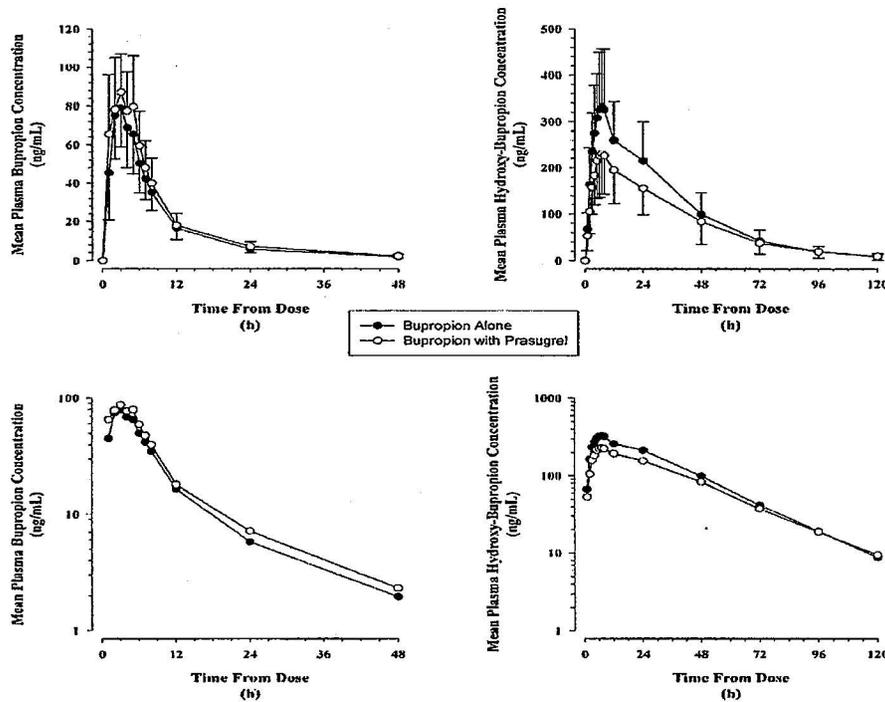


Parameter		R119251	
linearity		1 to 500 ng/ml	
		Intra-day	Inter-day
Precision (RSD)		1.4 to 4.6%	n/d
Accuracy (RE)		-10.3 to 1.3%	n/d
LLOQ		1 ng/ml	
Parameter		R106583	
linearity		1.56 to 400 ng/ml	
		Intra-day	Inter-day
%CV		4.4 to 5.0%	5.3 to 12.6%
Accuracy (%)		-8.4 to 17.3%	-19.8 to 17.3%
LLOQ		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>p</sub> /F (L/h)	200 (30.4)	169 <sup>b</sup> (26.6)	-c	-c
V <sub>d</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.

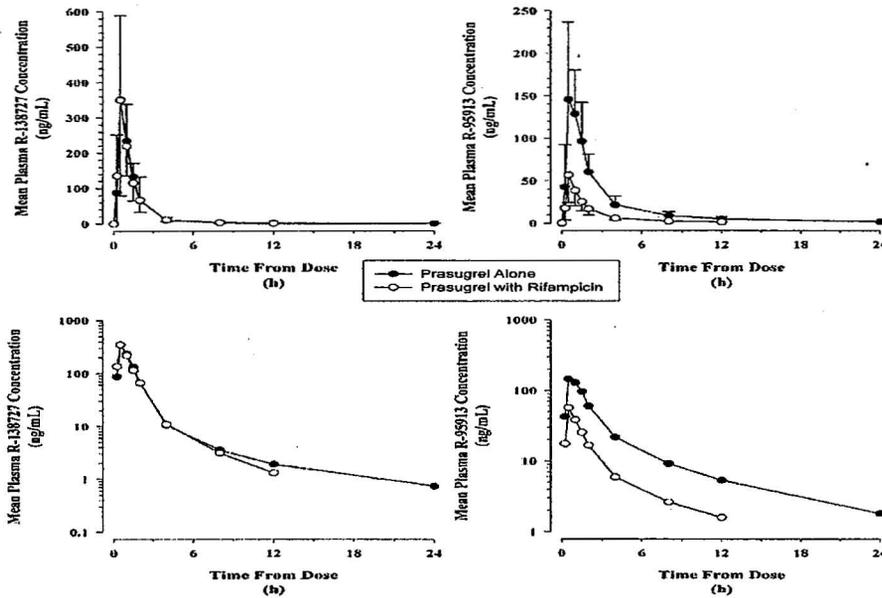


Figure 124 Plasma concentrations of R-138727 and R-95913 following a single 60-mg LD of prasugrel alone and with rifampicin.

