weight < 60 kg in the proposed label population [Table 7]. However, the point estimate still suggested a numerically worse efficacy for vorapaxar compared to placebo.

Table 6: Applicant's supplementary secondary analysis: Primary and key secondary composite efficacy endpoints in subjects with body weight < 60 kg: ITT Population [Event Accrual Period: Randomization to Last Visit]

	Placebo (n =921)		Vorapaxar (n =931)		
Endpoint & Contributing Component	Subjects With Events (%)	KM%[c]	Subjects With Events (%)	KM%[c]	Hazard Ratio[a,b] (95% CI)
Primary Efficacy Endpoint	75 (8.1%)	9.6%	96 (10.3%)	13.6%	1.28 (0.95 – 1.73)
CV Death	16 (1.7%)		16 (1.7%)		
MI	24 (2.6%)		35 (3.8%)		
Stroke	25 (2.7%)		29 (3.1%)		
Ischemic (Non-hemorrhagic CI)	23 (2.5%)		16 (1.7%)		
Hemorrhagic Stroke	1 (0.11%)		10 (1.1%)		
UCR	10 (1.1%)		16 (1.7%)		
Key Secondary Efficacy Endpoint	65 (7.1%)	8.4%	80 (8.6%)	11.5%	1.22 (0.88 – 1.69)
CV Death	16 (1.7%)		16 (1.7%)		
MI	24 (2.6%)		35 (3.8%)		
Stroke	25 (2.7%)		29 (3.1%)		
Ischemic (Non-hemorrhagic CI)	23 (2.5%)		16 (1.7%)		
Hemorrhagic Stroke	1 (0.1%)		10 (1.1%)		
Uncertain	1 (0.1%)		3 (0.3%)		

a: Kaplan-Meier estimate at 1080 days.
b: Hazard Ratio (HR) is vorapaxar group versus placebo group.
c: HR was calculated based on Cox PH model with covariates treatment and stratification factors (planned thienopyridine use).
d: Each subject was counted only once (first event) in the summary that contributed to primary or key secondary efficacy endpoint.
e: Hemorrhagic stroke includes primary intracerebral hemorrhage, non-hemorrhagic infarction with hemorrhagic conversion and subarachnoid hemorrhage.

Table 7: Applicant's supplementary secondary analysis: Primary and key secondary composite efficacy endpoints in subjects with no history of stroke or TIA whose qualifying condition was CAD with body weight < 60 kg: ITT Population [Event Accrual Period: Randomization to Last Visit]

Endpoint and Contributing Component	Placebo (n =429)		Vorapaxar (n =432)		Hazard Ratio[b,c] (95% CI)
	Subjects With Events (%)	KM%[a]	Subjects With Events (%)	KM%[a]	
Primary Efficacy Endpoint[d]	38 (8.9%)	10.0%	41 (9.5%)	11.5%	1.07 (0.69 – 1.66)
CV Death	4 (0.9%)		7 (1.6%)		
MI	20 (4.7%)		20 (4.6%)		
Stroke	5 (1.2%)		4 (0.9%)		
Ischemic (Non-hemorrhagic Cerebral Infarction)	5 (1.2%)		2 (0.5%)		
Hemorrhagic Stroke	0		2 (0.5%)		
UCR	9 (2.1%)		10 (2.3%)		
Key Secondary Efficacy Endpoint	29 (6.8%)	7.9%	31 (7.2%)	8.9%	1.06 (0.64 – 1.76)
CV Death	4 (0.9%)		7 (1.6%)		
MI	20 (4.7%)		20 (4.6%)		
Stroke	5 (1.2%)		4 (0.9%)		
Ischemic (Non-hemorrhagic Cerebral Infarction)	5 (1.2%)		2 (0.5%)		
Hemorrhagic Stroke[e]	0		2 (0.5%)		

a: Kaplan-Meier estimate at 1080 days.
b: Hazard Ratio is vorapaxar group versus placebo group.
c: HR was calculated based on Cox PH model with covariates treatment and stratification factors (planned thienopyridine use).
d: Each subject was counted only once (first component event) in the summary that contributed to the primary or key secondary efficacy endpoint.
e: Hemorrhagic stroke includes primary intracerebral hemorrhage, non-hemorrhagic infarction with hemorrhagic conversion and subarachnoid hemorrhage.

Similar resampling analysis was repeated for the proposed label population [N=16897]. The random chance of generating a subgroup [N=861] with a hazard ratio of 1.07 or larger was estimated to be 0.114. Given the increased bleeding risk in this subgroup, the efficacy result for this subgroup cannot justify the risk/benefit balance. The lack of clear efficacy in the non-bleeding related components of the efficacy endpoint [Table 7] in this subgroup also precludes the dose reduction strategy.

The applicant's rationale to use 60 kg as the cutoff was based on precedent set by product labeling for other anti-platelet agents. Further analyses were conducted to explore different cutoff values. Figure 9 shows that 60 kg is a reasonable choice to identify a subgroup with no clear benefit on the efficacy endpoint.

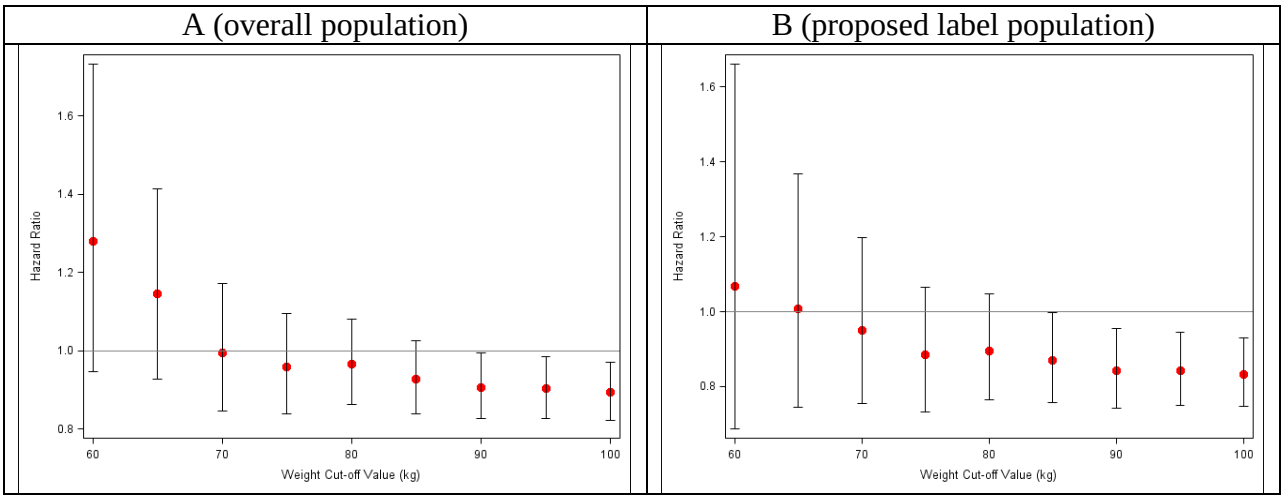


Figure 9: Hazard ratio of efficacy endpoint between vorapaxar and placebo for a subgroup based on different body weight cutoff values. Each dot represents the hazard ratio for subgroup of patients with body weight < cut-off value [error bars represent the 95% CI]

Prior stroke was considered the most important risk factor for intracranial hemorrhage by the data safety monitoring board [DSMB] and was the first exclusion criterion applied by the applicant to limit the patient population to achieve a favorable risk/benefit balance. However, the body weight based subgroup analyses suggested that the similar risk/benefit could be achieved by excluding patients with body weight < 60 kg [Table 8].

Table 8: Comparison of efficacy and safety results based on two different subgroups

Endpoint	**Subgroup**	**Hazard Ratio [95% CI]**	**Total sample size**
Efficacy	Post MI and ≥60 kg	0.82 [0.74-0.90]	16836
	Post MI and no prior stroke/TIA	0.82 [0.74-0.90]	16897
GUSTO severe or moderate bleeding	Post MI and ≥60 kg	1.45 [1.18-1.77]	16795
	Post MI and no prior stroke/TIA	1.48 [1.21-1.82]	16856

Further, within the post MI patient population with body weight ≥ 60 kg, patients with prior stroke showed numerically better efficacy between vorapaxar and placebo compared to patients without prior stroke [Table 9]. Despite the small sample size [N=543] in patients with prior stroke, the 95% CI of HR excluded 1, suggesting that vorapaxar showed statistically better efficacy than placebo in this subgroup. On the contrary, the prior TIA subgroup tends to numerically favor the control arm.

