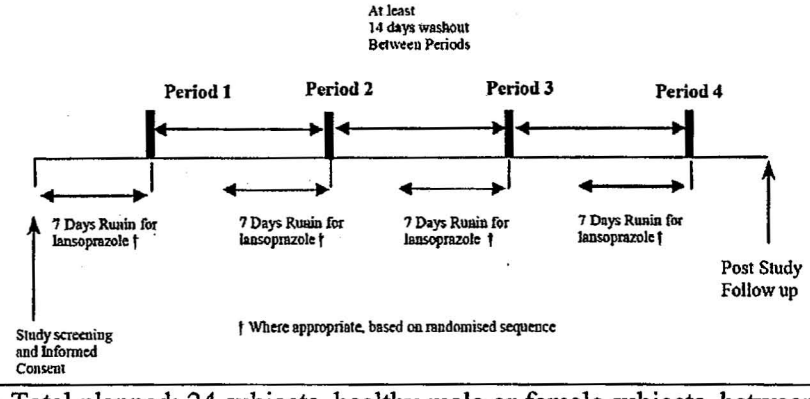
4.2.14 A Study of the Effects of a Proton Pump Inhibitor (Lansoprazole) on the Single Loading Dose Pharmacokinetics and Pharmacodynamics of CS-747.HCl and Clopidogrel in Healthy Subjects (TAAI)

Principal Investigator: M Turik, MD
Study Centre: Lilly Laboratory for Clinical Research, Indianapolis, Indiana, US
Dates of Study: 18 April 2003 through 06 June 2003
Clinical Phase: 1

<table>
<tr><td>Objectives</td><td>Primary: to investigate the effects of the proton pump inhibitor (PPI) lansoprazole on the pharmacokinetics of CS-747.HCl (R138727: the active CS-747 metabolite) and of clopidogrel (S26334: an inactive metabolite of clopidogrel).
Secondary: (i) to investigate the effects of the proton pump inhibitor lansoprazole on the pharmacodynamics of CS-747.HCl and of clopidogrel; (ii) to compare the pharmacodynamic effects of 60 mg CS-747.HCl with that of 300 mg clopidogrel, in the presence and absence of lansoprazole; (iii) to further define the concentrations of three inactive metabolites of CS-747 (R95913, R119251 and R106583); (iv) to assess and compare the safety of loading doses of CS-747.HCl and clopidogrel in healthy subjects.</td></tr>
<tr><td>Study Design</td><td>A single centre, open-label, randomized, four period crossover study. In two of four treatment periods, according to the randomization schedule, there was a 7 day run-in period of lansoprazole (Day –6 to Day 1). On Day 1, subjects were administered a dose of CS-747 or clopidogrel either in the presence or absence of lansoprazole.
<table>
<tr><th></th><th>Period 1</th><th>Period 2</th><th>Period 3</th><th>Period 4</th></tr>
<tr><td>Sequence 1</td><td>CS-747.HCl</td><td>Clopidogrel + PPI</td><td>CS-747.HCl + PPI</td><td>Clopidogrel</td></tr>
<tr><td>Sequence 2</td><td>CS-747.HCl + PPI</td><td>CS-747.HCl</td><td>Clopidogrel</td><td>Clopidogrel + PPI</td></tr>
<tr><td>Sequence 3</td><td>Clopidogrel</td><td>CS-747.HCl + PPI</td><td>Clopidogrel + PPI</td><td>CS-747.HCl</td></tr>
<tr><td>Sequence 4</td><td>Clopidogrel + PPI</td><td>Clopidogrel</td><td>CS-747.HCl</td><td>CS-747.HCl + PPI</td></tr>
</table>

</td></tr>
<tr><td>Population</td><td>Total planned: 24 subjects, healthy male or female subjects, between 18 and 65 years of age, inclusive, with a MPA response of = 70% for 5 and 20 μM ADP and arachidonic acid.</td></tr>
</table>

Investigational Drugs	<table><tr><th>Product</th><th>Dose</th><th>Lot No.</th><th>Storage conditions</th><th>Expiration Date</th></tr><tr><td>CS-747.HCl</td><td>15 mg</td><td>CT503396</td><td>15-30°C</td><td>March 2004</td></tr><tr><td>Clopidogrel</td><td>75 mg</td><td>2K68319</td><td>15-30°C</td><td>February 2005</td></tr><tr><td>Lansoprazole</td><td>30 mg</td><td>016982E21</td><td>15-30°C</td><td>September 2005</td></tr></table>
Administration	Each dose of drug was administered orally after an overnight fast
Sampling: Blood	A total of 44 samples were taken at the following times: Day 1 of each Period: 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 9, 12, and 24 hours postdose
Assay	HPLC with LC/MS/MS detection, chromatograms were shown. The assay characteristics of prasugrel metabolites are similar to the shown in Table 47 and for clopidogrel in Table 43.
PK Assessment	Plasma concentrations of the active CS-747 metabolite (R138727), the three inactive CS-747 metabolites (R95913, R119251, R106583), and of the carboxylic acid metabolite of clopidogrel (S26334). PK parameters: non-compartmental methods
PD Assessment	Platelet aggregation response to 5 and 20 μM ADP. A linear mixed-effect analysis of variance was carried out to compare mean inhibition of platelet aggregation (IPA) among treatments. The 90% CIs to estimate the differences among the mean of IPAs and for intra-subject CVs.

Demographics:
Out of 20 male and six female subjects participated in the study, 17 were Caucasians, and 3 were Afro-Caribbeans.

Table 95. Subject Demographics

Parameter	Mean (SD) (N=26)	Range (N=26)
Age (years)	42 (13.4)	19 - 59
Body weight (kg)	82.8 (14.33)	57.5 – 106.8
Height (cm)	176 (8.4)	158 – 190
Body mass index (kg/m^2)	26.6 (3.23)	21.1 – 31.5

Pharmacokinetics:
Effect of lansoprazole on the prasugrel PK.
The coadministration of lansoprazole did not influence the AUC(0-∞) and AUC(0-tlast) of each of the metabolites. However, the Cmax of the active metabolite R138727 decreased by 28.9% (90% CI 18.7-37.8%). Decreases of Cmax for inactive metabolites were as follows: R95913 (by 17.8%), R119251 (by 22.1%) and R106583 (16.1%). There were no differences in median Tmax for any of the detected metabolites, except for R95913 (increased from 0.55 to 1.00 h).

Table 96. Effect of Lansoprazole (PPI) on the Pharmacokinetics of CS-747 Metabolites following Oral Administration of 60 mg CS-747.HCl

Metabolites	PK Parameter (unit)	Geometric mean[a] (90% CI) [CS-747.HCl]	Geometric mean[a] (90% CI) [CS-747.HCl + PPI]	Ratio of Geometric mean[a] (90% CI)* [CS-747.HCl + PPI vs. CS-747.HCl]
R138727	AUC (0-∞) (ng·h/ml)	591 (521, 671)	523 (461, 592)	0.884 (0.833, 0.938)
	AUC (0-t_{last}) (ng·h/ml)	589 (520, 667)	511 (451, 580)	0.869 (0.823, 0.916)
	C_{max} (ng/ml)	570 (476, 683)	406 (338, 487)	**0.711 (0.622, 0.813)[b]**
R95913	AUC (0-∞) (ng·h/ml)	477 (420, 540)	469 (413, 532)	0.983 (0.928, 1.04)
	AUC (0-t_{last}) (ng·h/ml)	452 (399, 513)	444 (391, 504)	0.982 (0.924, 1.04)
	C_{max} (ng/ml)	235 (205, 268)	193 (168, 221)	**0.822 (0.731, 0.924)[b]**
R119251	AUC (0-∞) (ng·h/ml)	413 (358, 477)	373 (323, 431)	0.904 (0.838, 0.974)
	AUC (0-t_{last}) (ng·h/ml)	397 (342, 460)	355 (306, 412)	0.894 (0.826, 0.967)
	C_{max} (ng/ml)	259 (214, 314)	202 (167, 245)	**0.779 (0.669, 0.908)[b]**
R106583	AUC (0-∞) (ng·h/ml)	3070 (2760, 3410)	2790 (2510, 3100)	0.909 (0.872, 0.949)
	AUC (0-t_{last}) (ng·h/ml)	2700 (2440, 2990)	2390 (2160, 2640)	0.883 (0.853, 0.913)
	C_{max} (ng/ml)	489 (441, 541)	410 (370, 455)	0.839 (0.785, 0.897)

The PK profiles of the active metabolite are shown below:

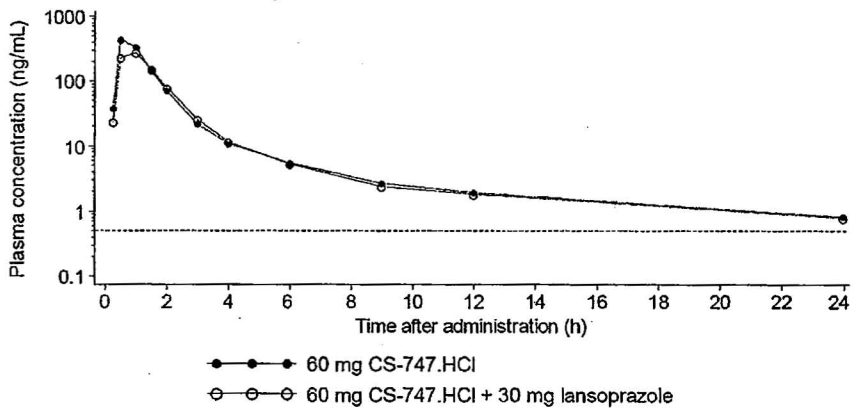


Figure 85. Geometric mean plasma concentrations for the active metabolite of CS-747 (R138727).

The effect of lansoprasole on the PK of clopidogrel.

Table 97. Effect of Lansoprazole (PPI) on the Pharmacokinetics of the Inactive Metabolite S26334 following Oral Adminstration of 300 mg Clopidogrel

PK Parameter (unit)	Geometric mean[a] (90% CI) [Clopidogrel]	Geometric mean[a] (90% CI) [Clopidogrel + PPI]	Ratio of Geometric mean[a] (90% CI)* [Clopidogrel + PPI vs. Clopidogrel]
AUC (0-∞) (ng·h/ml)	36500 (32800, 40600)	36200 (32500, 40300)	0.99 (0.95, 1.03)
AUC (0-t_{last}) (ng·h/ml)	33200 (29900, 37000)	32300 (29000, 35900)	0.97 (0.925, 1.02)
C_{max} (ng/ml)	9830 (8550, 11300)	8920 (7750, 10300)	0.908 (0.793, 1.04)

The comparisons of the inactive metavolite S26334 pharmacokinetics after 300 mg clopidogrel in the presence and absence of lansoprazole shows that both treatments are bioequivalent with respect to mean AUC(0-∞), AUC(0-tlast) and lansoprasol slightly (10%) decreased the Cmax values of clopidogrel.

Pharmacodynamics

The Figure below illustrates the time profile of the model predicted mean IPA for the four treatments.

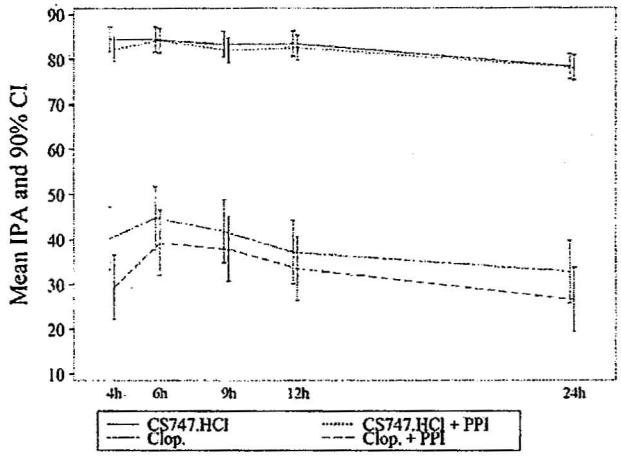


Figure 86. Time profile of the predicted median IPA (with 90% CI) to 20 μM ADP

Table below provides statistical assessing of differences in mean IPA among treatments.

Table 98. Effect of lanzoprazole on IPA to 20 mcM ADP point estimate and 90%CI for mean IPA for four treatments