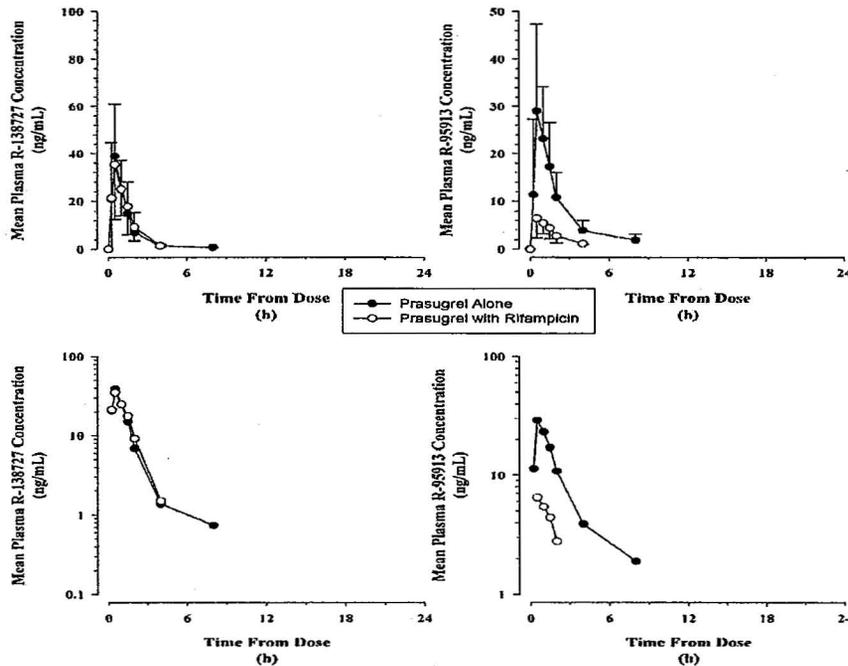


Figure 125 Plasma concentrations of R-138727 and R-95913 after the fifth once daily 10-mg MD of prasugrel alone and with rifampicin

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)
$t_{max}$ <sup>a</sup> (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)	0.937 (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)
	$t_{max}$ <sup>*</sup>	0 (0, 0.470)	0 (0, 0.500)	0.030 (0, 0.500)	0 (0, 0.500)

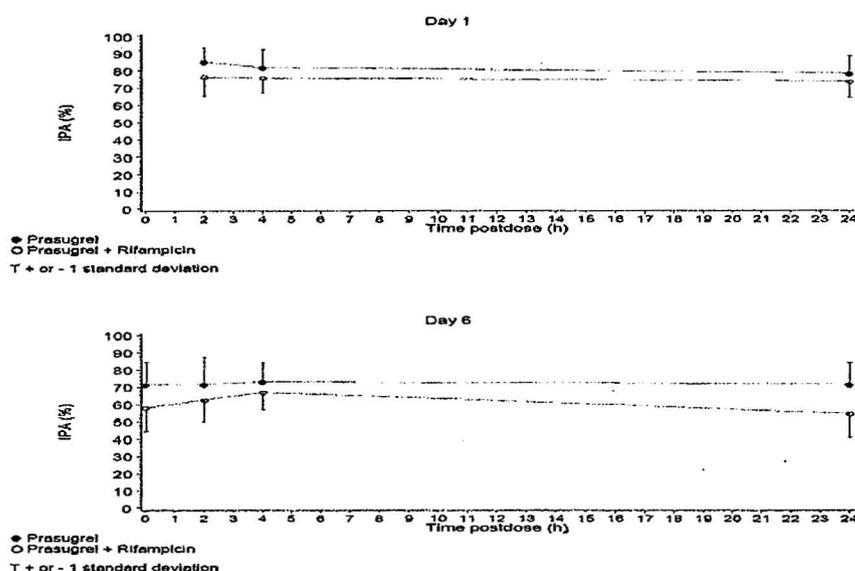
<sup>\*</sup> $t_{max}$ : median difference and approximately 90% CI.

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  $\mu$ M ADP following administration of prasugrel alone and with rifampicin..**

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

**Table 140 Statistical Comparison of IPA (%) to 20  $\mu$ M 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  $\mu$ M 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.

