

	and 3, and at 36 and 48 hours after the prasugrel dose on Day 6 for Period 3. PD, platelet aggregation: Induced by 5 and 20 $\mu$ M ADP were collected pre-dose and at 2, 4, and 24 hours post-dose on Days 1 and 6.
Assay	Plasma concentrations of bupropion, hydroxybupropion, and prasugrel metabolites, R-138727, R-95913, R-106583, R-119251 validated LC/MS/MS.
PK Assessment	$C_{max}$ (ng/mL), $T_{max}$ (hr), $AUC_{0-t}$ (ng·hr/mL), $AUC_{0-\infty}$ (ng·hr/mL) for bupropion, hydroxybupropion, and prasugrel metabolites, R-138727, R-95913, R-106583, R-119251. $CL_p/F$ (L/hr), $V_z/F$ (L) - (WinNonlin).
PD Assessment	Platelet aggregation: turbidometric method with 5 and 20 $\mu$ M ADP as the agonist.
Statistical methods	Log-transformed $AUC_{0-t}$ , $AUC_{0-\infty}$ and $C_{max}$ of all four prasugrel metabolites, and log-transformed $AUC(0-\infty)$ , $AUC(0-tlast)$ , and $C_{max}$ of bupropion and hydroxybupropion were analyzed using a linear mixed effect model. The 90% CI for the ratios of geometric means between treatments were calculated. A comparison of $T_{max}$ estimates between the treatments was performed using the Wilcoxon sign rank test. For CYP3A4 induction interaction; the test treatment was prasugrel + rifampicin and the reference treatment was prasugrel alone. For the CYP2B6 interaction, the test treatment was prasugrel + bupropion and the reference was bupropion alone. A linear mixed effect model was used to assess the effect of rifampicin on inhibition of platelet aggregation (IPA) and maximum platelet aggregation (MPA) to 5 and 20 $\mu$ M ADP.

## Results

### Demographics:

A total of 32 healthy male subjects, inclusive, participated in the study. 26 subjects were Caucasians, 2 afro-Caribbean and 4 mixed. The mean  $\pm$  SD age of the subjects was  $29 \pm 8.2$  years, height  $176 \pm 6.6$  cm, weight  $75.6 \pm 8.6$  kg and with BMI of  $24.3 \pm 2.1$  kg/m<sup>2</sup>.

### Assay:

Plasma concentrations of bupropion and hydroxybupropion, metabolites of prasugrel in samples from each subject were analyzed using LCMS/MS.

**Table 136 Method validation data using LCMS assay**

Parameter	R138727	
linearity	0.5 to 250 ng/ml	
	Intra-day	Inter-day
Precision (RSD)	0.4 to 2.6%	1.5 to 2.8%
Accuracy (RE)	1.9 to 18.4%	3.0 to 14.8%
LLOQ	0.5 ng/ml	
Parameter	R95913	
linearity	1.56 to 400 ng/ml	
	Intra-day	Inter-day
%CV	1.9 to 5.4%	2.4 to 8.1%
Accuracy (%)	-16.3 to 5.5%	-16.3 to 9.9%
LLOQ	1.56 ng/ml	

Parameter	R119251	
linearity	1 to 500 ng/ml	
	Intra-day	Inter-day
Precision (RSD)	1.4 to 4.6%	n/d
Accuracy (RE)	-10.3 to 1.3%	n/d
LLOQ	1 ng/ml	
Parameter	R106583	
linearity	1.56 to 400 ng/ml	
	Intra-day	Inter-day
%CV	4.4 to 5.0%	5.3 to 12.6%
Accuracy (%)	-8.4 to 17.3%	-19.8 to 17.3%
LLOQ	1.56 ng/ml	
Reviewer Comments	These assays characteristics and specificity are satisfactory, representative MS chromatograms are presented.	

Plasma concentrations of active and inactive metabolites of prasugrel and clopidogrel in samples from each subject were analyzed using LC/MS. Plasma SR26334 was analyzed using GC/MS. All the validations were conducted by selecting three nominal concentrations.

**Pharmacokinetics:**

**Bupropion pharmacokinetics in the presence and absence of prasugrel:**

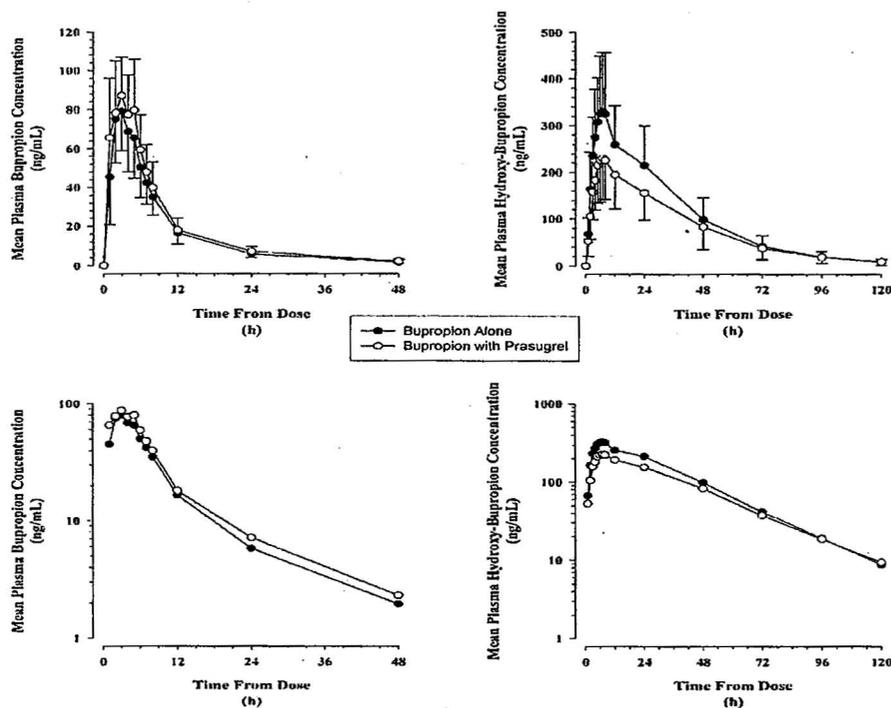


Figure 123 Plasma concentrations of bupropion and hydroxybupropion following a single 150-mg dose of bupropion alone or with prasugrel.

Figure 123 compares the plasma concentration vs time profiles of bupropion (parent drug) and hydroxybupropion (hydroxyl metabolite of bupropion) following single 150 mg dose of bupropion alone and with 10 mg daily prasugrel treatment at steady state. When administered with prasugrel, the exposure (AUC<sub>0-48</sub>) to bupropion was increased and the hydroxybupropion decreased in comparison with the same parameters obtained after the single oral dose of bupropion alone.

**Table 137 Noncompartmental Pharmacokinetic Parameter Estimates for Bupropion and Hydroxybupropion Following a Single 150-mg Dose of Bupropion Alone or with Prasugrel**

Parameter	Geometric Mean (%CV)			
	Bupropion		Hydroxybupropion	
	Bupropion alone (N=30)	Bupropion + Prasugrel (N=30)	Bupropion alone (N=30)	Bupropion + Prasugrel (N=30)
C <sub>max</sub> (ng/mL)	83.4 (25.6)	94.8 (24.4)	329 (33.5)	225 (34.4)
t <sub>max</sub> <sup>a</sup> (h)	3.00 (2.00-5.00)	3.00 (1.00-5.08)	6.51 (5.00-8.02)	7.01 (4.00-12.00)
AUC(0-t <sub>last</sub> ) (ng•h/mL)	726 (31.0)	856 (26.9)	11300 (36.1)	8580 (40.9)
AUC(0-∞) (ng•h/mL)	752 (30.4)	888 <sup>b</sup> (26.6)	11600 (36.5)	8870 (42.3)
CL <sub>r</sub> /F (L/h)	200 (30.4)	169 <sup>b</sup> (26.6)	-c	-c
V <sub>Z</sub> /F (L)	3420 (33.8)	3190 <sup>b</sup> (34.7)	-c	-c
t <sub>1/2</sub> (h)	11.9 (41.6)	13.1 <sup>b</sup> (31.8)	19.6 (18.9)	22.2 (22.3)

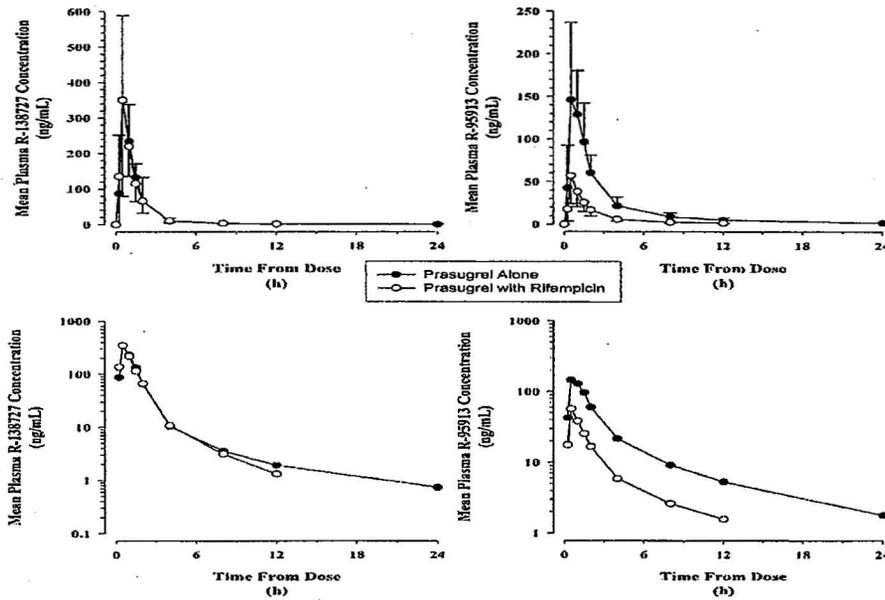
<sup>a</sup> t<sub>max</sub>: median (range); <sup>b</sup> N=29; <sup>c</sup> Parameter not estimated; CV: coefficient of variation

Table 137 compares the pharmacokinetic parameters of bupropion and its metabolite following a single 150 mg dose of bupropion in the presence and absence of prasugrel treatment. The hydroxybupropion C<sub>max</sub> occurred approximately 3.5 to 4 hours after bupropion C<sub>max</sub>. The C<sub>max</sub> and AUC<sub>0-48</sub> values of bupropion increased by 14% and 18% respectively when bupropion was co-administered with prasugrel. The C<sub>max</sub> and AUC<sub>0-120</sub> values of hydroxybupropion decreased by 32% and 24% respectively when bupropion was co-administered with prasugrel. The increase in the plasma bupropion levels as assessed by C<sub>max</sub> and AUC<sub>0-48</sub> confirms that prasugrel inhibits CYP2B6 that leads to the decrease in the plasma levels of hydroxyl metabolite of bupropion.

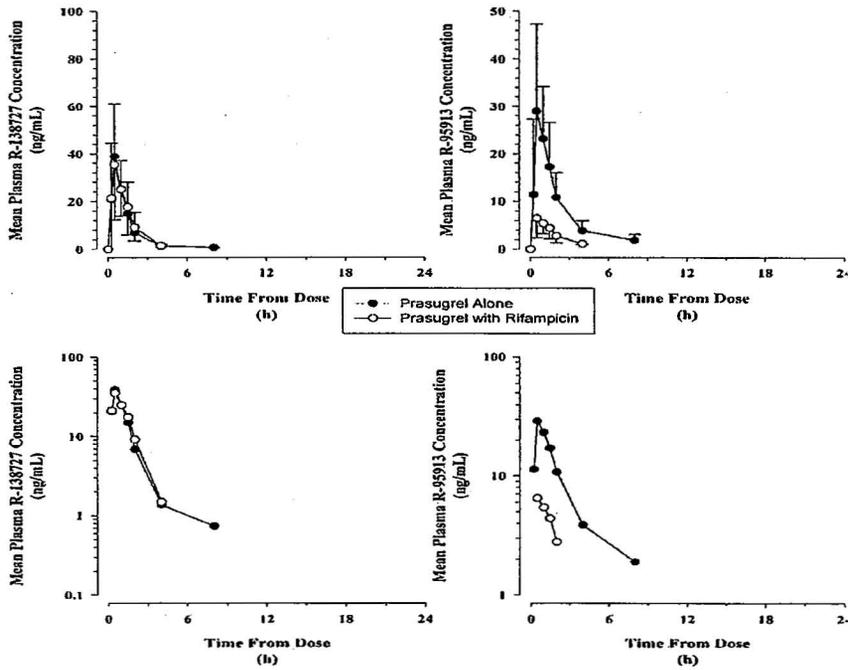
#### Pharmacokinetics of Prasugrel Metabolites during Rifampicin Treatment:

Figure 124 compares the plasma concentration time profile of R-138727 (Active metabolite of prasugrel) and R-95913 (Inactive metabolite of prasugrel) following a single 60 mg LD of prasugrel with and without rifampicin treatment. There was no change in the plasma concentration vs time profile for R-138727. The plasma concentrations of R-95913 were decreased when rifampicin was co-administered with prasugrel.

Figure 125 compares the plasma concentration time profile of R-138727 (Active metabolite of prasugrel) and R-95913 (Inactive metabolite of prasugrel) following once daily 10 mg MD of prasugrel with and without rifampicin treatment. There was no change in the plasma concentration vs time profile for R-138727. The plasma concentrations of R-95913 were decreased when rifampicin was co-administered with prasugrel. The last 1-2 data points were lacking for the plasma concentrations of R-95913 and R-138727 when prasugrel was co-administered with rifampicin.



**Figure 124** Plasma concentrations of R-138727 and R-95913 following a single 60-mg LD of prasugrel alone and with rifampicin.



**Figure 125** Plasma concentrations of R-138727 and R-95913 after the fifth once daily 10-mg MD of prasugrel alone and with rifampicin

Table 138 compares the PK parameters for R-138727 following a single 60 mg LD and daily 10 mg MD of prasugrel alone and coadministration along with 600 mg daily dose of rifampicin. The PK parameters of R-138727 were similar in both treatment groups.

**Table 138 Noncompartmental Pharmacokinetic Parameter Estimates for R-138727 Following a Single 60-mg LD and After the Fifth Once Daily 10-mg MD of Prasugrel Alone and with Rifampicin.**

Parameter	Geometric Mean (%CV)			
	R-138727 LD		R-138727 MD	
	Prasugrel alone (N=30)	Prasugrel + Rifampicin (N=29)	Prasugrel alone (N=30)	Prasugrel + Rifampicin (N=29)
$C_{max}$ (ng/mL)	362 (56.8)	367 (41.0)	44.1 (45.7)	39.3 (59.7)
$t_{max}$ (h)	0.52 (0.50-2.00)	0.50 (0.25-2.00)	0.50 (0.25-1.50)	0.50 (0.25-2.02)
AUC(0- $t_{last}$ ) (ng•h/mL)	431 (33.5)	416 (31.2)	48.1 (31.8)	48.6 (36.7)
AUC(0- $\infty$ ) (ng•h/mL)	439 (33.1)	425 <sup>b</sup> (30.8)	-- <sup>c</sup>	-- <sup>c</sup>
$t_{1/2}$ (h)	6.88 (26.4)	4.01 <sup>b</sup> (45.9)	-- <sup>c</sup>	-- <sup>c</sup>

<sup>a</sup>  $t_{max}$ : median (range)

<sup>b</sup> N=28

<sup>c</sup> Parameter not estimated.

The  $C_{max}$  and AUC<sub>0-t</sub> of R-95913 decreased by 79% and 84% respectively during the MD of prasugrel in the presence of rifampicin. The PK parameters of R-119251 and R-106583 were similar in both treatment arms.

**Table 139 Results of Statistical Analysis of Rifampicin's Effects on Pharmacokinetic Parameters Estimates of Prasugrel Metabolites.**

Treatment phase	Parameter	Ratio of geometric least square means (90% CI) [(prasugrel + rifampicin)/ prasugrel alone]			
		R-138727	R-95913	R-119251	R-106583
LD	$C_{max}$	1.02 (0.856, 1.21)	0.318 (0.282, 0.358)	0.910 (0.783, 1.06)	1.18 (1.08, 1.28)
	AUC(0- $t_{last}$ )	0.966 (0.898, 1.04)	0.265 (0.241, 0.291)	1.07 (0.985, 1.17)	0.957 (0.885, 0.993)
	AUC(0- $\infty$ )	0.954 (0.887, 1.03)	0.286 (0.262, 0.313)	1.07 (0.977, 1.16)	0.862 (0.811, 0.916)
MD	$C_{max}$	0.883 (0.747, 1.05)	0.209 (0.181, 0.242)	0.914 (0.777, 1.07)	1.06 (0.984, 1.14)
	AUC(0- $t_{last}$ )	1.00 (0.933, 1.08)	0.159 (0.138, 0.182)	1.21 (1.09, 1.33)	0.887 (0.837, 0.941)
	$t_{max}$ *	0 (0, 0.470)	0 (0, 0.500)	0.030 (0, 0.500)	0 (0, 0.500)

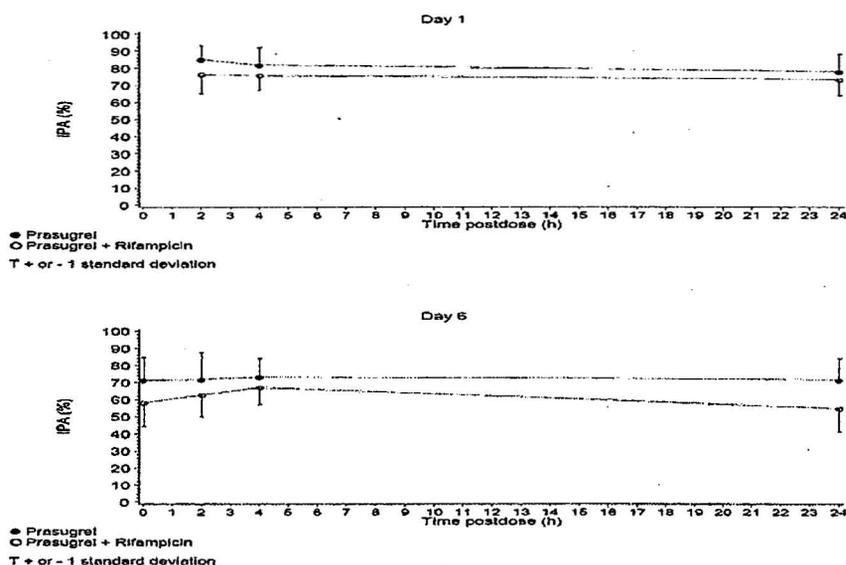
\* $t_{max}$ : median difference and approximately 90% CI.

The 90% CIs are within the interval 0.8-1.25, therefore, no statistically significant pharmacokinetic interaction was concluded (Table 139).

#### **Pharmacodynamics:**

Inhibition of platelet aggregation was measured using turbidometric methodology at 20  $\mu$ M ADP.

#### **Platelet Aggregation Study:**



**Figure 126 Mean IPA to 20 μM ADP following administration of prasugrel alone and with rifampicin..**

Figure 126 compares the % IPA responses to 20 μM ADP on day 1 and day 6 after the LD of prasugrel following rifampicin administration.

**Table 140 Statistical Comparison of IPA (%) to 20 μM ADP Following Administration of Prasugrel Alone and with Rifampicin**

Day	Time (hours)	LS mean IPA (90% CI)		(Prasugrel + Rifampicin) – (Prasugrel)		
		Prasugrel	Prasugrel + Rifampicin	Difference (90% CI)	P-value	
1	2	84.8 (81.1, 88.4)	76.3 (72.7, 80.0)	-8.43 (-12.0, -4.86)	0.0001	
	4	81.9 (78.3, 85.5)	76.0 (72.3, 79.6)	-5.90 (-9.39, -2.41)	0.0057	
	24	77.7 (74.1, 81.3)	73.6 (70.0, 77.2)	-4.10 (-7.62, -0.582)	0.0555	
6	Predose	71.4 (67.8, 75.0)	58.2 (54.6, 61.8)	-13.2 (-16.7, -9.71)	<0.0001	
	2	72.1 (68.4, 75.7)	63.2 (59.6, 66.8)	-8.87 (-12.4, -5.32)	<0.0001	
	4	71.8 (68.2, 75.4)	67.0 (63.3, 70.8)	-4.78 (-8.46, -1.10)	0.0330	
	24		71.4 (67.7, 75.1)	54.9 (51.2, 58.5)	-16.5 (-20.2, -12.9)	<0.0001

Table 140 compares the IPA response to 20 μM ADP for both treatment arms. Rifampicin reduced the IPA (%) response to prasugrel by 4-8% on Day 1 and by 5-17% on Day 6.

**COMMENTS:**

4. Because there was no PK and PD interaction between these drugs, the dose adjustment for prasugrel is not required when it is co-administered with CYP3A4 inducers.
5. Co-administration prasugrel with a single dose of bupropion (substrate for CYP2B6) changed its pharmacokinetic parameters. The  $C_{max}$  and  $AUC_{0-t}$  values of bupropion increased by 14% and 18% respectively and the  $C_{max}$  and  $AUC_{0-t}$  values of the hydroxybupropion decreased by 32% and 24% respectively. The effect of prasugrel on the pharmacokinetics of bupropion at steady state was not assessed in this study.

## 5 APENDIX III: Biopharmaceutics

### 5.1 Biopharmaceutics

The relative bioavailability studies were reviewed by Dr. P. Marroum.

#### 5.1.1 Relative Bioavailability of Stored Compared to Newly Manufactured Tablets after a 60 mg Prasugrel Loading Dose in Healthy Subjects

Technical Report no: H7T-EW-TACR.

Investigator and site:

Michael Turik MD  
Lilly Laboratories for Clinical Research  
550 North University Boulevard Indianapolis IN 46202-5250

Study Objectives:

To determine the effect of salt conversion to base during storage of prasugrel tablets on the pharmacokinetics of prasugrel's active metabolite after a 60 mg loading dose of prasugrel in healthy subjects. The secondary objective was to assess the safety and tolerability of prasugrel in healthy subjects.

Study Design:

This was a three treatment three period, open label, randomized crossover study. 84 subjects between the ages of 18 and 65 received study treatment out of which 82 completed the study. 2 subjects were withdrawn after completion of 2 treatment periods

Prasugrel was administered orally as a single 60 mg dose provided as 10 mg tablets with low 5 % 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. 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 low extent of conversion prasugrel.HCl tablets batch # CT533135  
10 mg intermediate extent of conversion prasugrel.HCl tablets batch # CT533136  
10 mg high extent of conversion prasugrel.HCl tablets batch # CT533137

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)

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 give the summary of the relevant PK parameters while Table give the statistical comparison for the relative bioavailability of the low, intermediate and high extent of conversion tablets.

The results show that the low, intermediate and high extent of conversion tablets are bioequivalent to each other with regards to the measured active metabolite.

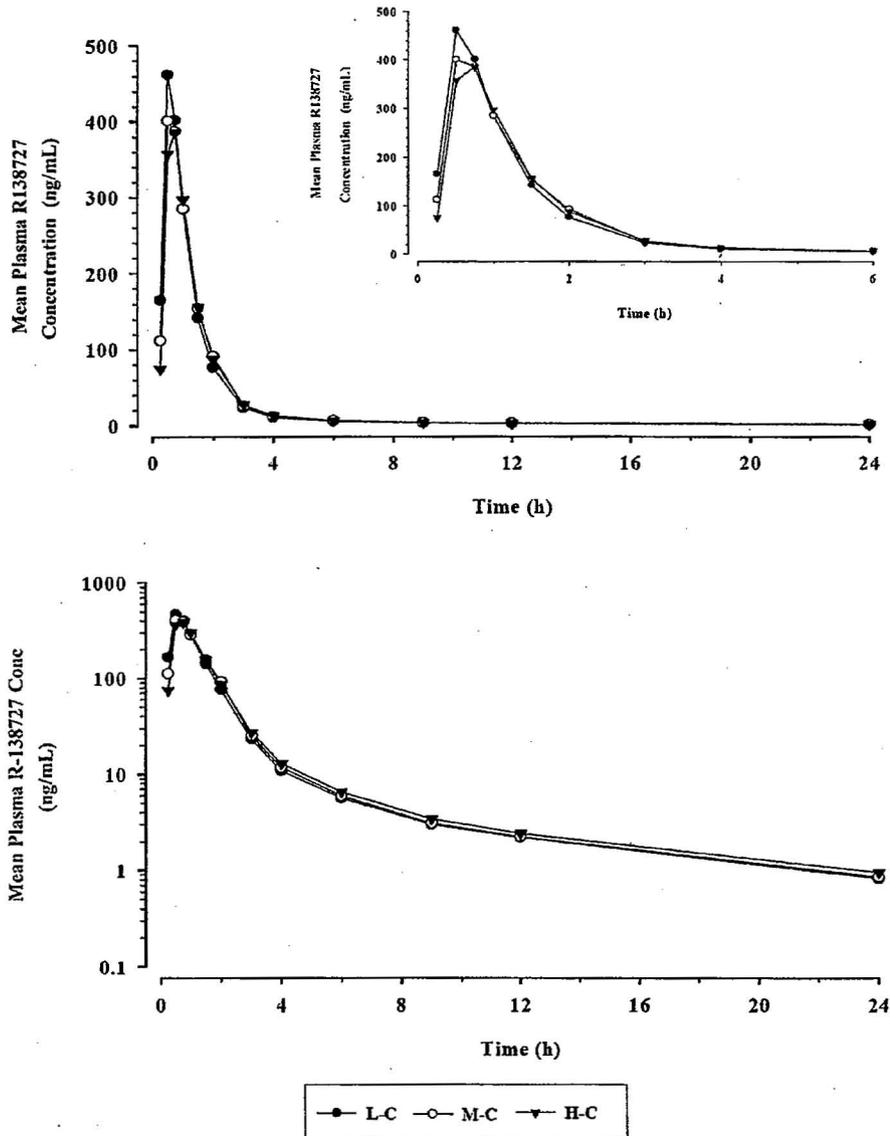


Figure TACR.7.1. Arithmetic mean plasma concentration-time profiles of R-138727 following the low (L-C), intermediate (M-C), and high (H-C) extents of conversion of prasugrel.HCl for 60-mg prasugrel (upper panel linear; lower panel log-linear).

**Table TACR.7.1. Summary of Geometric Mean (CV%) Pharmacokinetic Parameters of R-138727 for the Low, Intermediate, and High Extents of Conversion of Prasugrel.HCl for 60-mg Prasugrel**

Parameters	Geometric Mean (%CV)		
	60-mg prasugrel L-C (N=84)	60-mg prasugrel M-C (N=83)	60-mg prasugrel H-C (N=83)
C <sub>max</sub> (ng/mL)	477 (49)	433 (49)	421 (43)
t <sub>max</sub> <sup>a</sup> (h)	0.50 (0.25-3.00)	0.55 (0.25-2.00)	0.75 (0.50-2.00)
AUC(0-t <sub>last</sub> ) (ng·h/mL)	532 (31)	521 (31)	519 (27)

Abbreviations: CV - coefficient of variation; AUC(0-t<sub>last</sub>) - area under the plasma concentration-time curve from time of dosing through the sampling time of the last quantifiable concentration; C<sub>max</sub> - maximum observed plasma concentration; N - number of subjects; t<sub>max</sub> - time of C<sub>max</sub>.

<sup>a</sup> Median (range)

**Table TACR.7.2. Statistical Comparison of Relative Bioavailability of R-138727 between the Low, Intermediate, and High Extents of Conversion of Prasugrel.HCl for 60-mg Prasugrel**

Parameters (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 <sub>last</sub> ) (ng·h/mL)	532 (505, 560)	522 (495, 550)	521 (494, 549)	0.98 (0.95, 1.01)	0.98 (0.95, 1.01)	1.00 (0.97, 1.03)
C <sub>max</sub> (ng/mL)	476 (439, 516)	432 (399, 469)	422 (390, 458)	0.91 (0.84, 0.98)	0.89 (0.82, 0.96)	0.98 (0.90, 1.06)

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