Time postdose (hours)	Mean IPA (90% CI)				Difference in mean IPA (90% CI) [p-value]			
	CS-747.HCl	CS-747.HCl + PPI	Clopidogrel	Clopidogrel + PPI	CS-747.HCl vs CS-747.HCl + PPI	Clopidogrel vs Clopidogrel + PPI	CS-747.HCl + PPI vs Clopidogrel	CS-747.HCl + PPI vs Clopidogrel + PPI
4	84.5 (81.7, 87.3)	82.3 (79.5, 85.0)	40.2 (33.2, 47.2)	29.4 (22.2, 36.5)	2.24 (-0.08, 4.57) [0.112]	10.85 (1.33, 20.37) [0.061]	42.05 (35.18, 48.91) [<.001]	52.90 (45.88, 59.92) [<.001]
6	84.4 (81.6, 87.2)	84.2 (81.5, 87.0)	44.7 (37.7, 51.7)	39.2 (32.1, 46.4)	0.20 (-2.12, 2.52) [0.888]	5.45 (-4.07, 14.97) [0.345]	39.54 (32.68, 46.41) [<.001]	44.99 (37.97, 52.01) [<.001]
9	83.4 (80.6, 86.2)	82.0 (79.2, 84.7)	41.8 (34.8, 48.8)	37.8 (30.7, 45.0)	1.39 (-0.93, 3.71) [0.324]	3.95 (-5.57, 13.47) [0.494]	40.19 (33.32, 47.05) [<.001]	44.13 (37.11, 51.16) [<.001]
12	83.5 (80.7, 86.3)	82.6 (79.8, 85.4)	37.2 (30.2, 44.2)	33.5 (26.4, 40.7)	0.92 (-1.40, 3.24) [0.513]	3.66 (-5.86, 13.17) [0.526]	45.42 (38.56, 52.28) [<.001]	49.08 (42.06, 56.10) [<.001]
24	78.4 (75.6, 81.2)	78.1 (75.3, 80.8)	32.8 (25.8, 39.8)	26.6 (19.4, 33.8)	0.31 (-2.01, 2.64) [0.825]	6.23 (-3.29, 15.75) [0.281]	45.25 (38.38, 52.11) [<.001]	51.48 (44.46, 58.50) [<.001]

The co-administration of lansoprazole and prasugrel did not influence the mean IPA values. The co-administration of lansoprazole and clopidogrel reduced mean IPA values at 4 and 24 hours postdose for the clopidogrel loading dose. At 24 hours postdose, the observed reduction in IPA to 5 μM ADP due to lansoprazole exceeded 10% and the reduction was statistically significant.

Mean IPA for CS-747 in the presence of lansoprazole was statistically significantly higher ($p<0.001$) than clopidogrel in the presence or absence of lansoprazole at every time point.

Reviewer's Comments:

1. The exposures to the active metabolite (R138727) of prasugrel with and without lansoprazole passed the bioequivalence with respect to AUC(0-∞) and AUC(0-tlast). However, its rate of absorption (Cmax) was reduced by about 30%. The inactive prasugrel metabolites demonstrated a similar trend for Cmax, AUC(0-∞) and AUC(0-tlast) when the treatments with and without lansoprazole were compared.
2. Co-administration of lansoprazole with prasugrel did not affect the pharmacodynamic response to prasugrel.
3. The PK of the inactive metabolite of clopidogrel was not affected by coadministration of lansoprazole. The sponsor did not measure the PK of the clopidogrel active metabolite.
4. When clopidogrel was coadministered with lansoprazole, the pharmacodynamic response (IPA), was reduced at each measured time point, however, the differences (3-11%) were not statistically significant.
5. Since the 30% differences in Cmax values for the active metabolite of prasugrel did not change the PD response, this differences probably would not of clinical significance, and the dose adjustment of prasugrel when administered with lansoprazole is not required.

4.2.15 The Effect of Oral Ranitidine on the Pharmacokinetics and Pharmacodynamics of Prasugrel and Clopidogrel Active Metabolites in Healthy Subjects (TABS)

Responsible Investigators: Drs W Malyszczak and J Chiesa
Study Center: Veeda Clinical Trials Unit Ltd., Old Convent of Notre Dame, 119 Looseleigh Lane, Derriford, Plymouth, PL6 5HH, UK.
Length of Study: 27 March 2006 through 14 July 2006
Phase of Development: 1