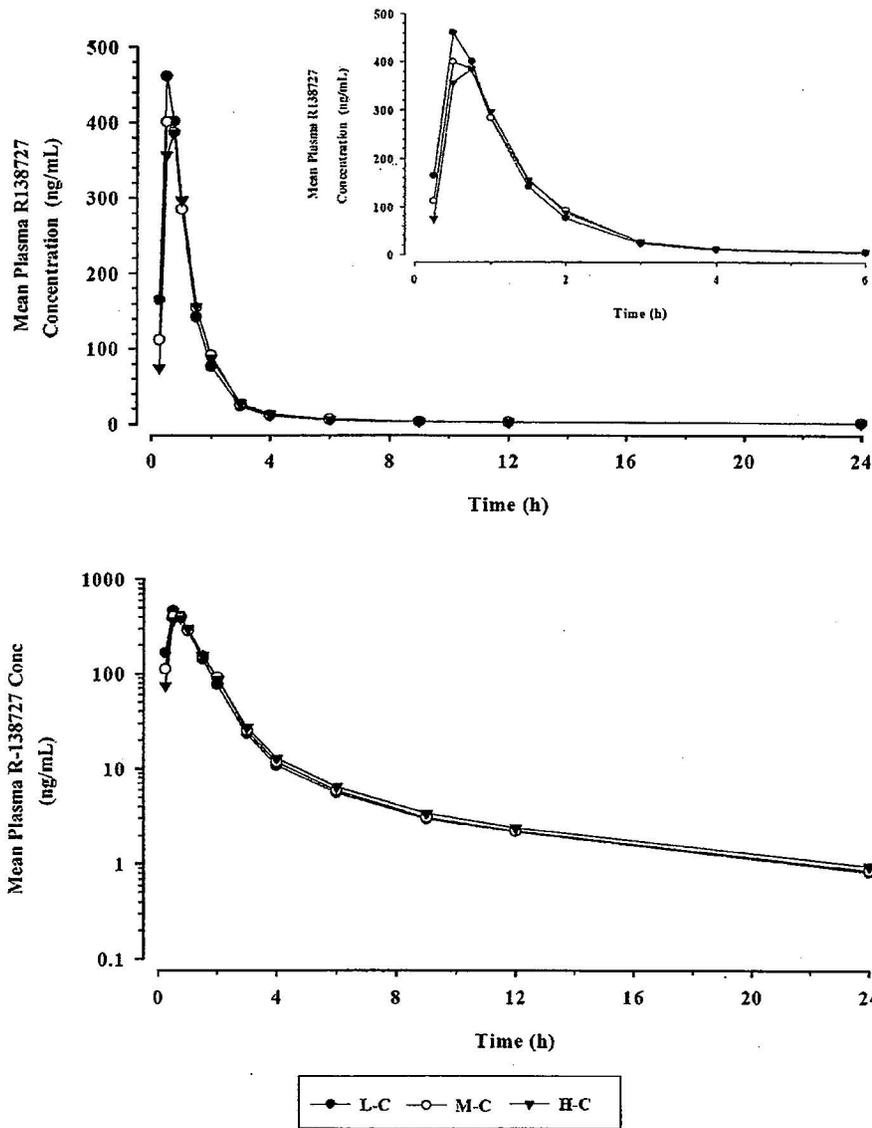


Figure TACR.7.1. Arithmetic mean plasma concentration-time profiles of R-138727 following the low (L-C), intermediate (M-C), and high (H-C) extents of conversion of prasugrel.HCl for 60-mg prasugrel (upper panel linear; lower panel log-linear).

**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

### 5.1.2 Relative Bioavailability of Stored Compared to Newly Manufactured Tablets after a 60 mg Prasugrel Loading Dose in Healthy Subjects taking a Proton Pump Inhibitor

Technical Report no: H7T-EW-TACS.

Investigator and site:

Gilbert Weiner MD  
Allied Research International Inc  
1405 NW 167<sup>th</sup> Street Miami Gardens Florida 33169

Study Objectives:

To determine the effect of salt conversion to base during storage of prasugrel tablets on the pharmacokinetics of the prasugrel's active metabolite in healthy subjects taking lansoprazole 30 mg once daily. The secondary objectives were to assess the effect of salt conversion to base during storage of prasugrel tablets on the time course of maximum platelet aggregation (MPA) after a 60 mg loading dose of prasugrel in healthy subjects taking lansoprazole 30 mg once a daily for at least 1 week and 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 in which subjects taking 30 mg lansoprazole once daily for at least one week received 60 mg prasugrel tablets with low, intermediate and high extent of conversion of prasugrel.HCl to prasugrel base. 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. Lansoprazole was administered orally as daily 30 mg doses provided as 30 mg capsules. The prasugrel formulations were as follows: low 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)

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.

The inhibition of platelet aggregation using LTA was assessed by the MPA and the inhibition of platelet aggregation (IPA) to 20  $\mu$ M ADP.

MPA to 20  $\mu$ M ADP was the primary pharmacodynamic parameter. The secondary pharmacodynamic parameter, IPA to 20  $\mu$ M ADP, was calculated using the equation:

$$IPAt = 100\% \times (1 - MPAt / MPA0)$$

where IPAt is the IPA at time t, MPAt is the observed MPA at time t, and MPA0 is the baseline (predose) MPA.

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 after pre-treatment with 30 mg lansoprazole, the low, intermediate and high rate of conversion tablets are not bioequivalent to each other as the CMAX fails to meet the 90 % confidence interval criteria of 80-125.

The extent of prasugrel salt to base conversion did not affect the time to or the magnitude of the peak effect on MPA. No statistically significant differences in MPA were detected between treatments except at 0.5 and 1 hour post dose when MPA following the high conversion tablet was significantly higher than both after the intermediate and low conversion tablets. The difference in MPA at the 0.5 hour was greater than 10 % and therefore clinically significant.

Conclusion: