4.2.4 A Study to Determine the Relative Bioavailability of 5 and 10 mg Prasugrel Tablets (Part A) and to Investigate the Pharmacokinetics of Prasugrel when Administered as a 5, 30 and 60 mg dose (Part B) in Healthy Subjects (TAAW).

Principal Investigator: Dr D. Lee, MD
Study center: Covance Clinical Research Unit Ltd., Springfield House, Hyde Street, Leeds, LS2 9LH, UK.
Study period: 08 June 2006 to 29 August 2006
Phase of development: Phase I

Objectives	Part A: Primary: to compare the relative bioavailability of the active metabolite (R-138727) after administration of 5 and 10 mg prasugrel tablets. Secondary: to compare the relative bioavailability of the inactive metabolites (R-95913, R-106583, and R-119251) after administration of 5 and 10 mg prasugrel tablets, and to further assess the safety and tolerability of prasugrel administered to healthy subjects. Part B: Primary: to assess the dose proportionality of the active metabolite (R-138727) across the prasugrel dose range of 5 to 60 mg. Secondary: to assess the dose proportionality of the inactive metabolites (R-95913, R-106583, and R-119251) across the prasugrel dose range of 5 to 60 mg, and to further assess the safety and tolerability of prasugrel administered to healthy subjects.
Study Design	This was a two-part study. Part A was an open-label, randomized, single oral dose, two-period crossover, relative bioavailability study. Part B was an open-label, randomized, single oral dose, three-period crossover, dose proportionality study. **Part A: Treatment Periods 1 and 2** Dose of 2 x 5 mg or 1 x 10 mg prasugrel* Minimum of 7 days washout between treatments Day -1 (Admission) 1 2 (Discharge) *according to randomisation schedule **Part B: Treatment Periods 1, 2 and 3** Dose of 5 mg, 30 mg or 60 mg prasugrel* Minimum of 7 days washout between treatments Day -1 (Admission) 1 2 (Discharge) *according to randomisation schedule
Study Population	In Part A, 27 subjects received two doses of prasugrel and one subject received a single dose of prasugrel. In Part B, 20 subjects received three doses of prasugrel and one subject received a single dose of prasugrel. Healthy subjects male and female subjects, aged 18 to 60 years, inclusive (N=49 subjects (28 in Part A and 21 in Part B))
Investigational Drug prasugrel	In Part A: a single dose of 10 mg. In Part B, single doses of 5, 30, and 60 mg. Prasugrel was provided as 5 and 10 mg tablets from lot numbers CT526167 and CT526166, respectively.
Dosage and Administration	In Part A, each subject was to receive 10 mg prasugrel on two separate occasions as 2 x 5 mg tablets and 1 x 10 mg tablet. In Part B, each subject was

	to receive 5, 30, and 60 mg prasugrel on three separate occasions as a 1 x 5 mg tablet, 3 x 10 mg tablets and 6 x 10 mg tablets, respectively. For each subject, there was a minimum of 7 days washout between each dose administered.
Blood Sampling:	PK: Samples were collected during each treatment period of Parts A and B at 0.25, 0.5, 1, 1.5, 2, 4, 8, 12 and 24 hours.
Assay	Plasma concentrations of prasugrel active (R-138727) and inactive metabolites (R-95913, R-106583 and R-119251): validated LC/MS/MS methods
PK Assessment	Cmax(ng/mL), Cmax/dose, Tmax (hr), AUC0-24(ng·hr/mL), AUC0-24/dose (ng·hr/mL/mg) for R-138727 and R-130964 (WinNonlin)
Statistical methods	Pharmacokinetic parameter estimates of prasugrel metabolites were evaluated to assess the relative bioavailability of 2 x 5 mg tablets and 1 x 10 mg tablet (Part A), and to assess dose proportionality from 5 to 60 mg prasugrel (Part B). Log-transformed AUC(0-tlast), partial AUCs, and Cmax were evaluated to estimate ratios of geometric means and the corresponding 90% confidence intervals (CI).

Results

Assay:

Table 34: Assay Characteristics of Inactive Metabolites in Plasma

Parameter	R119251	R106583	R95913
Linearity	1 ng/mL to 500 ng/mL		
	Intra-batch	Intra-batch	Intra-batch
Precision (CV %)	2.3 to 4.0	2.3 to 4.0	2.8 to 3.5
Accuracy, %	-2.2 to 2.2	–3.2 to 3.9	6.2 to 14.1
LLOQ	1ng/mL		
Reviewer Comment	The assay characteristics and specificity are satisfactory, representative mass-chromatograms are shown		

Table 35 Assay Characteristics of an Active Metabolite in Plasma

Parameter	R138727
Linearity	0.5 ng/mL to 250 ng/mL
	Intra-batch
Precision (CV %)	3.4 to 6.1
Accuracy, %	-8.45 to 3.9
LLOQ	0.5ng/mL
Reviewer Comment	The assay characteristics and specificity are satisfactory, representative mass-chromatograms are shown

Demographics:

Forty-nine healthy subjects participated in this study, with 28 subjects in Part A and 21 subjects in Part B. Most subjects were Caucasian. Part A comprised 23 male and 5 female subjects aged 18 to 59 years, and Part B comprised 21 male subjects aged 18 to 56 years.

Pharmacokinetics

The figure below shows mean concentration-time profiles of the active metabolite (R-138727) and the three inactive metabolites (R-95913, R-119251, and R-106583) after the two 10-mg doses in Part A and the 5-, 30-, and 60-mg doses in Part B.

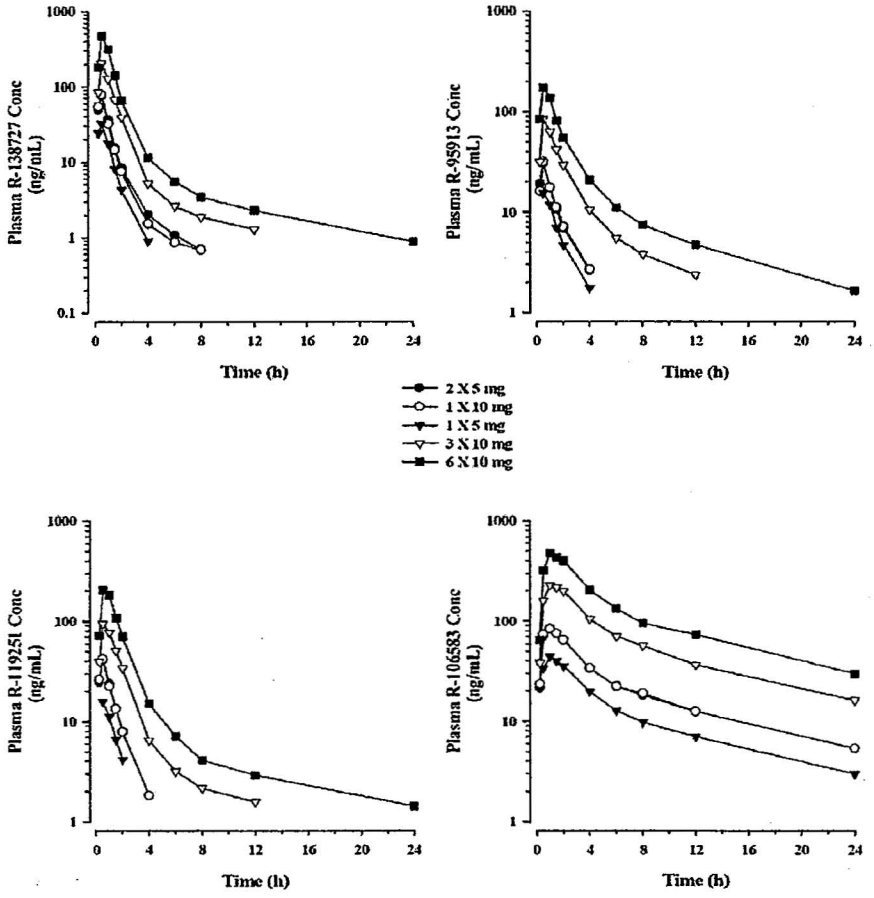


Figure 42. Plasma concentrations (arithmetic mean) of prasugrel's metabolites after single doses.

The tables below summarize the Cmax, tmax, AUC(0-tlast), and relevant partial AUC for the active metabolite and the three inactive metabolites.

Table 36. Noncompartmental Pharmacokinetic Parameter Estimates for R-138727 After Single Prasugrel Doses

	Geometric Mean (%CV)				
Dose (mg)	5	10		30	60
Parameter	1x5 mg (N=21)	2x5 mg (N=27)	1x10 mg (N=27)	3x10 mg (N=20)	6x10 mg (N=20)
C_{max}	37.6	88.3	81.8	225	487
(ng/mL)	(53)	(33)	(37)	(39)	(51)
t_{max}[a]	0.50	0.50	0.50	0.50	0.50
(h)	(0.25-1.00)	(0.25-1.00)	(0.25-4.00)	(0.25-1.00)	(0.25-1.03)
AUC(0-t_{last})	33.2	78.9	77.0	246	537
(ng•h/mL)	(36)	(32)	(37)	(32)	(31)
AUC(0-4h)	33.0[b]	74.1	71.4	224	482
(ng•h/mL)	(35)	(30)	(31)	(31)	(35)

Table 37. Noncompartmental Pharmacokinetic Parameter Estimates for R-95913 After Single Prasugrel Doses

	Geometric Mean (%CV)				
Dose (mg)	5	10		30	60
Parameter	1x5 mg (N=21)	2x5 mg (N=27)	1x10 mg (N=27)	3x10 mg (N=20)	6x10 mg (N=20)
C_{max}	17.9	29.3	28.8	91.6	185
(ng/mL)	(25)	(61)	(51)	(36)	(51)
t_{max}[a]	0.50	0.50	0.50	0.50	0.50
(h)	(0.25-1.00)	(0.25-1.50)	(0.25-1.50)	(0.32-1.50)	(0.25-1.50)
AUC(0-t_{last})	24.0	38.9	39.5	170	364
(ng•h/mL)	(29)	(57)	(55)	(30)	(27)
AUC(0-4h)	22.7	37.5[b]	35.9	129	257
(ng•h/mL)	(23)	(42)	(47)	(27)	(32)

Table 38. Noncompartmental Pharmacokinetic Parameter Estimates for R-119251 After Single Prasugrel Doses

	Geometric Mean (%CV)				
Dose (mg)	5	10		30	60
Parameter	1x5 mg (N=21)	2x5 mg (N=27)	1x10 mg (N=27)	3x10 mg (N=20)	6x10 mg (N=20)
C_{max}	16.7	43.2	40.7	106	226
(ng/mL)	(32)	(38)	(42)	(36)	(46)
t_{max}[a]	0.50	0.50	0.50	0.50	0.50
(h)	(0.25-1.00)	(0.25-1.50)	(0.25-1.50)	(0.32-1.50)	(0.50-1.50)
AUC(0-t_{last})	18.2	48.8	45.7	167	369
(ng•h/mL)	(38)	(36)	(39)	(30)	(32)
AUC(0-2h)	16.7[b]	39.5	37.5	111	235
(ng•h/mL)	(29)	(33)	(37)	(30)	(40)

Table 39. Noncompartmental Pharmacokinetic Parameter Estimates for R-106583 After Single Prasugrel Doses

	Geometric Mean (%CV)				
Dose (mg)	5	10		30	60
Parameter	1x5 mg (N=21)	2x5 mg (N=27)	1x10 mg (N=27)	3x10 mg (N=20)	6x10 mg (N=20)
C_{max} (ng/mL)	46.5 (27)	87.4 (29)	87.7 (30)	242 (31)	479 (36)
t_{max}[a] (h)	1.00 (0.50-2.00)	1.00 (0.50-2.00)	1.00 (0.50-1.52)	1.00 (0.50-2.02)	1.00 (0.50-4.00)
AUC(0-t_{last}) (ng•h/mL)	246 (40)	459 (34)	453 (36)	1310 (40)	2550 (38)

The results of the statistical comparisons between the treatment groups for all metabolites are shown in the table below.

Table 40. Statistical Analysis of Relative Bioavailability between 2x5 mg and 1x10 mg Prasugrel Tablets (Part A)

		Least Squares geometric means		Ratio of geometric least squares means (90% CI)
Metabolite	Parameters	2x5 mg	1x10 mg	2x5 mg / 1x10 mg
R-138727	AUC(0-t_{last}) (ng.h/mL)	78.9	77.1	1.02 (0.988, 1.06)
	AUC(0-4h) (ng.h/mL)	74.1	71.5	1.04 (1.00, 1.07)
	C_{max} (ng/mL)	88.5	82.3	1.08 (0.990, 1.17)
R-95913	AUC(0-t_{last}) (ng.h/mL)	38.9	39.6	0.983 (0.913, 1.05)
	AUC(0-4h) (ng.h/mL)	36.4	36.0	1.01 (0.955, 1.07)
	C_{max} (ng/mL)	29.3	28.8	1.02 (0.940, 1.10)
R-119251	AUC(0-t_{last}) (ng.h/mL)	48.8	45.8	1.07 (1.01, 1.13)
	AUC(0-2h) (ng.h/mL)	39.6	37.7	1.05 (0.993, 1.11)
	C_{max} (ng/mL)	43.3	40.9	1.06 (0.961, 1.16)
R-106583	AUC(0-t_{last}) (ng.h/mL)	459	453	1.01 (0.975, 1.05)
	C_{max} (ng/mL)	87.5	87.9	0.996 (0.955, 1.04)

Two 5-mg prasugrel tablets were bioequivalent to one 10-mg prasugrel tablet. For the active metabolite and the three inactive metabolites, the 90% CI of the ratio of geometric least squares means for Cmax, AUC(0-tlast), and the appropriate partial AUC fell between 0.80 and 1.25. Tmax did not differ between two 5-mg prasugrel tablets and one 10-mg prasugrel tablet (Table below).

Table 41. Statistical Comparison of tmax between 2x5 mg and 1x10 mg Prasugrel Tablets (Part A)

Metabolite	Parameters	Median 2x5 mg	Median 1x10 mg	Median difference (90% CI) 2x5 mg - 1x10 mg
R-138727	t_{max} (h)	0.500	0.500	0 (-0.0200, 0)
R-95913	t_{max} (h)	0.500	0.500	0 (-0.130, 0)
R-119251	t_{max} (h)	0.500	0.500	0 (-0.0200, 0)
R-106583	t_{max} (h)	1.00	1.00	0 (0, 0.0200)

Dose Proportionality (Part B)

Since two 5-mg prasugrel tablets were bioequivalent to one 10-mg tablet, the sponsor combined the pharmacokinetic data from both of the 10-mg treatments in Part A with the same data from the 5-, 30-, and 60-mg prasugrel doses in Part B.

The dose proportionality of the active metabolite could not be concluded over the entire prasugrel dose range of 5 mg to 60 mg. The active metabolite Cmax met the acceptance criterion for dose proportionality, the dose-normalized AUC(0-tlast) exceeded 1.25.

Table 42. Dose Proportionality Analysis between 5, 10, 30, and 60 mg Prasugrel (Parts A and B)

Metabolite	Parameters	Power model equation[a]	95% CI of exponent	R_{dnm} (90% CI)[b]	DPI[c]
R-138727	$AUC(0\text{-}t_{last})$ (ng.h/mL)	$(e^{1.75})*(dose^{1.12})$	(1.09, 1.14)	1.34 (1.27, 1.42)	4.90
	AUC(0-4h) (ng.h/mL)	$(e^{1.79})*(dose^{1.07})$	(1.04, 1.10)	1.20 (1.13, 1.28)	9.36
	C_{max} (ng/mL)	$(e^{2.05})*(dose^{1.02})$	(0.954, 1.08)	1.05 (0.916, 1.20)	22.0[d]
R-95913	$AUC(0\text{-}t_{last})$ (ng.h/mL)	$(e^{1.27})*(dose^{1.09})$	(1.06, 1.12)	1.25 (1.18, 1.34)	6.75
	AUC(0-4h) (ng.h/mL)	$(e^{1.43})*(dose^{0.975})$	(0.945, 1.01)	0.940 (0.883, 1.00)	86.9[d]
	C_{max} (ng/mL)	$(e^{1.28})*(dose^{0.935})$	(0.883, 0.987)	0.850 (0.763, 0.947)	7.78
R-119251	$AUC(0\text{-}t_{last})$ (ng.h/mL)	$(e^{1.01})*(dose^{1.21})$	(1.18, 1.24)	1.70 (1.60, 1.81)	2.54
	AUC(0-2h) (ng.h/mL)	$(e^{115})*(dose^{1.06})$	(1.02, 1.11)	1.17 (1.08, 1.28)	9.52
	C_{max} (ng/mL)	$(e^{1.27})*(dose^{1.09})$	(0.978, 1.09)	1.09 (0.968, 1.22)	15.9[d]
R-106583	$AUC(0\text{-}t_{last})$ (ng.h/mL)	$(e^{3.96})*(dose^{0.947})$	(0.927, 0.968)	0.877 (0.841, 0.916)	24.5[d]
	C_{max} (ng/mL)	$(e^{2.31})*(dose^{0.939})$	(0.910, 0.968)	0.860 (0.810, 0.913)	13.8[d]

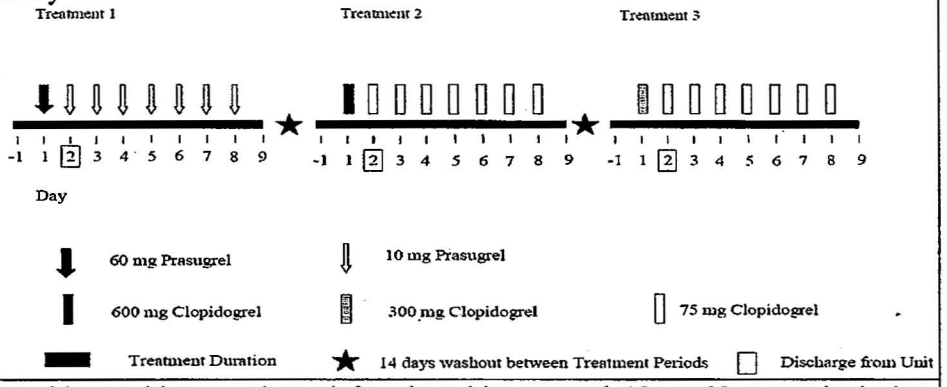
The inactive metabolites R-95913 and R-119251 were not dose-proportional both with respect to AUC and Cmax values. Only R-106583 met the criteria of dose proportionality both with respect to AUC and Cmax values.
The sponsor applied the power model in order to explain the non-proportionality at the high 60 mg dose; however, this model is not acceptable.

Reviewer Comments:

1. Two 5-mg prasugrel tablets were bioequivalent to one 10-mg prasugrel tablet. For the active metabolite and the three inactive metabolites, the 90% CI of the ratio of geometric least squares means for Cmax, AUC(0-tlast), and the appropriate partial AUC fell between 0.80 and 1.25. Tmax did not differ between two 5-mg prasugrel tablets and one 10-mg prasugrel tablet.
2. The active metabolite of prasugrel did not pass the test for the dose proportionality in the dose range from 5 mg to 60 mg for AUC values although it was dose proportional with respect to Cmax.
3. The inactive metabolites R-95913 and R-119251 were not dose-proportional both with respect to AUC and Cmax values. Only late metabolite met the criteria of dose proportionality both with respect to AUC and Cmax values.

4.2.5 Inhibition of platelet aggregation following loading and maintenance dose administration of 60/10 mg prasugrel, 300/75 mg and 600/75 mg clopidogrel in healthy subjects (H7T-EW-TAAZ)

Principal Investigator: Dr Jennie Francis, MD
Study center: Lilly Laboratories for Clinical Research, 550 North University Boulevard, Indianapolis, IN 46202-5250, USA.
Study period: 2 July 2005 to 04 January 2006
Phase of development: Phase I

Objectives	Primary: To compare the pharmacodynamic effect of 300 mg and 600 mg clopidogrel loading doses (LD) and a 60 mg prasugrel loading dose (LD) in healthy subjects. Secondary: To compare the pharmacodynamic effect of 300 mg and 600 mg clopidogrel loading doses followed by 7 days of 75 mg maintenance dosing (MD), and a 60 mg prasugrel loading dose followed by 7 days of 10 mg maintenance dosing (MD) in healthy subjects. To assess the pharmacokinetics of clopidogrel's and prasugrel's active metabolites in healthy subjects after a 300 mg and 600 mg clopidogrel loading dose followed by 7 days of 75 mg maintenance dosing, and after a 60 mg prasugrel loading dose followed by 7 days of 10 mg maintenance dosing. To evaluate the response of the vasodilator-stimulated phosphoprotein (VASP) assay after loading doses of clopidogrel and prasugrel. To assess the safety and tolerability of loading and maintenance doses of prasugrel and clopidogrel in healthy subjects.
Study Design	This was an open-label, randomized, three treatment, three sequence crossover study 
Study Population	Healthy subjects male and female subjects, aged 18 to 65 years, inclusive (N=41)
Investigational Drug	Prasugrel was provided as 10 mg tablets from lot number CT520919.
Comparator drug	Clopidogrel was provided as 75 mg tablets from lot number 1392A.
Dosage and Administration	Prasugrel or clopidogrel treatments in three separate periods, each consisting of single LD on Day 1 followed by 7 daily MDs on Days 2 to 8. Expressed as mg

	LD/mg MD, the specific treatments were prasugrel 60/10, clopidogrel 600/75, and clopidogrel 300/75. A washout of at least 14 days between treatment periods.
Blood Sampling:	PK: Predose (Day 8) and at 0.25, 0.5, 1, 1.5, 2, 4, 8, 12 and 24 hours after the prasugrel or clopidogrel doses on Days 1 and 8. PD, platelet aggregation: predose and at 0.25, 0.5, 1, 2, 4 and 6 hours after the prasugrel and clopidogrel doses on Day 1, predose on Days 2 to 7, and predose and 24 hours after dosing on Day 8. PD,VASP phosphorylation: predose and at 2, 4, 6 and 24 hours after the prasugrel and clopidogrel doses on Day 1.
Assay	Plasma concentrations of R-138727 and R-130964: validated LC/MS/MS methods
PK Assessment	Cmax(ng/mL), Cmax/dose, Tmax (hr), AUC0-24(ng·hr/mL), AUC0-24/dose (ng·hr/mL/mg) for R-138727 and R-130964 (WinNonlin)
PD Assessment	Platelet aggregation: turbidometric method with 5 and 20 μM ADP as the agonist. VASP phosphorylation: flow cytometry.
Statistical methods	Maximum platelet aggregation (MPA) and inhibition of platelet aggregation (IPA): linear mixed effect models (90% CI). Dose proportionality of AUC and Cmax for R-130964: a linear mixed effect model to compare ratios and 90% CI of the dose normalized geometric mean between 75 and 600 mg clopidogrel, and 300 and 600 mg clopidogrel.

Results

Demographics: A total of 41 healthy subjects, 25 males and 16 females, aged 20 to 63 years, inclusive, participated in this study. Subjects were mainly Caucasian, except for 2 males and 7 females of African descent. 33 subjects completed the study. The demographics are shown in the table below.

Assay:

Due to improper blood collection or shipping procedures, 163 plasma samples from 19 subjects (8% of the 2022 samples) were not analyzed. A few samples were not analyzed for VASP phosphorylation because they were received at the analytical laboratory beyond the stability period.

Table 43. Assay Characteristics of the active metabolites of Prasugrel and Clopidogrel

Parameter	R130964		R106583	
Linearity	0.5 ng/mL to 250 ng/mL			
	Inter-batch	Intra-day	Inter-batch	Intra-batch
Precision (CV %)	3.6 to 6.0	0.4 to 3.8	2.7 to 3.6	1.6 to5.2
Accuracy, %	-11.9 to -1.4	-7.9 to -1.0	–9.9 to 3.9	-9.9 to 7.9
LLOQ	1ng/mL			
Reviewer Comment	The assay characteristics and specificity are satisfactory, representative mass-chromatograms are shown			

Pharmacokinetics

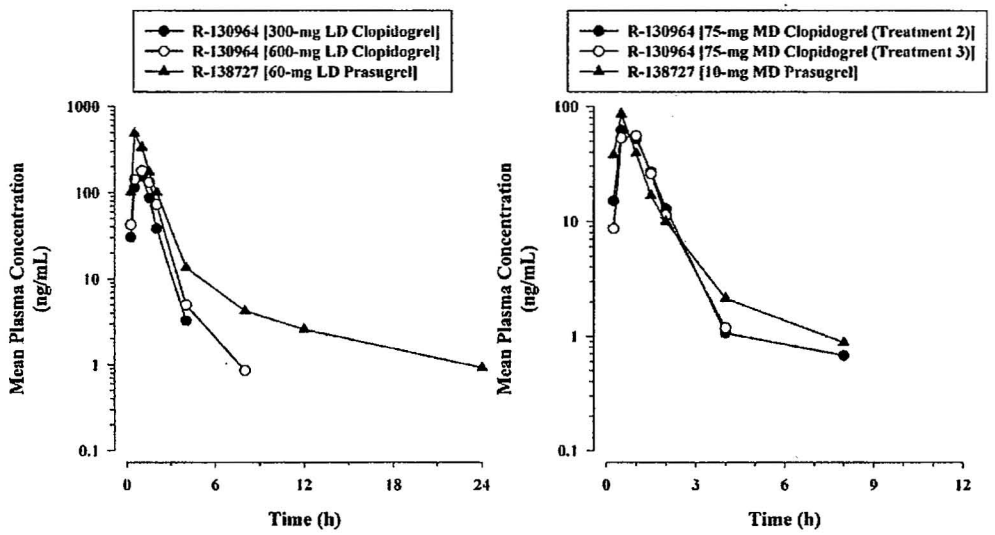


Figure 43. Plasma concentrations (arithmetic mean ± SD) of R-130964 and R-138727 following a single LD (A) and the seventh MD (B) of clopidogrel and prasugrel

In the clopidogrel arm, and in the subjects, who received MD of prasugrel, there were too few samples in the terminal elimination, and parameters based on the elimination phase were not estimated in these treatment groups. The terminal elimination half-life was estimated in all but one subject (Subject 32) after the 60-mg prasugrel LD. The geometric mean half-life (CV) for R-138727 after the LD was 7.4 hours (18%).

Table 44. Pharmacokinetic Parameter Estimates for R-130964 and R-138727 Following a Single LD and the Seventh MD of Clopidogrel and Prasugrel

	Geometric Mean (%CV)		
Parameter	R-130964[a]		R-138727[b]
Dosing Regimen	600-mg LD Clopidogrel (N=31)	300-mg LD Clopidogrel (N=31)	60-mg LD Prasugrel (N=33)
C_{max} (ng/mL)	163 (61)	141 (57)	511 (42)
t_{max}[c] (h)	1.00 (0.50-1.50)	1.00 (0.50-1.10)	0.50 (0.50-2.00)
AUC(0-t_{last}) (ng•h/mL)	267 (47)	185 (55)	594 (32)
Dosing Regimen	75-mg MD Clopidogrel (N=31)	75-mg MD Clopidogrel (N=33)	10-mg MD Prasugrel (N=31)[d]
C_{max} (ng/mL)	57.5 (68)	64.4 (62)	87.4[e] (47)
t_{max}[c] (h)	1.00 (0.50-1.50)	0.50 (0.50-2.00)	0.50[f] (0.25-2.00)
AUC(0-t_{last}) (ng•h/mL)	60.7 (58)	66.1 (55)	82.7[g] (35)

Table 45. Dose Proportionality for the Pharmacokinetic Parameter of R-130964 Following a Single LD and the Seventh MD of Clopidogrel

Dose range	Parameter	Power model equation	Ratio of dose normalised geometric means (90% CI)
75 to 600 mg clopidogrel	AUC(0-t_{last})	1.08*dose$^{0.717}$	0.555 (0.506, 0.609)
	C_{max}	1.94*dose$^{0.509}$	0.360 (0.318, 0.409)
300 to 600 mg clopidogrel	AUC(0-t_{last})	Not applicable	0.740 (0.660, 0.829)
	C_{max}	Not applicable	0.584 (0.529, 0.644)

Pre-defined dose proportional range 0.70, 1.43.

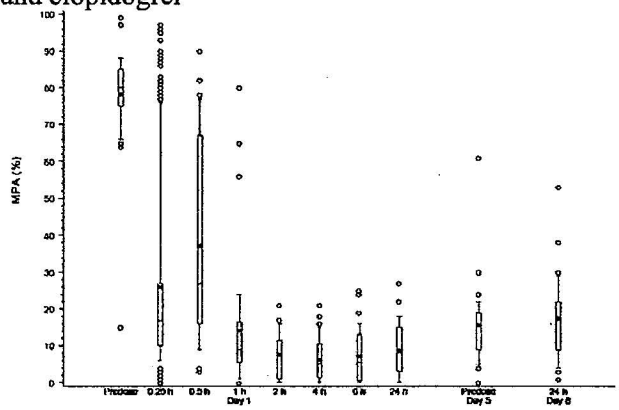
Dose proportionality was assessed for the clopidogrel groups. The mean Cmax and AUC(0-tlast) of R-130964 show a less-than-proportional increase with dose over the clopidogrel dose range of 75- to 600-mg.

For prasugrel's active metabolite R-138727, as the dose changed 6-fold from 10- to 60-mg, R-138727 Cmax changed 5.9-fold, while AUC(0-tlast) changed 7.2-fold.

Pharmacodynamics

Platelet Aggregation

The figures below show the mean MPA to 20 mcM of ADP vs time after the doses of prasugrel and clopidogrel



Box shows median and interquartile range (25% to 75%), and solid block is arithmetic mean. Bars show 10th and 90th percentiles and open circles show values outside these range.

Figure 44. Box plots of MPA response to 20 μM ADP following a single 60-mg LD and daily 10-mg MDs of prasugrel.

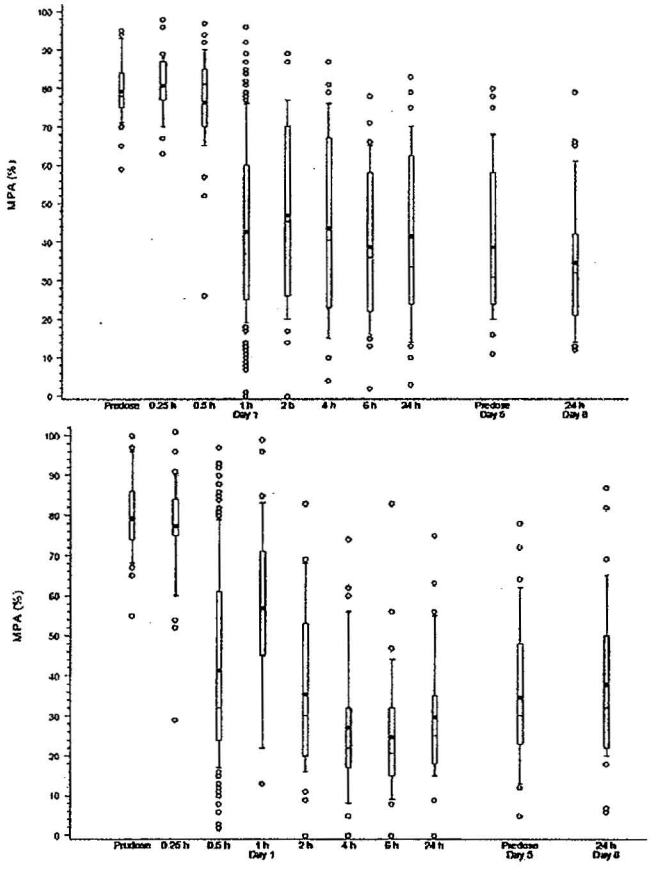


Figure 45. Box plots of MPA response to 20 μM ADP following a single 300 mg (upper panel) or 600-mg (lower panel) LD and daily 75-mg MDs of clopidogrel.

Platelet aggregation was suppressed more quickly after a prasugrel 60-mg LD than after either clopidogrel LD. The median MPA after the prasugrel LD fell to below 20% within 15 minutes postdose, whereas substantial declines in MPA after a clopidogrel LD did not occur until after 15 minutes (for 600-mg) or after 30 minutes (for 300-mg).

The median MPA during the 60-mg/10-mg dosing regimen of prasugrel was lower than that during either the 600-mg/75-mg or 300-mg/75-mg clopidogrel treatment.

The variability in MPA response during the 60-mg/10-mg prasugrel dosing regimen is substantially lower than that during either clopidogrel treatment.

The mean IPA response (90%CI) to 20 mcM ADP after the single doses of prasugrel and clopidogrel compared in the following Figure.

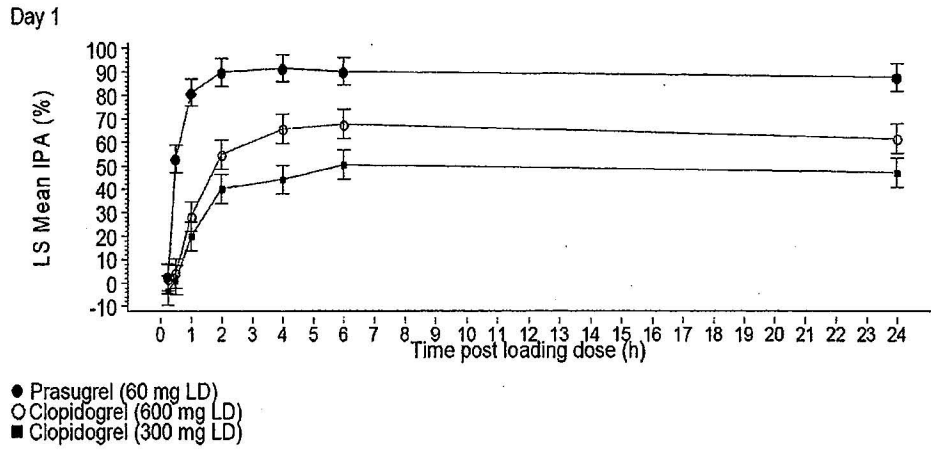


Figure 46. Time profile of least squares mean IPA response (± 90% CI) to 20 μM ADP following a single LD of prasugrel and clopidogrel.

Following a single LD of 60 mg prasugrel, the mean IPA induced by 20 μM ADP was greater compared to single LDs of 300 and 600 mg clopidogrel from 0.5 to 24 hours postdose.
Following single LDs of clopidogrel, maximum mean IPA induced by 20 μM ADP occurred by 6 hours postdose for the 300-mg dose (50%) and by 4 hours for the 600-mg dose (66%). The IPA was greater after the 600-mg dose compared to the 300-mg dose from 1 to 24 hours postdose. Following a single prasugrel LD, maximum mean IPA induced by 20 μM ADP (90%) occurred by 2 hours postdose. The IPA response to 20 μM ADP by 1 hour after the prasugrel LD (81%) exceeded the maximum response after either clopidogrel LD.

The mean IPA response (90%CI) to 20 mcM ADP after the multiple doses of prasugrel and clopidogrel compared in the following Figure.

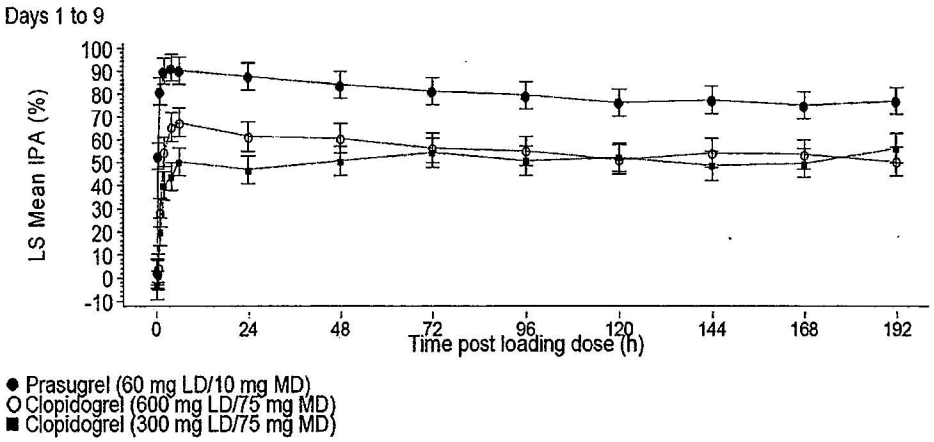


Figure 47. Time profile of least squares mean IPA response (± 90% CI) to 20 μM ADP following a single LD and daily MDs of prasugrel and clopidogrel.