Objectives	Primary: to assess the physiological effect of oral ranitidine on the loading and maintenance dose PK of the prasugrel active metabolite, R-138727. Secondary : (1) to assess the physiological effect of orally administered ranitidine on the loading and maintenance dose pharmacokinetics of the clopidogrel active metabolite, R-130964, (2) to assess the physiological effect of orally administered ranitidine on the inhibition of platelet aggregation after administration with prasugrel and clopidogrel, and (3) to assess the safety and tolerability of prasugrel and clopidogrel given alone and in combination with ranitidine.
Study Design	An open-label, two-period, two-treatment crossover study conducted in parallel. Subjects received either a 60-mg prasugrel LD on Day 1, followed by 7 days of 10-mg MDs (Days 2 to 8) or a 600-mg clopidogrel LD on Day 1, followed by 7 days of 75-mg MDs (Days 2 to 8) in each of the two treatment periods. In the treatment period in which prasugrel or clopidogrel were coadministered with ranitidine, subjects received 9 days of 150-mg bid ranitidine (Days -1 to 8), with coadministration of ranitidine and a 60-mg prasugrel or 600-mg clopidogrel LD on Day 1, and 7 days of coadministration of ranitidine with 10-mg prasugrel or 75-mg clopidogrel MDs on Days 2 to 8.
Population	Forty-seven healthy male and female subjects
Investigational Drugs Comparator	Prasugrel: 10 mg tablets, lot number CT524918. Ranitidine: 150 mg tablets lot number RAOE 0079. Clopidogrel was provided as 75 mg tablets from lot number AP168.
Sampling: Blood	Blood samples were collected for the measurement of plasma concentrations of the active metabolites of prasugrel (R-138727) and clopidogrel (R-130964), and for the assessment of platelet aggregation (induced by 5 and 20 μM ADP).
Assays	HPLC with LC/MS/MS detection, chromatograms were shown. Platelet aggregation in platelet-rich plasma was measured using the turbidometric method with 5 and 20 μM ADP as the agonists.
PK Assessment	Noncompartmental methods PK for the active metabolite of prasugrel (R-138727) and clopidogrel (R-130964)
Statistical	A linear mixed effect model was fitted to analyze the log-transformed AUC(0-tlast) and Cmax for the active metabolites of prasugrel and clopidogrel. The 90% CI for the geometric mean ratio of each parameter between treatments was calculated. The parameter tmax was analyzed using

	the Wilcoxon sign rank test. MPA and IPA to 5 and 20 μM ADP were evaluated to estimate the mean differences and corresponding 90% CI between test and reference treatments using a repeated measures linear mixed effect model.

Assay:
Determination of the plasma concentration of prasugrel (R138727) and clopidogrel (R361015) active metabolites were performed using the validated methods (Tables below).

Table 99. Assay Characteristics of R138727

Parameter	R138727	
Linearity	0.5 ng/mL to 250 ng/mL	
	Inter-batch	Intra-batch
Precision (CV %)	2.37 to 3.67	2.62 to 3.24
Accuracy, %	-9.3 to 6.3	-11.1 to 6.33
LLOQ	0.5ng/mL	
Reviewer Comment	The assay characteristics and specificity are satisfactory, representative mass-chromatograms are shown	

Table 100. Assay Characteristics of R361015

Parameter	R361015	
Linearity	0.5 ng/mL to 250 ng/mL	
	Inter-batch	Intra-batch
Precision (CV %)	4.47 to 7.6	3.95 to 11.2
Accuracy, %	-4.0 to 2.8	-1.5 to 4.0
LLOQ	0.5ng/mL	
Reviewer Comment	The assay characteristics and specificity are satisfactory, representative mass-chromatograms are shown	

In the text of this study report the sponsor says that they intend to measure the active metabolite of clopidogrel R-130964, however, in the study Appendix for the assay validation, the results are listed for the other metabolite, R361015 without any explanation.

Demographics
Forty-seven healthy male and female subjects, aged 18 to 65 years (inclusive), and with a body mass index (BMI) of 18.5 to 32.0 kg/m2 (inclusive) were enrolled and 45 completed the study.

Pharmacokinetics

Figures below show the mean concentration-time profiles of active metabolite after a LD and during MD of prasgurel or clopidogrel with and without ranitidine coadministration.

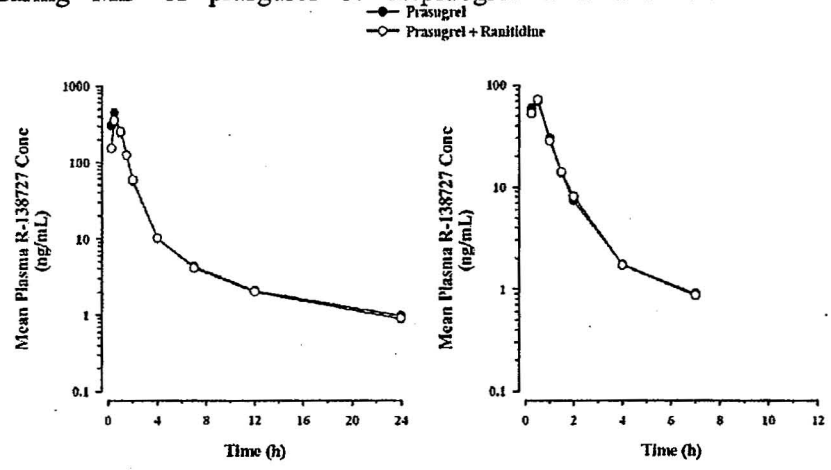


Figure 87. Plasma concentrations of R-138727 after a 60-mg prasugrel loading dose (left) and after the seventh daily 10-mg prasugrel maintenance dose (right) alone and with ranitidine.

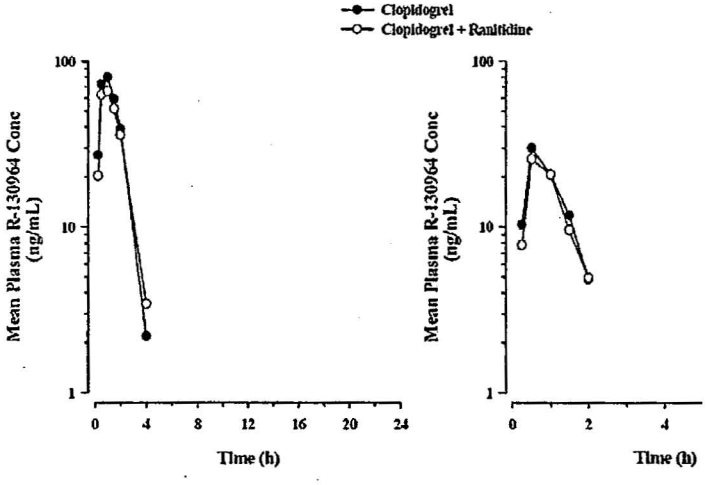


Figure 88. Plasma concentrations of R-130964 after a 600-mg clopidogrel loading dose (left) and after the seventh daily 75-mg clopidogrel maintenance dose (right) alone and with ranitidine.

Tables below summarize the pharmacokinetic parameter estimates.

Table 101. PK Parameters of R138727

	Geometric Mean (%CV)			
	R-138727 LD		R-138727 MD	
Parameter	Prasugrel alone (N=23)	Prasugrel + Ranitidine (N=22)	Prasugrel alone (N=23)	Prasugrel + Ranitidine (N=22)
C_{max} (ng/mL)	470 (45)	402 (35)	77.6 (38)	80.0 (44)
t_{max}[a] (h)	0.50 (0.25-1.50)	0.50 (0.17-1.00)	0.50 (0.25-1.50)	0.50 (0.25-1.50)
AUC(0-t_{last}) (ng•h/mL)	511 (26)	462 (20)	73.0 (25)	71.2 (24)

Table 102. PK Parameters of R130964

	Geometric Mean (%CV)			
	R-130964 LD		R-130964 MD	
Parameter	Clopidogrel alone (N=24)	Clopidogrel + Ranitidine (N=24)	Clopidogrel alone (N=23)	Clopidogrel + Ranitidine (N=24)
C_{max} (ng/mL)	83.9 (41)	75.6 (39)	32.0 (30)	29.2 (36)
t_{max}[a] (h)	0.78 (0.50-1.50)	1.00 (0.50-2.05)	0.50 (0.50-1.50)	0.50 (0.50-1.50)
AUC(0-t_{last}) (ng•h/mL)	128 (48)	118 (37)	30.1 (37)	27.1 (30)

The statistical analysis of ranitidine's effect on exposure to prasugrel's and clopidogrel's active metabolites is shown below.

Prasugrel		Clopidogrel	
LD	MD	LD	MD
Ratio of geometric LS means (90% CI) (Prasugrel + ranitidine): prasugrel	Ratio of geometric LS means (90% CI) (Prasugrel + ranitidine): prasugrel	Ratio of geometric LS means (90% CI) (Clopidogrel + ranitidine): clopidogrel	Ratio of geometric LS means (90% CI) (Clopidogrel + ranitidine): prasugrel
0.856 (0.704, 1.04)	1.02 (0.894, 1.17)	0.901 (0.790, 1.03)	0.914 (0.790, 1.06)
0.901 (0.835, 0.971)	0.983 (0.931, 1.04)	0.927 (0.807, 1.06)	0.901 (0.818, 0.993)
0 (-0.25, 0) (p=0.49)	0 (-0.20, 0) (p=0.415)	-0.01 (-0.50, 0) (p=0.135)	0 (-0.50, 0) (p=0.514)

Ranitidine did not affect the AUC(0-tlast) or tmax of the active metabolite of either prasugrel or clopidogrel. The Cmax of both active metabolites after a LD and the Cmax of clopidogrel's active metabolite during MD were lower when administered with ranitidine but the changes were not statistically significant

Pharmacodynamics

Inhibition of Platelet Aggregation Induced by ADP

Figure below shows the changes in IPA to 20 μM ADP following prasugrel alone, prasugrel with ranitidine, clopidogrel alone, and clopidogrel with ranitidine, during LD (Day 1) and MD (Day 8).

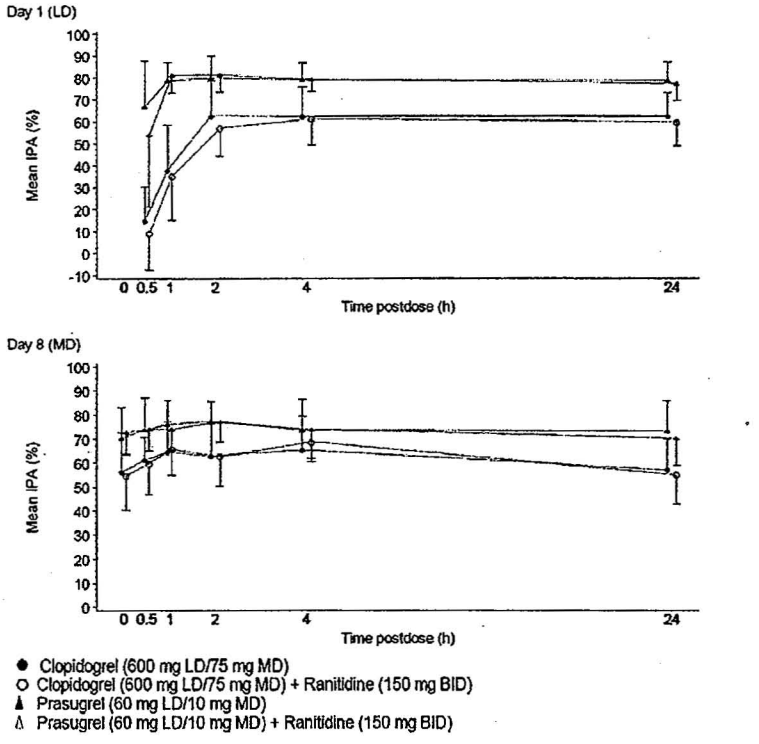


Figure 89. Arithmetic mean IPA to 20 μM ADP time profile of clopidogrel and prasugrel alone and with ranitidine. LD, Day 1, top panel. MD, Day 8, bottom panel.

At all time points except for the 0.5 hour sample after prasugrel LD and ranitidine the differences in IPA were not statistically significant. The reduction of IPA at 0.5 hour was 12 percentage points, which was associated with a 9 percentage point increase in MPA to 20 μM ADP.

Table 103 Statistical Comparison of IPA (%) to 20 μM ADP Following LD of Prasugrel and Clopidogrel alone and with Ranitidine (Day 1)

	LS Mean IPA (90% CI)		IPA Difference (90% CI) [P-value]
Time (h)	Prasugrel	Prasugrel + ranitidine	(Prasugrel + ranitidine) vs prasugrel
0.5	67.4 (63.4, 71.5)	55.1 (50.3, 59.8)	-12.34 (-17.0, -7.67) [<0.001]
1	79.3 (75.3, 83.4)	82.3 (77.5, 87.1)	2.97 (-1.70, 7.64) [0.295]
2	80.7 (76.7, 84.8)	82.3 (77.6, 87.1)	1.60 (-3.07, 6.27) [0.571]
4	79.8 (75.7, 83.8)	80.4 (75.6, 85.2)	0.62 (-4.05, 5.29) [0.827]
24	79.5 (75.4, 83.5)	78.4 (73.6, 83.1)	-1.08 (-5.75, 3.58) [0.702]
	LS Mean IPA (90% CI)		IPA Difference (90% CI) [P-value]
Time (h)	Clopidogrel	Clopidogrel + ranitidine	(Clopidogrel + ranitidine) vs clopidogrel
0.5	13.8 (9.2, 18.3)	8.6 (4.0, 13.1)	-5.20 (-10.2, -0.20) [0.087]
1	36.8 (32.3, 41.4)	35.2 (30.7, 39.8)	-1.61 (-6.67, 3.46) [0.601]
2	62.1 (57.6, 66.5)	56.3 (51.7, 60.8)	-5.82 (-10.7, -0.94) [0.050]
4	61.8 (57.3, 66.3)	60.3 (55.8, 64.8)	-1.51 (-6.45, 3.43) [0.615]
24	62.2 (57.7, 66.7)	58.9 (54.4, 63.4)	-3.30 (-8.25, 1.64) [0.271]

Table 104. Statistical Comparison of IPA (%) to 20 μM ADP Following MD of Prasugrel and Clopidogrel alone and with Ranitidine (Day 8)

	LS Mean IPA (90% CI)		IPA Difference (90% CI) [P-value]
Time (h)	Prasugrel	Prasugrel + ranitidine	(Prasugrel + ranitidine) vs prasugrel
0	71.0 (67.0, 75.1)	73.8 (69.0, 78.5)	2.73 (-1.94, 7.40) [0.336]
0.5	74.5 (70.4, 78.5)	75.1 (70.3, 79.8)	0.59 (-4.08, 5.25) [0.836]
1	76.6 (72.6, 80.7)	75.4 (70.5, 80.2)	-1.27 (-6.02, 3.48) [0.659]
2	78.1 (74.0, 82.1)	78.2 (73.4, 82.9)	0.10 (-4.57, 4.77) [0.972]
4	74.4 (70.3, 78.4)	75.0 (70.3, 79.8)	0.64 (-4.03, 5.31) [0.821]
24	74.0 (69.9, 78.0)	71.5 (66.8, 76.3)	-2.46 (-7.12, 2.21) [0.386]
	LS Mean IPA (90% CI)		IPA Difference (90% CI) [P-value]
Time (h)	Clopidogrel	Clopidogrel + ranitidine	(Clopidogrel + ranitidine) vs clopidogrel
0	55.9 (51.3, 60.4)	53.7 (49.1, 58.2)	-2.20 (-7.14, 2.74) [0.464]
0.5	60.7 (56.2, 65.2)	59.0 (54.5, 63.5)	-1.69 (-6.63, 3.25) [0.573]
1	64.1 (59.6, 68.7)	64.8 (60.3, 69.3)	0.69 (-4.26, 5.63) [0.819]
2	62.6 (58.0, 67.1)	61.9 (57.4, 66.4)	-0.68 (-5.62, 4.26) [0.821]
4	65.0 (60.5, 69.5)	67.8 (63.3, 72.3)	2.80 (-2.14, 7.75) [0.350]
24	56.7 (52.2, 61.2)	53.9 (49.4, 58.5)	-2.78 (-7.78, 2.22) [0.360]

Sposor's Conclusions

1. Ranitidine, coadministered with a prasugrel 60-mg LD, slightly lowered the Cmax of prasugrel's active metabolite but did not affect the AUC. Ranitidine, coadministered with prasugrel during 10-mg once-daily maintenance dosing, did not affect the pharmacokinetics of prasugrel's active metabolite.
2. Ranitidine coadministration with a prasugrel 60-mg LD did not affect the time to, or magnitude of, the peak effect on IPA. Ranitidine coadministration with prasugrel 10-mg MD had no effect on IPA.
3. Ranitidine, coadministered with a clopidogrel 600-mg LD, slightly lowered the Cmax of the active metabolite but did not affect the AUC. Ranitidine, coadministered with clopidogrel during 75-mg MD, did not affect the pharmacokinetics of clopidogrel's active metabolite.
4. Ranitidine coadministration with a clopidogrel 600-mg LD/75-mg MD had no effect on IPA.

Reviewer's Comments:

1. The sponsor properly performed the DDI study between prasugrel or clopidogrel and ranitidine (PPI inhibitor).
2. In the text of this study report the sponsor says that they intend to measure the active metabolite of clopidogrel R-130964, however, in the study Appendix for the assay validation, the results are listed for the other metabolite, R361015 without any explanation.
3. The pharmacokinetics of either of studied drugs were not significantly affected by the coadministration of ranitidine.
4. The sponsor assessed the IPA to 20 and 5 μM ADP in each of the studied arms of the study. At all time points except for the 0.5 hour sample after prasugrel LD and ranitidine the differences in IPA were not statistically significant. The reduction of IPA at 0.5 hour was 12 percentage points, which was associated with a 9 percentage point increase in MPA to 20 μM ADP. This effect is not considered to be of clinical importance.
5. There is no need for the adjustment of the prasugrel dose when it is coadministered with ranitidine.