

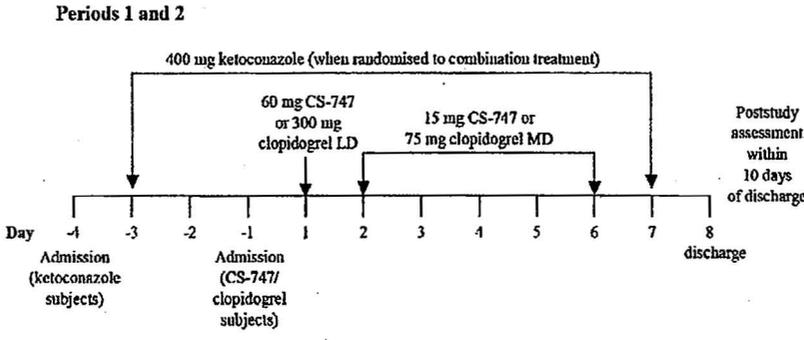
#### 4.2.16 Effect of Ketoconazole on the Pharmacokinetics and Pharmacodynamics of Prasugrel and Clopidogrel Metabolites in Healthy Subjects (H7T-EW-TAAK)

Principal Investigator: J van de Wetering de Rooij, MD

Study center: Pharma Bio-Research, Zuidlaren, The Netherlands.

Study period: 18 December 2003 to 22 April 2004

Phase of development: Phase I

Objectives	<p>Primary: To assess the effect of CYP3A4 inhibition by ketoconazole on the loading dose (LD) and maintenance dose (MD) pharmacokinetics of the prasugrel active metabolite, R-138727.</p> <p>Secondary: To assess and compare the effects of ketoconazole-mediated CYP3A4 inhibition on the pharmacodynamics (inhibition of platelet aggregation (IPA) to 5 and 20 <math>\mu</math>M ADP and bleeding time) of prasugrel and clopidogrel after loading and maintenance dose administration.</p> <p>To assess the effects of ketoconazole mediated CYP3A4 inhibition on the loading and maintenance dose pharmacokinetics of the clopidogrel active and inactive metabolites.</p> <p>To further define the pharmacokinetics and pharmacodynamics of prasugrel metabolites after loading and maintenance dosing.</p> <p>To assess the safety and tolerability of prasugrel given alone and in combination with ketoconazole.</p>
Study Design	<p>This was a single centre, open-label, randomized, two-arm, parallel group study</p> <p>Periods 1 and 2</p>  <p>LD = loading dose; MD = maintenance dose</p>
Study Population	Healthy male and female subjects, aged 19 and 54, inclusive (N=36)
Investigational Drug	<p>Prasugrel: 15 mg tablets, lot number CT508742.</p> <p>Ketoconazole: 200 mg tablets, lot number 03CL171.</p>
Comparator drug	Clopidogrel was provided as 75 mg tablets from lot number 03H01A.
Dosage and Administration	<p>Prasugrel: 60 mg LD (4 x 15 mg), followed by 15 mg MD, given orally in the presence and absence of 400 mg ketoconazole. Clopidogrel: 300 mg LD (4 x 75 mg), followed by 75 mg MD, given orally in the presence and absence of 400 mg ketoconazole. On Day 1 of LD, followed by 5 days MD (Days 2 to 6) of prasugrel or clopidogrel. Ketoconazole co-administration commenced 3</p>

	days prior to LD (Days -3 to -1) and continued throughout MD until Day 7.
Blood Sampling:	PK: 0.25, 0.5, 1, 1.5, 2, 4, 8, 12 and 24 hours (Day 1), 2 hours (Day 2 to 4), and 0.25, 0.5, 1, 1.5, 2, 4, 8, 12, 24, 36 and 48 hours after prasugrel or clopidogrel dosing. PD, platelet aggregation: predose and 4 hours after the prasugrel and clopidogrel doses on Day 1, predose (approximately 24 hours after the previous dose) on Days 2 to 4, and predose, 4, 24, and 48 hours after dosing on Day 6. PD, bleeding time assessment: predose and 4 hours after the prasugrel and clopidogrel doses on Day 1, 4 hours after dosing on Day 2 to 5, and 4, 24, and 48 hours after dosing on Day 6
Assay	Plasma concentrations of metabolites of prasugrel, R-138727, R-95913, R-106583, R-119251, and metabolites of clopidogrel R-130964, SR26334: validated LC/MS/MS methods
PK Assessment	$C_{max}$ (ng/mL), $T_{max}$ (hr), $AUC_{0-24}$ (ng·hr/mL), for R-138727, R-130964, R95913, R119251, R106583 and SR26334 (WinNonlin)
PD Assessment	Platelet aggregation: turbidometric method with 5 and 20 $\mu$ M ADP as the agonist. Bleeding time assessment: Ivy technique.
Statistical methods	Maximum platelet aggregation (MPA) and inhibition of platelet aggregation (IPA): The sample size for CS-747 provided a 90% chance of declaring no clinically meaningful effect on exposure if no interaction exists. This sample size is based on the higher of the two within-subject variability (as described by the CV estimates) of 16% for R-138727 AUC during multiple dosing and 20% for R-95913 AUC during multiple dosing. The variability in $C_{max}$ , which has a CV of about 40%, was not considered when sizing this study. This assumed that lack of CYP3A inhibition was declared if the 90% confidence interval for the ratio of means for AUC of R-138727 was contained within the range of 0.80 to 1.25. If ketoconazole affected the AUC of CS-747, 18 subjects were expected to be adequate to estimate the AUC ratio, with and without ketoconazole, of R-95913 to within 11% of the true ratio with 90% confidence and to estimate the AUC ratio, with and without ketoconazole, of R-138727 to within 9% of the true ratio with 90% confidence.

## Results

### Demographics:

A total of 36 healthy subjects, 35 males and 1 females, aged 20 to 63 years, inclusive, participated in this study. Subjects were mainly Caucasian, except for 5 Afro-Caribbean and 1 Mongolian/Caucasian subject. Summary of demographics is presented in the table below.

**Table 105 Summary of subject demographics**

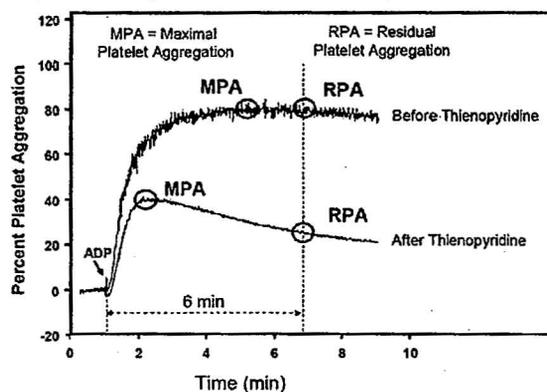
Parameter	CS-747 Group		Clopidogrel Group	
	Mean (SD) (N=18)	Range (N=18)	Mean (SD) (N=20)	Range (N=20)
Age (years)	35 (10)	19-54	30 (9)	20-53
Body weight (kg)	83.1 (9.3)	70.5-110.9	76.7 (10.7)	60.7-95.8
Height (cm)	183 (6)	175-202	182 (8)	161-199
Body mass index (kg/m <sup>2</sup> )	24.8 (2.4)	21.5-30.1	23.2 (2.4)	19.0-28.6

**Assay:****Table 106 Method validation data using LCMS assay.**

<b>Parameter</b>	<b>R138727</b>	
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	
<b>Parameter</b>	<b>R130964</b>	
linearity	1.0 to 200 ng/ml	
	Intra-day	Inter-day
%CV	3.9 to 11.4%	1.6 to 5.2%
%RE	-9.8 to -1.5%	-0.1 to 15.0%
LLOQ	1.0 ng/ml	
<b>Parameter</b>	<b>R95913</b>	
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	
<b>Parameter</b>	<b>R119251</b>	
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	
<b>Parameter</b>	<b>R106583</b>	
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	
<b>Parameter</b>	<b>SR26334</b>	
linearity	5 to 250 ng/ml	

	Intra-day	Inter-day
%CV	0.9 to 1.9%	1.9 to 3.6%
Accuracy (%)	-2.0 to 3.7%	0.0 to 4.3%
LLOQ	4.92 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 were analyzed using LC/MS. Plasma SR26334 was analyzed using GC/MS. All the validations were conducted by selecting three nominal concentrations.



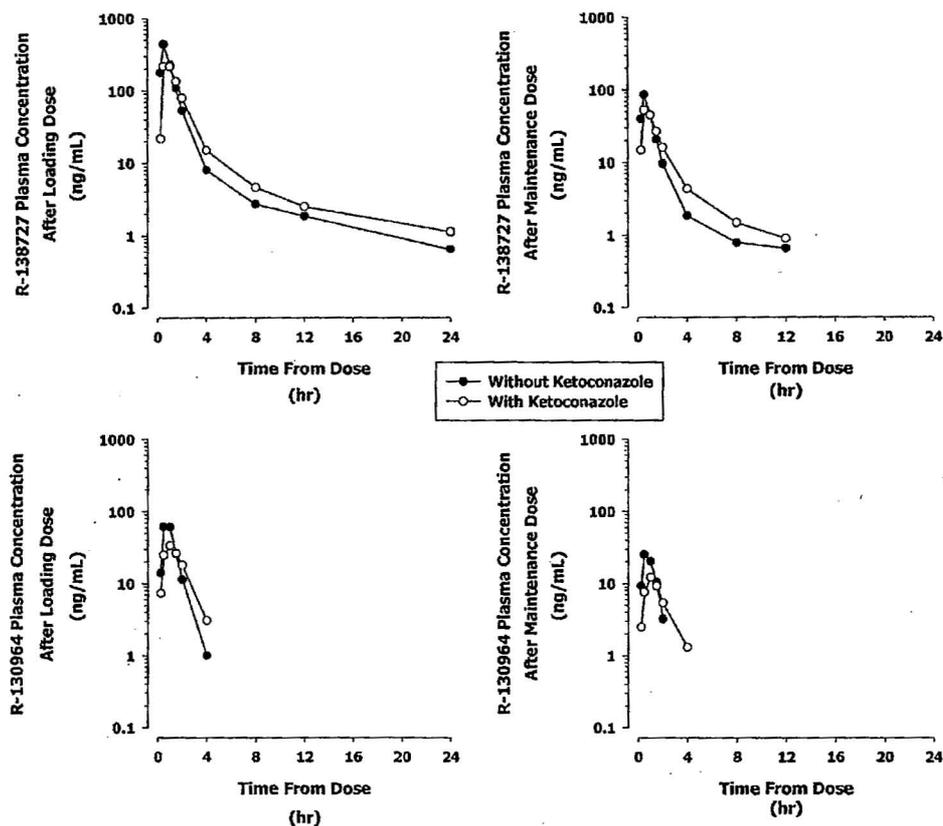
**Figure 90 Light transmission aggregation tracings from pre and post administration of a thienopyridine.**

The above figure represents aggregation tracings from pre and post administration of thienopyridine. After ADP addition, light transmission / aggregation increases due to the platelet aggregation that is recorded. Maximal platelet aggregation is defined as the maximum aggregation (increase in the light transmission) seen during the monitoring period. Residual platelet aggregation is the percent aggregation presented after 6 minutes following addition of ADP.

#### **Pharmacokinetics:**

##### **Effect of ketoconazole on the active metabolites of prasugrel and clopidogrel:**

The figure below compares the plasma concentration time profile of R-138727 and R-130964 for all treatment arms.



**Figure 91** The mean plasma concentrations of the active metabolites after a 60 mg loading dose and the final 15 mg maintenance dose of prasugrel (upper plots) and a 300 mg loading dose and the final 75 mg maintenance dose of clopidogrel (lower plots).

The mean  $C_{max}$  of the active metabolites of prasugrel and clopidogrel, R-138727 and R-130964 were reduced by 46% and 47%, respectively, after co-administration of LD of prasugrel or clopidogrel with ketoconazole. After co-administration of LD of prasugrel or clopidogrel with ketoconazole, the  $AUC_{0-t}$  values of R-138727 and R-130964 were reduced by 11% and 20%,. The mean  $C_{max}$  of R-138727 and R-130964 was reduced by 34% and 60%, , after co-administration of MD of prasugrel or clopidogrel with ketoconazole. After co-administration of MD of prasugrel or clopidogrel with ketoconazole, the  $AUC_{0-t}$  values of R-138727 were increased by 9%, and R-130964 were reduced by 32% (Table below).

**Table 107 Pharmacokinetic parameters for R-138727 and R-130964 after prasugrel or clopidogrel dosing without or with steady-state ketoconazole**

Loading Dose: 60 mg CS-747 or 300 mg Clopidogrel				
Parameter	CS-747 Active Metabolite R-138727		Clopidogrel Active Metabolite R-130964 <sup>a</sup>	
	Without Ketoconazole (N <sub>PK</sub> = 18)	With Ketoconazole (N <sub>PK</sub> = 18)	Without Ketoconazole (N <sub>PK</sub> = 18)	With Ketoconazole (N <sub>PK</sub> = 18)
t <sub>max</sub> <sup>b</sup> (h)	0.50 (0.50 - 1.00)	0.51 (0.50 - 1.50)	0.50 (0.50 - 1.05)	1.00 (0.50 - 1.50)
C <sub>max</sub> (ng/mL)	465 (32.0)	253 (45.5)	65.9 (39.9)	34.8 (42.1)
AUC(0-t <sub>last</sub> ) (ng·h/mL)	451 (23.3)	401 (34.0)	75.4 (31.3)	60.1 (47.4)
AUC(0-24) (ng·h/mL)	452 (22.9)	403 (33.6)	76.7 (30.7)	62.3 (46.2)
t <sub>1/2</sub> <sup>c</sup> (h)	6.56 (32.8)	7.20 (37.0)	0.524 (22.6)	1.28 (136)

Maintenance Dose: 15 mg CS-747 or 75 mg Clopidogrel Once-Daily				
Parameter	CS-747 Active Metabolite R-138727		Clopidogrel Active Metabolite R-130964 <sup>a</sup>	
	Without Ketoconazole (N <sub>PK</sub> = 18)	With Ketoconazole (N <sub>PK</sub> = 18)	Without Ketoconazole (N <sub>PK</sub> = 18)	With Ketoconazole (N <sub>PK</sub> = 17)
t <sub>max</sub> <sup>b</sup> (h)	0.50 (0.25 - 1.03)	0.50 (0.50 - 1.02)	0.50 (0.25 - 1.50)	1.00 (0.50 - 2.00)
C <sub>max,ss</sub> (ng/mL)	89.7 (43.0)	59.6 (39.5)	29.3 (36.9)	11.6 (61.3)
AUC(0-t <sub>last</sub> ) (ng·h/mL)	87.3 (30.8)	95.2 (34.9)	25.8 (36.0)	17.5 (59.3)
AUC(0-24) (ng·h/mL)	91.0 (29.9)	97.1 (33.9)	27.0 (34.4)	19.5 (53.7)
t <sub>1/2</sub> <sup>c</sup> (h)	4.65 (52.3)	6.51 (87.9)	0.374 (46.2)	0.850 (26.1)

**Effect of ketoconazole on the inactive metabolites of prasugrel and clopidogrel:**

There was an increase in the exposure (AUC<sub>0-t</sub>) for R-95913 and decrease in R-119251 and R-106583 with ketoconazole administration after a 60 mg of LD and during a 10 mg MD of prasugrel administration. The mean C<sub>max</sub> of the inactive metabolites of prasugrel and clopidogrel R-95913 and SR26334 increased by 72% and 18%, and the C<sub>max</sub> of the other inactive metabolites of prasugrel (R-119251, R-106583) were reduced by 56%, 60% respectively, after co-administration of 60 mg LD of prasugrel or clopidogrel with ketoconazole. The AUC<sub>0-t</sub> of R-95913 and SR26334 increased by 99% and 46%, and R-119251 and R-106583 reduced by 25% and 40%, after co-administration of 60 mg LD of prasugrel or clopidogrel with ketoconazole.

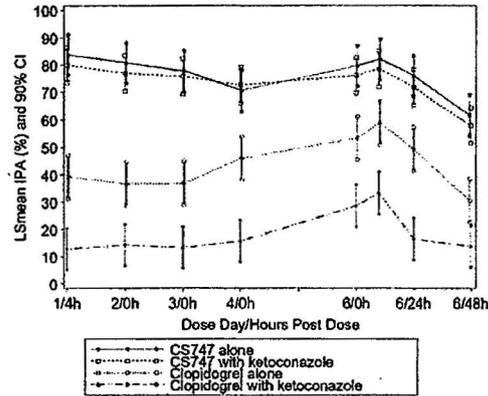
The mean C<sub>max</sub> of R-95913 and SR26334 increased by 94% and 16% respectively, and R-119251, R-106583 were reduced by 44%, 59% respectively, after co-administration of a 10 mg MD of prasugrel or clopidogrel with ketoconazole. The AUC<sub>0-t</sub> of R-95913 and SR26334 were increased by 110% and 65% respectively, and R-119251 and R-106583 were reduced by 13% and 35% respectively, after co-administration of 10 mg MD of prasugrel or clopidogrel with ketoconazole.

**Pharmacodynamics:**

Inhibition of platelet aggregation was measured using turbidometric methodology at two concentrations of ADP: 5 μM and 20 μM. A concentration of 20 μM ADP provides better assessment of P2Y12 inhibition.

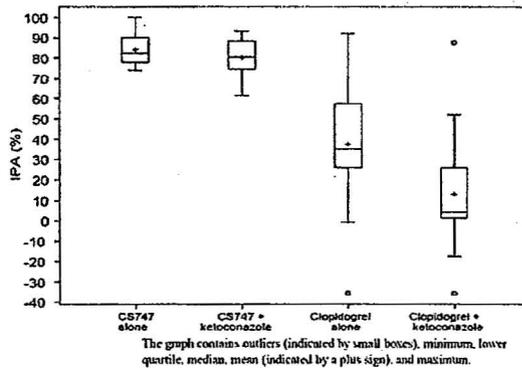
**Platelet Aggregation:**

The figure below compare the % IPA response to 20 μM ADP for all treatment arms. The IPA (%) response were similar when prasugrel administered alone compared with co-administration of prasugrel along with ketoconazole.



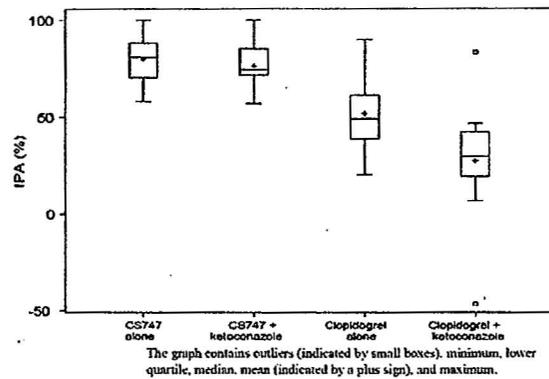
**Figure 92 Time profile of the estimated mean IPA response (with 90% CI) to 20 μM ADP.**

The figure below compares the IPA response to 20 μM ADP on Day 1 at 4 hours for all treatment arms. The IPA response was similar when prasugrel was administered alone compared to the administration of prasugrel with ketoconazole.



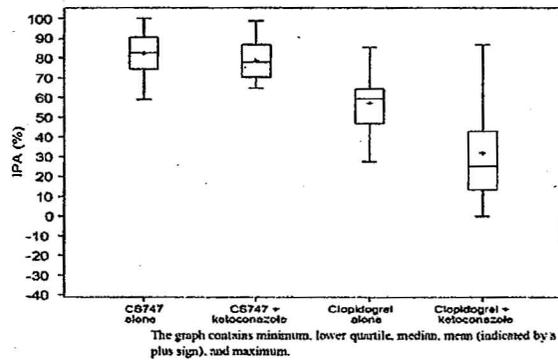
**Figure 93 Distribution of IPA response to 20 μM ADP on Day 1 at 4 hours after the loading dose.**

The figure below compares the IPA response to 20 μM ADP on Day 6 for all treatment arms. The IPA response was similar when prasugrel administered alone compared to the administration of prasugrel with ketoconazole.



**Figure 94 Distribution of IPA response to 20 μM ADP predose on Day 6.**

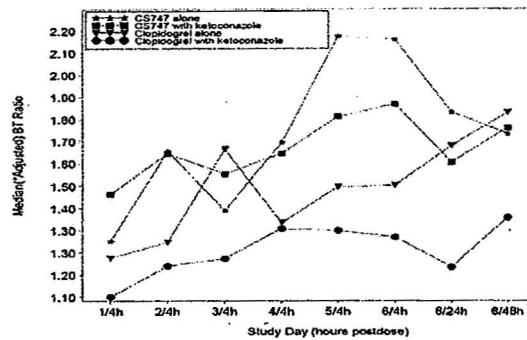
The figure below compares the IPA response to 20 μM ADP on Day 6 at 4 hours for all treatment arms. The IPA response was similar when prasugrel administered alone compared with co-administration of prasugrel along with ketoconazole.



**Figure 95 Distribution of IPA response to 20 μM ADP 4 hours postdose on Day 6.**

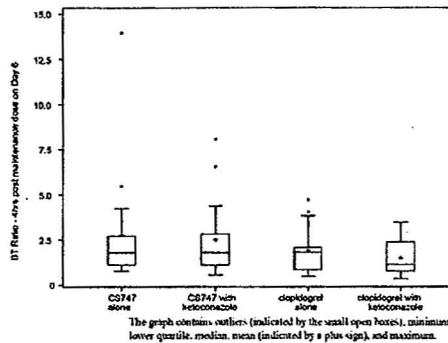
**Bleeding time assessment:**

The figure below compares the bleeding time ratios for all treatment arms. The prolongation in the bleeding time ratio following prasugrel administration was higher than the prolongation induced by clopidogrel on Day 5 at 4 hours postdose. The bleeding time ratio was reduced from Day 4 to Day 6 following co-administration of the prasugrel with ketoconazole.



**Figure 96 Time profiles of predicted median bleeding time ratios.**

The figure below compares the bleeding time ratios on Day 6 at 4 hours for all arms. The prolongation in the bleeding time ratio following prasugrel administration was higher than the prolongation induced by clopidogrel.



**Figure 97 Distribution of bleeding time ratios by treatment group on Day 6 at 4 hours postdose.**

**COMMENTS:**

1. The mean  $C_{max}$  of active metabolites of prasugrel and clopidogrel, R-138727 and R-130964 were reduced by 34% and 60%, respectively, after co-administration of MD of prasugrel or clopidogrel with ketoconazole. The  $AUC_{0-t}$  of R-138727 was not affected by co-administration of MD of prasugrel with ketoconazole.
2. Following prasugrel administration, the bleeding time ratios on Day 5 at 4 hours postdose increased by 45% compared to clopidogrel arm.
3. Since the co-administration of ketoconazole with prasugrel has a minimal effect on the PK of prasugrel the interaction with other CYP3A4 inhibitors will not be the major concern. The dose adjustment is not necessary.

**4.2.17 Effect of Atorvastatin on the Pharmacokinetics and Pharmacodynamics of Prasugrel and Clopidogrel Metabolites in Healthy Male Subjects (H7T-EW-TAAV)**

Principal Investigator: Dr Dick de Vries, Dr Renger Tiessen.

Study center: Pharma Bio-Research Group B.V, Stationsweg 163, 9471 GP Zuidlaren, The Netherlands.

Study period: 13 October 2005 through 27 June 2006.

Phase of development: Phase I

<p>Objectives</p>	<p>Primary: To assess the effect of atorvastatin on the inhibition of platelet aggregation (IPA) response to 5 and 20 <math>\mu</math>M adenosine diphosphate (ADP) after a 60-mg prasugrel loading dose (LD) and 10-mg maintenance dose (MD) administration in healthy male subjects..</p> <p>Secondary: To assess the effect of atorvastatin on the IPA response to 5 and 20 <math>\mu</math>M ADP after 300-mg clopidogrel LD and 75-mg MD administration.</p> <p>To assess the effect of atorvastatin on the LD and MD pharmacokinetics of the prasugrel active metabolite, R-138727, inactive metabolites R-95913, R-106583, and R-119251, and clopidogrel active metabolite, R-130964.</p> <p>To explore the effect of warfarin on inhibition of platelet aggregation.</p> <p>To assess the safety and tolerability of clopidogrel and prasugrel given alone and in combination with atorvastatin.</p> <p>To evaluate the response of the vasodilator-stimulated phosphoprotein (VASP) assay after LD of clopidogrel and prasugrel.</p>
<p>Study Design</p>	<p>This was an open-label, two-arm crossover study conducted in parallel.</p> <p style="text-align: center;">Study Day</p> <p> <span style="display: inline-block; width: 10px; height: 10px; background-color: black; margin-right: 5px;"></span> 60 mg Prasugrel or 300 mg Clopidogrel  <span style="display: inline-block; width: 10px; height: 10px; border: 1px solid black; margin-right: 5px;"></span> 10 mg Prasugrel or 75 mg Clopidogrel  <span style="display: inline-block; width: 10px; height: 10px; border: 1px solid black; margin-right: 5px;"></span> 80 mg Atorvastatin  <span style="display: inline-block; width: 10px; height: 10px; background-color: black; margin-right: 5px;"></span> Residential period  <span style="font-size: 1.2em;">★</span> A minimum of 14 days washout between Treatment Periods         </p>
<p>Study Population</p>	<p>Healthy male and female subjects aged between 18 and 60 years, inclusive (N=69).</p>
<p>Investigational Drug</p>	<p>Prasugrel: 10 mg tablets, lot number CT522762. Atorvastatin: 80 mg tablets.</p>
<p>Comparator drug</p>	<p>Clopidogrel: 75 mg tablets.</p>
<p>Dosage and Administration</p>	<p>A single dose of 60 mg prasugrel or 300 mg of clopidogrel LD on Day 1, followed by 10 mg of prasugrel or 75 mg of clopidogrel MD for 10 days in each of the 2 treatment periods. In other treatment period subjects received 80 mg of daily atorvastatin for 17 days (Days -6 to 11). Co administration of a single dose of 60 mg prasugrel or 300 mg of clopidogrel LD (on Day 1), followed by 10 mg of prasugrel or 75 mg of clopidogrel MD for 10 days in each of the treatment periods. There was a washout period of 14 days between the two treatment periods.</p>

Blood Sampling:	<p>PK: Blood samples for the determination of plasma concentrations of R-138727 (prasugrel active metabolite) and R-130964 (clopidogrel active metabolite) were collected predose, 0.25, 0.5, 1, 1.5, 2, 4, 6, 8, 12, and 24 hours postdose on Day 1 and 11 in each treatment periods. R-95913, R-106583, and R-119251 (prasugrel inactive metabolites) at 0.5, 1, 2, 4, 6, 8 and 12 hours postdose on Day 1, and predose, 0.5, 1, 2, 4, 6, 8 and 12 hours postdose on Day 11.</p> <p>PD, platelet aggregation: Blood samples were collected at 0.5, 1, 2, 4, 6, and 24 hours post prasugrel or clopidogrel LD dose on Day 1, and predose, 0.5, 1, 2, 4, 6 and 24 hours post prasugrel or clopidogrel MD dose on Day 11.</p> <p>PD, VASP phosphorylation: Blood samples were collected at predose, 2, 4, 6, and 24 hours postdose on Day 1.</p>
Assay	<p>Plasma concentrations of prasugrel active and inactive metabolites and the clopidogrel active metabolite were assayed using validated liquid chromatography with tandem mass spectrometric detection (LC/MS/MS) methods.</p> <p>Platelet aggregation in platelet-rich plasma was measured using the turbidometric method with 5 and 20 <math>\mu\text{M}</math> ADP as the agonists. VASP phosphorylation was measured using flow cytometry.</p>
PK Assessment	<p><math>C_{\text{max}}</math> (ng/mL), <math>T_{\text{max}}</math> (hr), <math>\text{AUC}_{0-t}</math> (ng-hr/mL) were calculated for active metabolites of prasugrel and clopidogrel (WinNonlin).</p>
PD Assessment	<p>Platelet aggregation: Inhibitory platelet activity (% IPA), Maximum platelet activity (% MPA), Platelet aggregation in platelet-rich plasma was measured using the turbidometric method.</p> <p>VASP phosphorylation. Platelet reactivity index (PRI), VASP phosphorylation was measured using flow cytometry.</p>
Statistical methods	<p>A linear mixed effect model was fitted to analyze the log-transformed pharmacokinetic parameters including AUC and <math>C_{\text{max}}</math> for the active metabolites of prasugrel or clopidogrel. The 90% CI for the geometric mean ratio of each parameter between treatments was calculated through this model. The <math>T_{\text{max}}</math> analyzed using the Wilcoxon sign rank test. The test treatment was prasugrel or clopidogrel with atorvastatin; the reference was prasugrel or clopidogrel alone. MPA and IPA to 5 and 20 <math>\mu\text{M}</math> ADP, and VASP platelet reactivity index (PRI) were evaluated to estimate the pharmacodynamic mean differences and corresponding 90% CI between test and reference treatments using a linear mixed effect model.</p>

## Results

### Demographics:

A total of 69 healthy male subjects, aged 18 to 60 years, inclusive, participated in the study. 62 subjects were Caucasians, 4 were Afro-Caribbean, 2 were Caucasian / Asian and 1 was Caucasian / South American. The mean age of all the subjects participated in the study was 36.5 years, mean body weight of 78.8 kg, mean height of 179.5 cm, and mean BMI of 24.5  $\text{kg}/\text{m}^2$ .

In 4 subjects there were increased liver enzymes during atorvastatin administration alone, prasugrel LD and MD alone, co-administration of atorvastatin along with clopidogrel LD and MD. In 1 subject there was an increase in ALT, AST, CK levels during exercise following co-

administration with clopidogrel LD and MD along with atorvastatin. Epistaxis was resulted in 1 subject during administration of atorvastatin. A serious adverse event resulted in liver failure during coadministration of prasugrel LD and MD along with atorvastatin.

**Assay:**

The samples were analyzed for R- and S-warfarin using a validated liquid chromatography with tandem mass spectrometric detection (LC/MS/MS) method. The LLOQ for R-138727, R-119251, R-106583, R-95913 were 0.5, 1, 1, 1 ng/ml respectively.

**Table 108 Validation parameters for plasma metabolites of prasugrel and clopidogrel.**

	<b>Plasma R-138727</b>
linearity	0.5 to 250 ng/ml
Precision (RSD)	2.59 to 4.56%
Accuracy (RE)	-7.20 to 7.00%
LLOQ	0.5 ng/ml
	<b>Plasma R-119251</b>
linearity	1 to 500 ng/ml
Precision (RSD)	3.57 to 5.12%
Accuracy (RE)	-3.25 to 4.00%
LLOQ	1 ng/ml
	<b>Plasma R-106583</b>
linearity	1 to 500 ng/ml
Precision (RSD)	2.73 to 5.31%
Accuracy (RE)	-3.75 to 2.00%
LLOQ	1 ng/ml
	<b>Plasma R-95913</b>
linearity	1 to 500 ng/ml
Precision (RSD)	2.89 to 4.75%
Accuracy (RE)	-3.20 to 2.80%
LLOQ	1 ng/ml
Reviewer Comment	This assay characteristics and specificity are satisfactory, and representative MS chromatograms are presented.

**Pharmacokinetics:**

**Pharmacokinetics of active metabolites prasugrel and clopidogrel in the presence and absence of atorvastatin:**

Figure 98 compares the plasma concentration time profile of R-138727 for all treatment arms.. There was no change in the plasma concentration with time ( $AUC_{0-24}$ ) for R-138727 with atorvastatin administration after 60 mg of prasugrel LD. However there was an increase in the plasma concentration with time ( $AUC_{0-8}$ ) for R-138727 with atorvastatin administration during prasugrel MD.