Table 9: The impact of prior stroke, prior TIA on efficacy within patients with post MI and body weight ≥ 60 kg

Population	Hazard Ratio [95% CI]	Total sample size
With prior stroke*	0.66 [0.46-0.96]	543
With prior TIA*	1.56 [0.97-2.5]	357
Without prior stroke or prior TIA	0.80 [0.73-0.89]	16012

* 77 patients had both prior stroke and TIA

The relative risk for GUSTO severe or moderate bleeding events in the prior stroke subgroup was 0.96 [95% CI: 0.42-2.17], indicating that the benefit-risk of vorapaxar in this subgroup is maintained [Table 10].

Table 10: The impact of prior stroke, prior TIA on GUSTO severe or moderate bleeding events within patients with post MI and body weight >=60 kg

Population	Hazard Ratio [95% CI]	Total sample size
With prior stroke*	0.96 [0.42-2.17]	540
With prior TIA*	1.79 [0.66-4.83]	354
Without prior stroke or prior TIA	1.46 [1.18-1.81]	15977

* 77 patients had both prior stroke and TIA

Similar body weight effect can also be observed in the TRACER trial [Table 11].

Table 11: The impact of body weight on efficacy and safety in TRACER trial

Endpoint	Subgroup	Hazard Ratio [95% CI]	Total sample size
Efficacy	<60 kg	1.07 [0.80-1.42]	987
	≥60 kg	0.91 [0.83-1.00]	11898
GUSTO severe or moderate bleeding	<60 kg	1.64 [1.06-2.54]	982
	≥60 kg	1.34 [1.16-1.56]	11856

Based on these analyses, vorapaxar should be avoided in patients with body weight < 60 kg.

2.7. Extrinsic Factors

2.7.1. Is there an in vitro basis to suspect in vivo drug-drug interactions?

CYP3A4 is involved in the metabolism of vorapaxar to M19 and M20. Hence, *in vivo* studies with ketoconazole [strong CYP3A inhibitor] and rifampin [potent CYP3A inducer] were conducted.

In vivo drug interaction studies with warfarin and rosiglitazone were performed as vorapaxar showed a very modest potential to inhibit CYP2C8 [IC_{50}=1.5 µM] and 2C9 [IC_{50}=~30 µM] *in vitro*. The inhibition potential towards other CYP enzymes [2A6, 2C19, 2D6] is minimal as shown by IC_{50} values ≥ 30 µM. Vorapaxar and M20 did not demonstrate time-dependent inhibition of CYP enzymes nor CYP-induction potential at clinically relevant concentrations.

Vorapaxar is not a substrate of P-glycoprotein [P-gp], but inhibited the transport of digoxin with an IC_{50} of 1.2 µM. The steady-state peak plasma concentration following a one daily administration of 2.5 mg vorapaxar sulfate is 0.11 µM. This suggests that vorapaxar can possibly act as a P-gp inhibitor at the intestinal level, but not systemically. An *in vivo* drug interaction study with digoxin was conducted to validate the *in vitro* findings.

The potential for vorapaxar being a substrate for OATP1B1, OATP1B3, BCRP, OAT1, OAT3 and OCT2 has not been evaluated. However, given the absence or very minimal renal and biliary component in the clearance of vorapaxar, the potential for vorapaxar being a substrate is low. Vorapaxar and M20 were also not potent inhibitors of these transporters and the interaction liability is minimal.

2.7.2. What are the drug-drug interactions?

The applicant conducted 5 *in vivo* drug interaction studies to evaluate the impact of CYP3A modulators [ketoconazole, rifampin] on the pharmacokinetics of vorapaxar and the effect of vorapaxar on other concomitantly administered drugs [digoxin, warfarin, rosiglitazone, prasugrel].

Impact of CYP3A modulators on vorapaxar PK

The effect of 400 mg once-daily ketoconazole [strong CYP3A, weak CYP2J2, P-gp inhibitor] on vorapaxar following first dose [20 mg, day 7] and at steady state [2.5 mg once-daily, day 28] was evaluated. Following the first dose of co-administration of vorapaxar with ketoconazole, there was no change in C_{max}, but, a modest 20% increase in $AUC_{0-\tau}$ of vorapaxar. However, upon repeat administration of both vorapaxar and ketoconazole, there was a 2-fold increase in C_{max} and $AUC_{0-\tau}$ as observed on day 28 [Fig. 10]. The effect of ketoconazole is consistent for a victim drug with long half-life as observed by a marginal increase in exposure following the first dose and significant increase in exposure at steady state. The plasma concentrations of M20 were not measured in this study.

Upon concomitant administration of 600 mg once-daily rifampin [strong CYP3A inducer], there was no change in exposures following the first dose of vorapaxar. However, a 39% and 55% decrease in C_{max} and $AUC_{0-\tau}$, respectively at steady state were observed [Fig. 10]. The efficacy or bleeding risk for a change in exposure of this magnitude [2-fold increase or 55% decrease] is not known due to the absence of concentration-outcome relationship. Therefore, avoid use of vorapaxar with strong inhibitors or inducers of CYP3A.

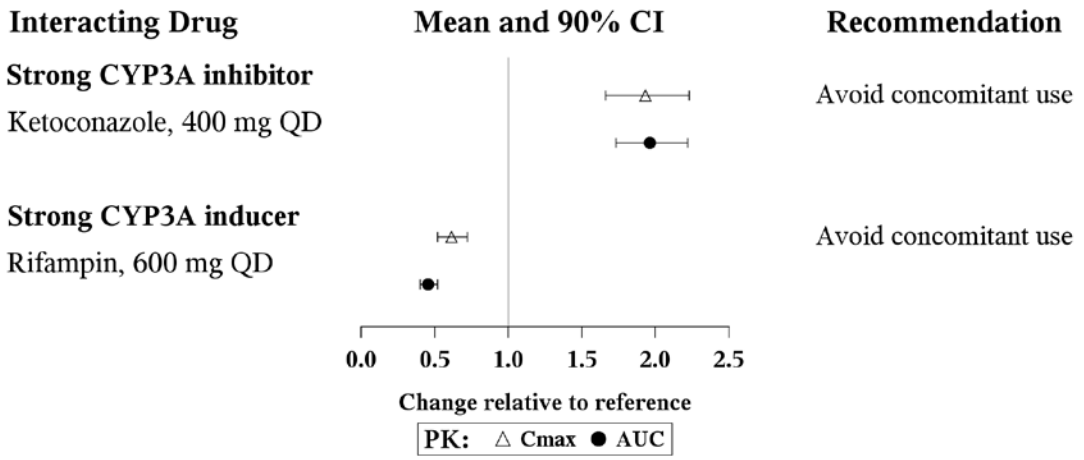


Figure 10: Impact of ketoconazole and rifampin on the PK measures of vorapaxar at steady state [day 21]

There was no dedicated drug interaction study performed to evaluate the impact of mild or moderate CYP3A inhibitors on the pharmacokinetics of vorapaxar. However, in TRA2°P - TIMI 50, 57% of the patients were on mild or moderate CYP3A inhibitors for a period of at least 7 days. An analysis of bleeding endpoints stratified by use of CYP3A inhibitors shows no increase in bleeding events [data not shown]. Hence, co-administration of vorapaxar with mild or moderate CYP3A inhibitors does not require dose-adjustments.

Impact of vorapaxar on other co-administered drugs

Digoxin: Upon administration of 2.5 mg vorapaxar sulfate on days 1 to 6 and co-administration of digoxin 0.5 mg with vorapaxar sulfate 40 mg on day 7, showed that the C_{max} of digoxin increased by 50% with no change in AUC_{0-t}. Hence, the potential for vorapaxar at clinically relevant dose of 2.5 mg to interact with digoxin or other P-gp substrates is expected to be lower.

