

The high, intermediate and low conversion tablets were found to be bioequivalent in healthy volunteers pre-treated with 30 mg lansoprazole. This difference in plasma levels translated into differences in mean platelet aggregation which potentially can be clinically significant.

Table TACS.7.1. Summary of Geometric Mean (CV%) Pharmacokinetic Parameter Estimates of R-138727 for the Low, Intermediate, and High Extents of Conversion of Prasugrel.HCl after a 60-mg Dose of Prasugrel on a Background of 30-mg Lansoprazole Once-Daily

Parameter	Geometric Mean (%CV)		
	60-mg prasugrel ^a L-C (N=35)	60-mg prasugrel M-C (N=36)	60-mg prasugrel H-C (N=36)
C _{max} (ng/mL)	327 (67)	299 (61)	235 (51)
t _{max} ^a (h)	0.75 (0.25-3.00)	0.75 (0.50-3.00)	0.89 (0.50-2.00)
AUC(0-t _{last}) (ng•h/mL)	465 (42)	468 (42)	406 (40)

Abbreviations: CV - coefficient of variation; AUC(0-t_{last}) - area under the plasma concentration-time curve from time zero through the sampling time of the last quantifiable concentration; C_{max} - maximum observed plasma concentration; N = Number of subjects; t_{max} - time of C_{max}.

^a Median (range)

Table TACS.7.2. Statistical Comparison of the Relative Bioavailability of R-138727 Between the Low, Intermediate, and High Extents of Conversion of Prasugrel.HCl after a 60-mg Dose of Prasugrel on a Background of 30-mg Lansoprazole Once-Daily (L-C as Reference)

Parameter (units)	Geometric LS means (90% CI)			Ratio of geometric LS means (90% CI)		
	60-mg prasugrel L-C	60-mg prasugrel M-C	60-mg prasugrel H-C	M-C/ L-C	H-C/ L-C	H-C/ M-C
AUC(0-t _{last}) (ng•h/mL)	470 (424, 522)	467 (421, 518)	409 (368, 454)	0.99 (0.93, 1.06)	0.87 (0.82, 0.93)	0.88 (0.82, 0.93)
C _{max} (ng/mL)	331 (285, 384)	297 (257, 344)	236 (204, 274)	0.90 (0.77, 1.04)	0.71 (0.62, 0.83)	0.80 (0.69, 0.92)

Model: Log(PK) = SUBJECT(SEQUENCE) + TREATMENT + PERIOD + SEQUENCE + RANDOM ERROR

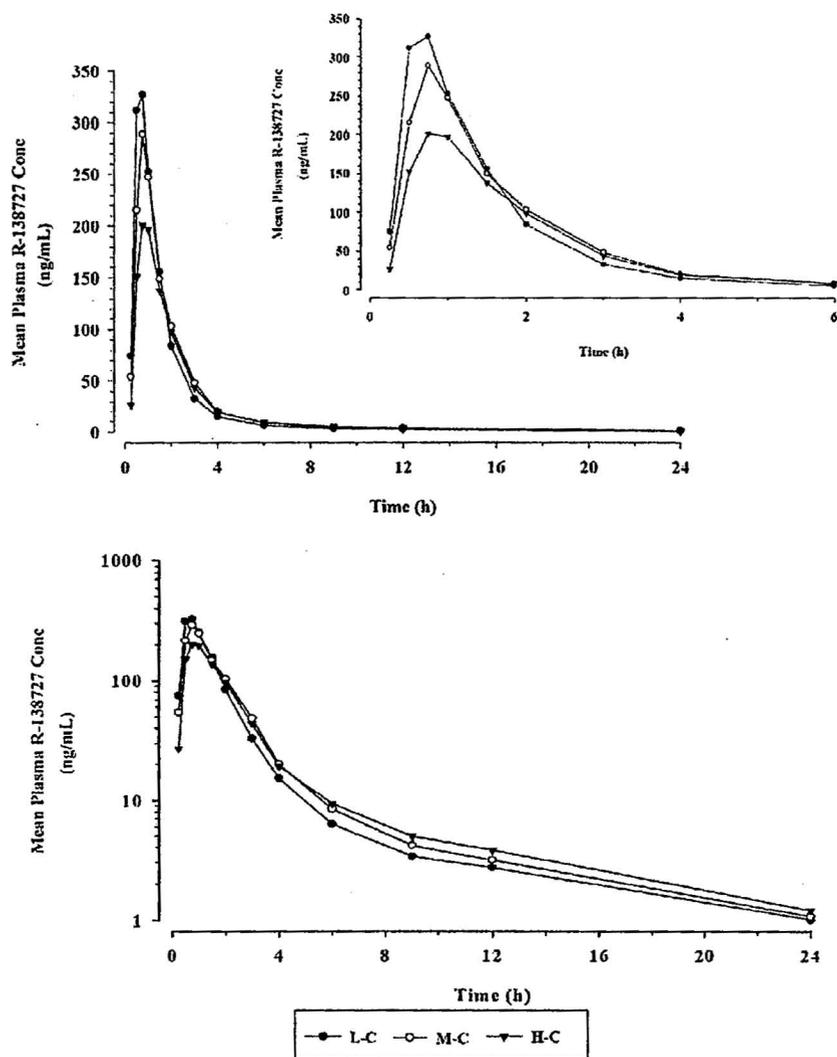
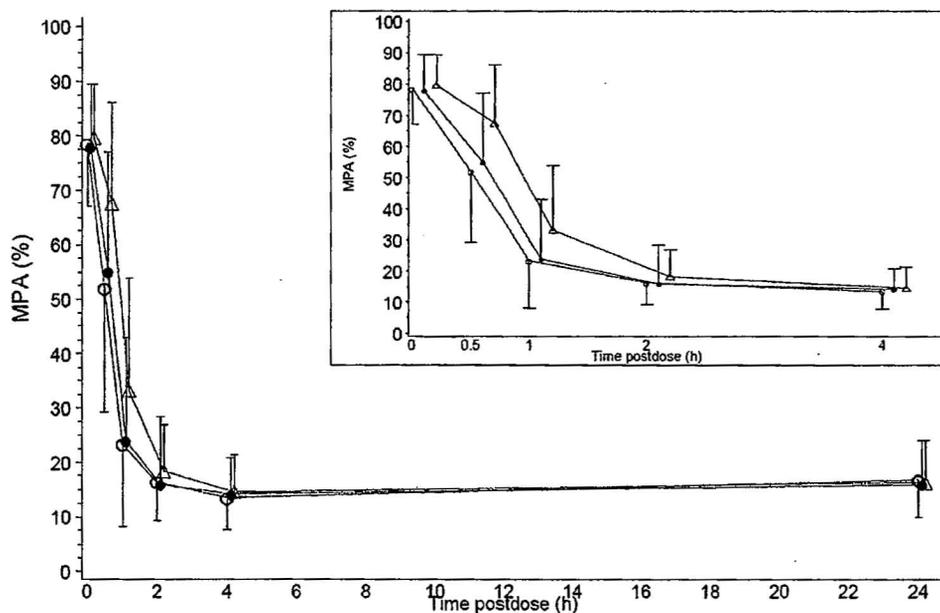


Figure TACS.7.1. Arithmetic mean plasma concentration-time profiles of R-138727 following a 60-mg dose of prasugrel containing a low (L-C), intermediate (M-C), or high (H-C) extent of conversion of prasugrel.HCl to prasugrel base, on a background of 30-mg lansoprazole once-daily (upper panel linear; lower panel log-linear).



○ = L-C (Low extent of conversion of prasugrel HCl)
 ● = M-C (Intermediate extent of conversion of prasugrel HCl)
 △ = H-C (High extent of conversion of prasugrel HCl)

T + or - Standard Deviation

Table TACS.7.5. Statistical Comparison of MPA to 20 μM ADP Following a 60-mg Dose of Prasugrel Containing Low, Intermediate, or High Extents of Conversion of Prasugrel.HCl, on a Background of 30-mg Lansoprazole Once-Daily

Time	LS means MPA (90% CI)			Difference of LS means (90% CI) [p-value]		
	L-C	M-C	H-C	(M-C) - (L-C)	(H-C) - (L-C)	(H-C) - (M-C)
Predose ^a	79.0 (76.0, 82.0)	77.7 (74.8, 80.7)	79.9 (77.0, 82.9)	-1.3 (-4.7, 2.2) [0.539]	0.9 (-2.6, 4.4) [0.662]	2.2 (-1.3, 5.7) [0.294]
0.5 h	51.0 (47.1, 54.8)	55.0 (51.2, 58.7)	67.0 (63.2, 70.8)	4.0 (-0.7, 8.7) [0.165]	16.0 (11.3, 20.8) [<0.001]	12.0 (7.4, 16.7) [<0.001]
1 h	22.8 (18.9, 26.6)	24.1 (20.3, 27.9)	32.6 (28.8, 36.4)	1.3 (-3.4, 6.1) [0.645]	9.8 (5.1, 14.5) [<0.001]	8.5 (3.8, 13.2) [0.003]
2 h	15.9 (12.1, 19.7)	15.9 (12.0, 19.7)	17.9 (14.1, 21.6)	0.0 (-4.8, 4.7) [0.993]	2.0 (-2.8, 6.7) [0.495]	2.0 (-2.7, 6.7) [0.489]
4 h	13.1 (9.3, 17.0)	14.2 (10.4, 18.0)	14.1 (10.3, 17.9)	1.1 (-3.6, 5.8) [0.710]	1.0 (-3.7, 5.7) [0.735]	-0.1 (-4.8, 4.6) [0.973]
24 h	16.3 (12.5, 20.2)	16.1 (12.2, 19.9)	15.8 (12.0, 19.6)	-0.3 (-5.0, 4.5) [0.927]	-0.5 (-5.2, 4.2) [0.852]	-0.3 (-5.0, 4.4) [0.925]

^a Model: MPA = Subject + Treatment + Random Error

Model: MPA = MPA at Day 1, Predose + SUBJECT + SUBJECT*TIME + SUBJECT*TREATMENT + TREATMENT + TIME + TREATMENT*TIME + RANDOM ERROR

5.1.3 The effect of Active Pharmaceutical Ingredient Surface Area on the Relative Bioavailability of a 60 mg Prasugrel Loading Dose in Healthy Subjects Taking a Proton Pump Inhibitor

Technical Report no: H7T-EW-TACK.

Investigator and site:

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Study Objectives:

To assess the effect of active pharmaceutical ingredient surface area on the pharmacokinetics of prasugrel's active metabolite in healthy subjects taking lansoprazole 30 mg once daily. The secondary objective was to assess the safety and tolerability of prasugrel in healthy subjects taking a proton pump inhibitor.

Study Design:

This was a three treatment three period, open label, randomized crossover study. 34 subjects between the ages of 18 and 65 taking 30 mg lansoprazole received study treatment out of which 30 completed the study. 2 subjects were withdrawn after completion of the lansoprazole lead in phase and prior to the first dose of prasugrel and one subject was withdrawn after receiving the first dose of prasugrel. One further withdrawn subject was given lansoprazole doses although it was not known if these were administered and this subject did not receive prasugrel.

Prasugrel was administered orally as a single 60 mg dose provided as 10 mg tablets with high surface area.

Lansoprazole was administered orally as daily 30 mg doses provided as 30 mg capsules extent of conversion of prasugrel.HCl (5 %), intermediate (58 %) or high extent of conversion (70 %)

Subjects received each of the treatments with a washout period of at least 7 days between doses. Subjects had a 7 day lead in phase of once a day 30 mg lansoprazole before the first dose of prasugrel and continued taking lansoprazole until the last dose of prasugrel was given. Blood samples for the determination of plasma concentrations of prasugrel's active metabolite R-138727 were collected pre-dose and 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 9 12 and 24 hours post dose administration.

Test Drug:

10 mg high surface area prasugrel tablets batch # CT530045
10 mg medium surface area prasugrel tablets batch # CT53047
10 mg low surface area prasugrel tablets batch # CT530568
30 mg Prevacid capsules lot #478272E80.

Assay:

Plasma samples were analyzed for the determination of plasma concentrations of prasugrel's active metabolite at Advion Bioservices using a validated liquid chromatography with tandem mass spectrometric detection (LC/MS/MS).

The inter assay accuracy expressed as % relative error) ranged from 3 to 14.8 % and the inter assay precision (5 relative standard deviation was <2.8 %. Intra assay accuracy ranged from 1.9 % to 18.4 % and the intra assay precision was <2.6 %.

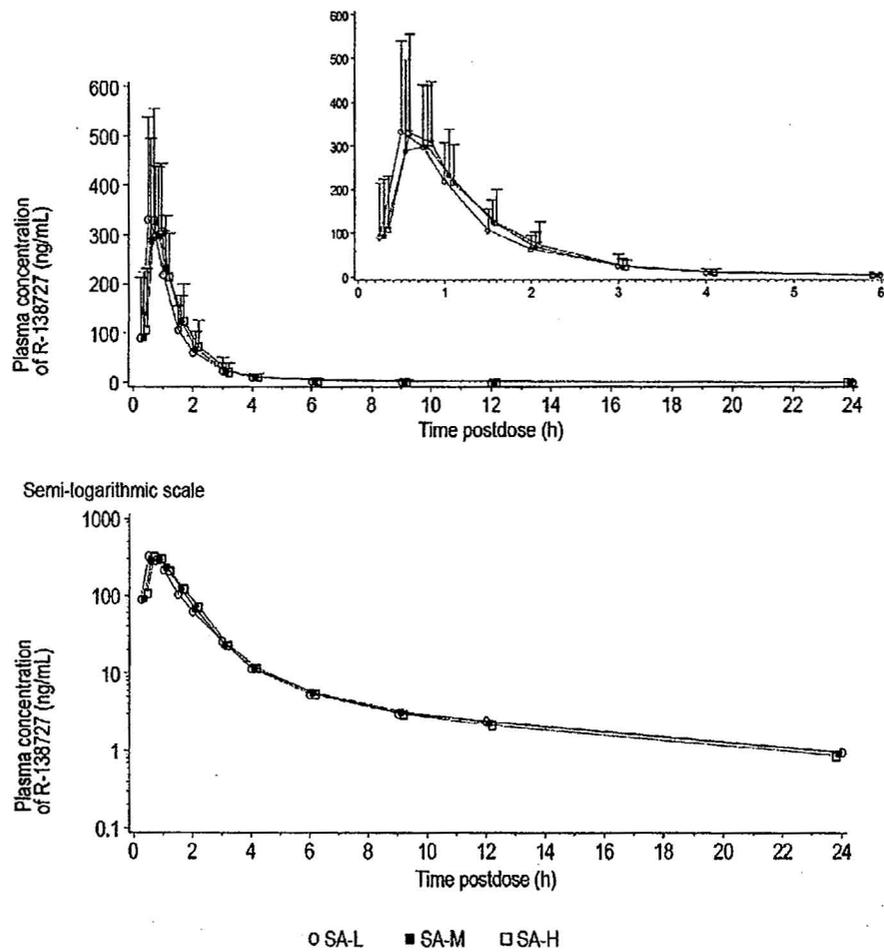
Data Analysis

Pharmacokinetic parameters were determined for R-138727 by non-compartmental techniques. The 90% confidence intervals were constructed by the two one-sided tests procedure to assess bioequivalence.

Results:

Figure 1 shows the plasma concentration time profiles while Table 1 gives the summary of the relevant PK parameters. Table 2 gives the statistical comparison for the relative bioavailability of the low, medium and high surface area tablets.

The results show that both the low and medium surface area tablets are not bioequivalent to the high surface area since the CMAX is outside slightly outside the 80 to 125 % 90 % confidence limits. In terms of exposure (AUC) both the low and medium surface area tablets are bioequivalent to the high surface area.



Error bars on Cartesian plot represent standard deviations

Figure TACK.7.1. Arithmetic mean plasma concentration-time profiles of R-138727 following the low (SA-L), medium (SA-M), and high (SA-H) API surface areas of 60-mg prasugrel on a background of 30-mg lansoprazole (upper panel linear; lower panel log-linear).

Table TACK.7.1. Summary of Geometric Mean (CV%) Pharmacokinetic Parameters of R-138727 for the Low (SA-L), Medium (SA-M), and High (SA-H) API Surface Areas of 60-mg Prasugrel on a Background of 30-mg Lansoprazole

Parameters	60 mg prasugrel	60 mg prasugrel	60 mg prasugrel
	SA-L (N=31)	SA-M (N=30)	SA-H (N=29)
AUC(0-t _{last}) (ng·h/mL)	425 (29.0)	426 (35.2)	420 ^b (31.1)
AUC(0-∞) (ng·h/mL)	442 ^b (29.1)	455 ^c (30.9)	445 ^d (27.8)
C _{max} (ng/mL)	336 (61.0)	328 (48.7)	348 (60.6)
t _{max} ^a (h)	0.517 (0.250-3.00)	0.750 (0.250-1.50)	0.750 (0.500-2.00)

N = Number of subjects

^a Median (range)

Table TACK.7.2. Statistical Comparison of Relative Bioavailability of R-138727 Between the Low (SA-L), Medium (SA-M), and High (SA-H) API Surface Areas of 60-mg Prasugrel on a Background of 30-mg Lansoprazole

Parameters (units)	Geometric LS means (90% CI)			Ratio of geometric LS means (90% CI)	
	60 mg prasugrel SA-L	60 mg prasugrel SA-M	60 mg prasugrel SA-H	SA-L/ SA-H	SA-M/ SA-H
AUC(0-t _{last}) (ng·h/mL)	425 (386, 467)	423 (384, 466)	425 (386, 469)	0.99 (0.91, 1.09)	0.99 (0.91, 1.08)
AUC(0-∞) (ng·h/mL)	442 (404, 484)	449 (410, 493)	451 (411, 494)	0.98 (0.91, 1.05)	0.99 (0.93, 1.06)
C _{max} (ng/mL)	334 (285, 390)	328 (280, 384)	350 (298, 411)	0.95 (0.79, 1.14)	0.93 (0.78, 1.12)

Model: Log(PK) = SUBJECT(SEQUENCE) + TREATMENT + PERIOD + SEQUENCE + RANDOM ERROR

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

The to-be-marketed formulation of prasugrel was used in the pivotal Study TAAL. In the submission, Table APP.2.7.1.4 lists the prasugrel formulations used in the clinical studies, including TAAL.

Table APP.2.7.1.1. Summary of Formulations Used in Clinical Studies

Formulation Used	Study Alias
Prasugrel base tablets	148-007, S001, S002, S003, S004, TAAA, TAAC, TAAD, TAAE, TAAF, TAAH
Commercial Tablet: Prasugrel.HCl tablets	TAAF, TAAI, TAAJ, TAAK, TAAL, TAAN, TAAO, TAAP, TAAQ, TAAR, TAAS, TAAT, TAAU, TAAV, TAAW, TAAX, TAAZ, TABF, TABL, TABM, TABN, TABR, TABS, TABV, TABW, TABX, TABZ, TACF, TACG, TACJ, TACK, TACR, TACS
Prasugrel.HCl tablets used in Japan studies	J101, J102, J103, J105, J106, J201
Radiolabeled Prasugrel base Solution	TAAB

6 APPENDIX IV: OCP Filing Review Form

Office of Clinical Pharmacology and Biopharmaceutics New Drug Application Filing and Review Form				
General Information About the Submission				
	Information		Information	
NDA Number	22-307	Brand Name	Effient	
OCPB Division (I, II, III)	DIV-1	Generic Name	Prasugrel	
Medical Division	CARDIORENAL	Drug Class	ADP receptor antagonist of the thienopyridine class	
OCPB Reviewer	ELENA MISHINA	Indication(s)	Reduction of atherothrombotic events and stent thrombosis in ACS patients with stable angina or NSTEMI	
OCPB Team Leader	P. Marroum	Dosage Form	Tablet, 5, and 10 mg	
		Dosing Regimen	Starting from _____	
Date of Submission	12/26/2007	Route of Administration	oral	
Estimated Due Date of OCPB Review		Sponsor	Eli Lilly	
PDUFA Due Date	6/26/2008	Priority Classification	P	
Division Due Date	5/26/2008			
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		
Isozyme characterization:	X	5		
Blood/plasma ratio:	X	1		
Plasma protein binding:	X	1		
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	X	1		
multiple dose:	X	9		
Patients-				
single dose:				
multiple dose:	X	5		
Dose proportionality -				
fasting / non-fasting single dose:	X	1		
fasting / non-fasting multiple dose:		1		
Drug-drug interaction studies -				
In-vivo effects on primary drug:	X	8		
In-vivo effects of primary drug:	X	6		
In-vitro:	X	7		
Subpopulation studies -				
ethnicity:		2		
gender:				
pediatrics:				
geriatrics:		1		
renal impairment:	X	2		
hepatic impairment:	X	3		
PD:				
Phase 2:				
Phase 3:	X	1		
PK/PD:				

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Phase 1 and/or 2, proof of concept:	X	3		
Phase 3 clinical trial:	X	1		
Population Analyses -				
Data rich:	X	2		
Data sparse:	X	1		
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:	X	4		
Bioequivalence studies -				
traditional design; single / multi dose:	X	3		
replicate design; single / multi dose:				
Food-drug interaction studies:	X	1		
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:	X	1		
Chronopharmacokinetics				
Pediatric development plan				
Literature References	X			
Electrophysiology Study				
Pharmacodynamic studies		19		
Total Number of Studies Reviewed		36		
Filability and QBR comments				
	"X" if yes	Comments		
Application filable ?	X			
Comments sent to firm ?				
QBR questions (key issues to be considered)				
Other comments or information not included above				
Primary reviewer Signature and Date				
Secondary reviewer Signature and Date				