Warfarin, Rosiglitazone and Prasugrel: Dedicated *in vivo* interaction studies show that vorapaxar does not alter the pharmacokinetics or pharmacodynamics of warfarin and rosiglitazone. There was no pharmacokinetic interaction between prasugrel and vorapaxar. The pharmacodynamic interaction potential was not assessed in this study. Though we know that vorapaxar does not affect platelet aggregation induced by ADP, this study would have informed if prasugrel affected platelet aggregation induced by TRAP.

2.7.3. What extrinsic factors influence exposure and/or response, and what is the impact of any differences in exposure on efficacy or safety responses?

Other extrinsic factors that may affect the systemic exposures to vorapaxar are (i) a high fat meal, (ii) co-administration with an antacid, and (iii) co-administration with a proton pump inhibitor. The impact of these factors has been addressed in response to Q. 2.4.3 and Q. 2.8.3.

2.8. General Biopharmaceutics

2.8.1. Based on the biopharmaceutics classification system (BCS) principles, in what class is this drug and formulation? What solubility, permeability, and dissolution data support this classification?

Vorapaxar is a BCS class II drug [low solubility, high permeability]. Refer to Table 1 for solubility values across a range of pH medium. Permeability of vorapaxar is high, as exhibited by an apparent permeability [P_{app}] of 3 x 10^{-5} cm/s across Caco-2 cell monolayers.

2.8.2. What is the relative bioavailability of the to-be-marketed formulation with Phase 3 trial formulation?

Vorapaxar sulfate salt converts partially to the amorphous free base upon manufacturing and storage. The phase 3 trial had batches with varying salt content ranging from 23% to 46% free base. A pivotal bioequivalence study was performed by the applicant to compare the bioavailability of low base lot [23%] and high base lot [46%]. This study was performed by co-administering vorapaxar with a proton pump inhibitor [7 day pretreatment with 40 mg pantoprazole], so as to maximize the ability to detect differences in bioavailability between the two products. The results show that the rate and extent of absorption of vorapaxar was bioequivalent between the products with 23% and 46% free base [Fig. 11].

The to-be-marketed formulation of vorapaxar sulfate is compositionally identical [base content range] to the formulation used in Phase 3 trial with changes only to colorants [blue or white to yellow] and shape [round to oval]. These changes were bridged using dissolution data and did not require an in vivo evaluation of product performance.

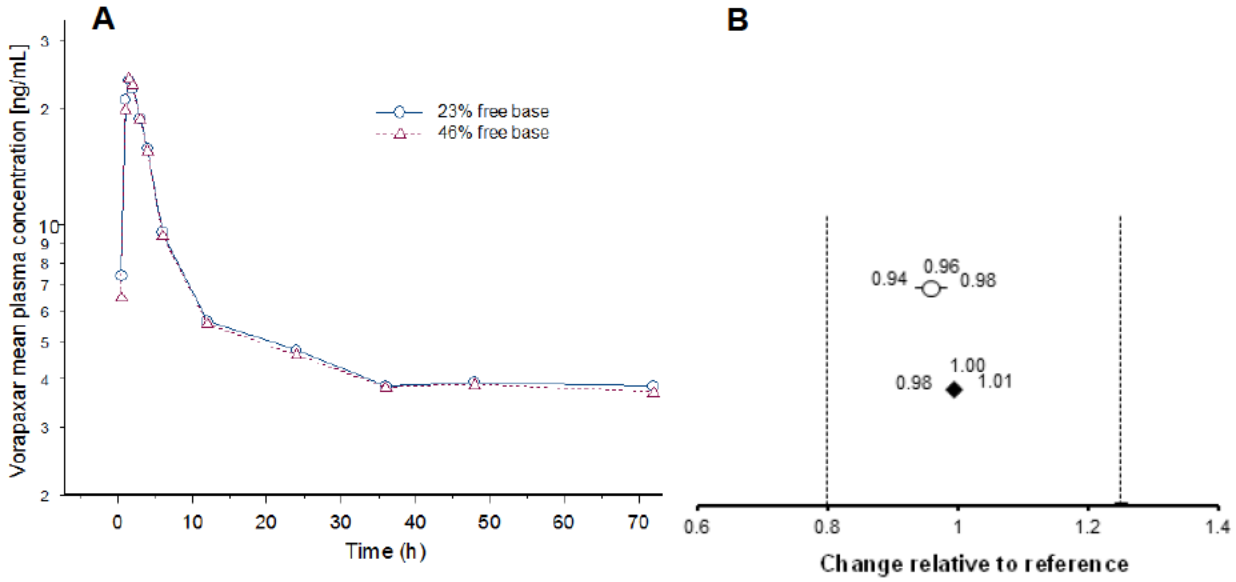


Figure 11: [A] Mean vorapaxar plasma concentration-time profile following single dose of 2.5 mg vorapaxar sulfate containing 23% and 46% free base content. [B] Impact of 46% free base vorapaxar sulfate on PK measures when compared with 23% free base product.

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

The effect of food on the pharmacokinetics of vorapaxar was evaluated in four studies – P03445, P03448 [pilot] and P03447, P07969 [definitive]. To directly support the present application, the effect of a standardized high fat breakfast on the pharmacokinetics of vorapaxar following 2.5 mg registration dose was evaluated. The results show that a high fat meal decreased mean peak concentration by 21%, delayed time to peak concentration by 45 min, but, did not affect the extent of absorption [AUC_{0-t}] to vorapaxar [Fig. 12]. The phase 3 registration trial [TRA°2P TIMI], which demonstrated efficacy and safety of vorapaxar was performed by administering vorapaxar sulfate without regards to meals.

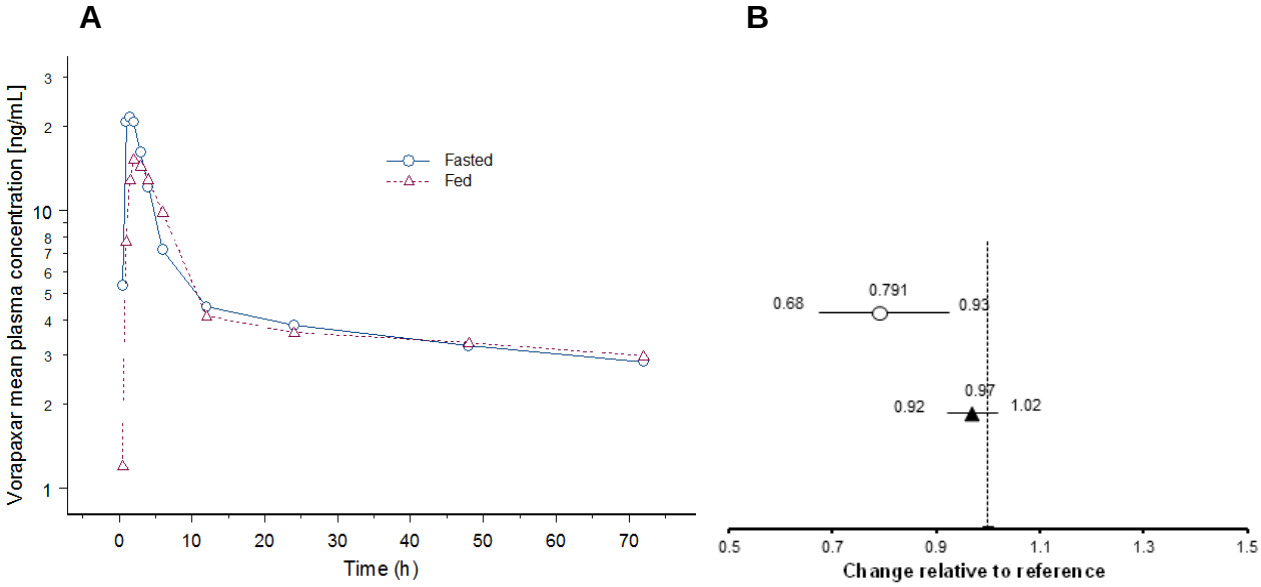


Figure 12: [A] Mean vorapaxar plasma concentration-time profile following single dose of 2.5 mg vorapaxar sulfate in fed and fasted states. [B] Impact of a high fat meal on PK measures of vorapaxar compared to fasted state.

2.9. Bioanalytical Method

Plasma concentrations of vorapaxar and M20 were quantified using validated UPLC-MS/MS methods. Standard curves were constructed in the range of 0.1 to 50 ng/mL or 1 to 1000 ng/mL [vorapaxar] and 0.5 to 500 ng/mL [M20]. The accuracy and precision values of at least two-thirds of the overall quality control [QC] samples from all supporting bio-analytical reports were equal to or better than 15% [20% at the LLOQ]. All the supporting bio-analytical methods [inclusive of HPLC-accelerator mass spectrometry (AMS) method for quantification of radiolabeled vorapaxar concentration in plasma and that of co-administered drugs used in DDI studies] satisfy the criteria for 'method validation' and 'application to routine analysis' set by the 'Guidance for Industry: Bioanalytical Method Development', and is acceptable [Table 12].

Table 12: Summary of bioanalytical methods

Report	**Range [ng/mL]**	**Accuracy**	**Precision**
LC-MS/MS - Vorapaxar			
SN03176	0.1 to 50	1.1 to 6.0	0.9 to 10.8
DM27304	1 to 1000	-14.8 to 3.6	5.7 to 12.7
DM27721	0.834 to 1000	-2.3 to 0.4	3.0 to 10.5
DM11003	1 to 1000	-1.8 to 1.8	3.1 to 7.9
LC-MS/MS – M20			
DM27721	0.5 to 500	-4.5 to -0.8	5.0 to 11.9
AMS - Vorapaxar			
P1180	0.011 to 3.92	-7.3 to 3.1	3.1 to 4.6

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/s/

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12/16/2013

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CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA/BLA Number	204886	**Brand Name**	ZONTIVITY
OCP Division (I, II, III, IV, V)	I	**Generic Name**	Vorapaxar sulfate
Medical Division	DCRP	**Drug Class**	Protease Activated Receptor-1 (PAR-1) antagonist
OCP Reviewer(s)	Sudharshan Hariharan	**Indication(s)**	Reduction in atherothrombotic events in patients with a history of myocardial infarction (MI)
OCP Team Leader	Raj Madabushi	**Dosage Form/Strength**	IR tablets/2.5 mg
Pharmacometrics Reviewer	Fang Li	**Dosing Regimen**	Once daily
Date of Submission	05/10/2013	**Route of Administration**	Oral
Estimated Due Date of OCP Review	12/10/2013	**Sponsor**	Merck Sharp & Dohme Corp.
AC Meeting	Yes, dates TBD	**Priority Classification**	Standard
PDUFA Due Date	05/10/2014		

Clin. Pharm. and Biopharm. 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**			
I. Clinical Pharmacology				
Mass balance:	**X**	**1**	**1**	
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	**X**	**1**	**1**	
multiple dose:	**X**	**2**	**2**	
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:	**X**	**2**	**2**	
In-vivo effects of primary drug:	**X**	**3**	**3**	**PK & PD**
In-vitro:	**X**	**9**	**9**	
Subpopulation studies -				
ethnicity:	**X**	**2**	**1**	**PK & PD**

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS
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gender:				
pediatrics:				
geriatrics:				
renal impairment:	**X**	**1**	**1**	**PK & PD**
hepatic impairment:	**X**	**1**	**1**	
PD -				
Phase 2:				
Phase 3:				
PK/PD -				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Pop PK	**X**	**1**	**1**	**PM consult**
Pop PK/PD	**X**	**1**	**1**	**PM consult**
II. Biopharmaceutics				
Absolute bioavailability	**X**	**1**	**1**	**Microdosing**
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:	**X**	**2**	**0**	
Bioequivalence studies -				
traditional design; single / multi dose:	**X**	**1**	**1**	
replicate design; single / multi dose:				
Food-drug interaction studies	**X**	**2**	**1**	
Bio-waiver request based on BCS				
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies				
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		**30**	**26**	**In vitro studies: 9** **In vivo studies: 15** **PM consult: 2**

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			
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?	X			
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	X			

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS
FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

	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?			X	
	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?	X			
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?	X			
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	

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?

YES

Sudharshan Hariharan 06/12/2013
Reviewing Clinical Pharmacologist Date

Raj Madabushi 06/12/2013
Team Leader/Supervisor Date

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SUDHARSHAN HARIHARAN
06/14/2013

RAJANIKANTH MADABUSHI
06/17/2013