

During daily MD of 10 mg prasugrel, mean IPA to 20 μ M ADP gradually decreased up to Day 6 predose, and thereafter was maintained at approximately 77%. During daily MD of 75 mg clopidogrel, mean IPA to 20 μ M ADP decreased slightly after the 600-mg LD through approximately Day 4, after which the mean IPA in the two clopidogrel treatment groups remained essentially the same at about 50%.

VASP Phosphorylation

Following administration of a single LD of prasugrel or clopidogrel, there was a significant reduction in VASP phosphorylation from 2 to 24 hours after dosing (Figure below). After the prasugrel 60 mg dose the maximal change was 75 PRI%, after the clopidogrel 600 mg dose the maximal change was 47 PRI%, and after the clopidogrel 300 mg dose the maximal change was 31 PRI%.

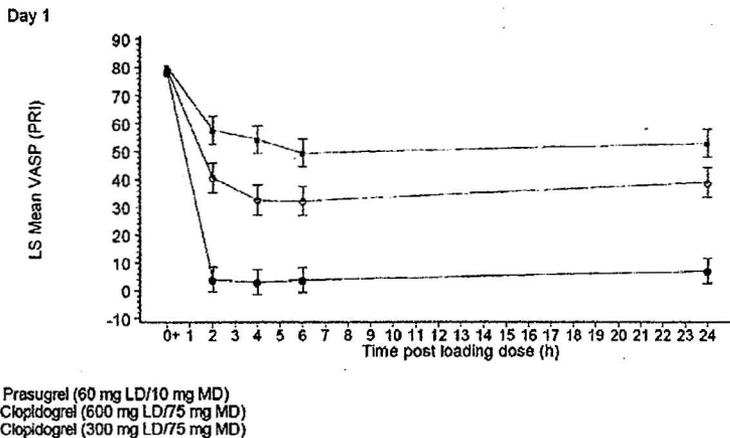
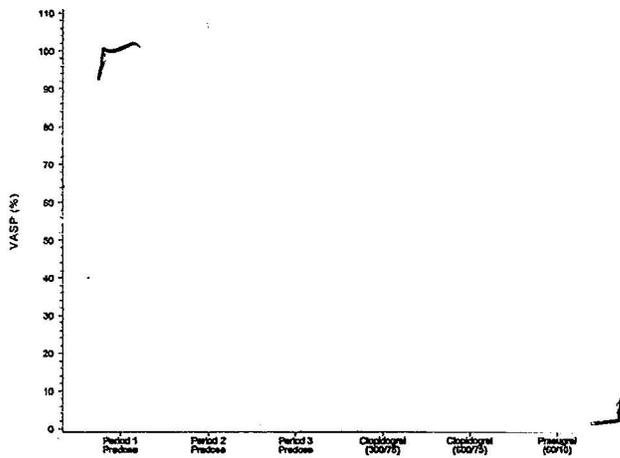


Figure 48. Time profile of least squares mean (90% CI) VASP phosphorylation following a single LD of prasugrel and clopidogrel.

A value of 64.1 PRI% was used as the lower limit of the normal range, representing the mean baseline VASP minus two standard deviations. The VASP phosphorylation response at 24 hours following LDs of prasugrel and clopidogrel is shown in the figure below.

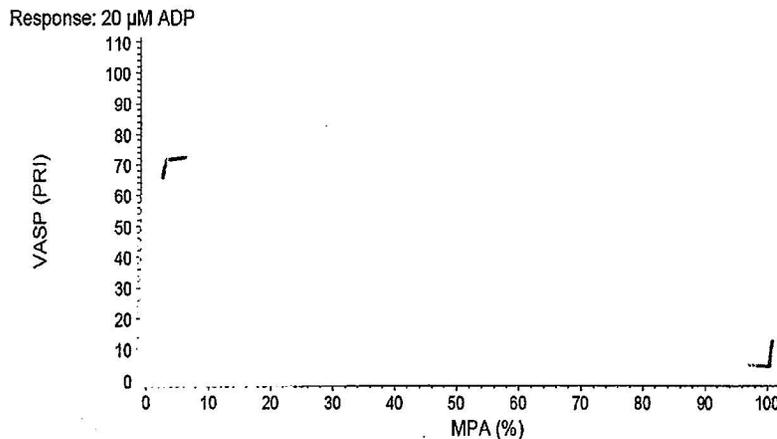


b(4)

Figure 49. VASP phosphorylation response at 24 hours following LDs of prasugrel and clopidogrel.

The response to VASP, as measured by VASP values below the lower limit of normal, were similar to those determined on the basis of IPA to 20 μ M ADP, with generally the same subjects showing no response to both IPA and VASP following LDs of clopidogrel.

The sponsor attempted to correlate these two biomarkers, MPA measured by turbidometric platelet aggregation and VASP PRI (Figure below).



b(4)

Figure 50. MPA to 20 μ M ADP vs VASP phosphorylation at 6 hours following LDs of prasugrel and clopidogrel.

The Pearson correlation coefficient was 0.72, indicating that the correlation was between weak and moderate. The sponsor did not discuss the outcome of these correlation analysis.

Pharmacokinetic/Pharmacodynamic Correlation

The sponsor's scatter plots of IPA to 20 μ M ADP at 24 hours postdose versus AUC(0-tlast) after LDs and MDs of clopidogrel and prasugrel are shown in Figures below.

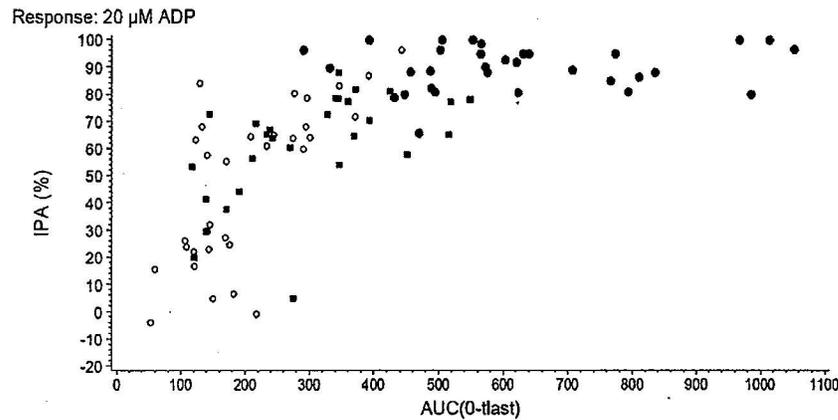


Figure 51. Scatter plot of IPA response to 20 μ M ADP at 24 hours versus AUC(0-tlast) (ng•hr/mL) following LDs of prasugrel and clopidogrel

The sponsor concluded that a prasugrel LD of 60 mg approached the maximum effect (E_{max}) in most subjects. The increase of AUC(0-tlast) above 600 ng•hr/mL did not produce a further increase in IPA. The exposure and the IPA response to a 60 mg LD of prasugrel were generally higher than that produced by a 600 mg LD of clopidogrel, and that only the 60 mg prasugrel LD produced an AUC(0-tlast) above 600 ng•hr/mL whereas all AUC estimates after the clopidogrel LDs are below 600 ng•hr/mL.

This conclusion base don the Figure above deems arbitrary.

The sponsor performed a Spearman Rank Test correlation analyses between plasma levels of

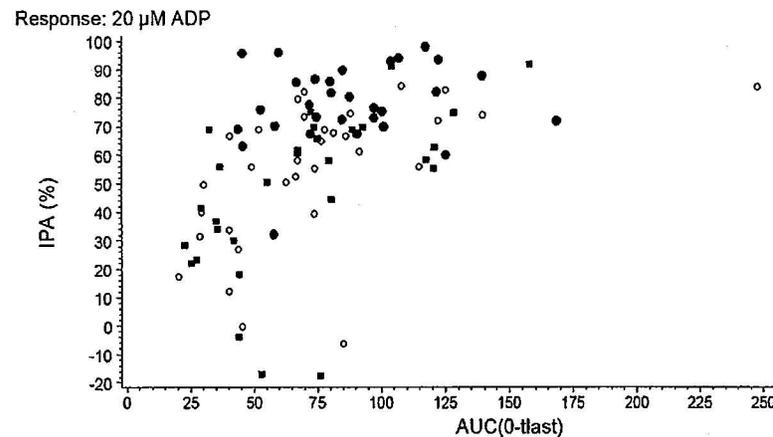


Figure 52. Scatter plot of IPA response to 20 μ M ADP at 24 hours versus AUC(0-tlast) (ng•hr/mL) following the seventh MD of prasugrel and clopidogrel

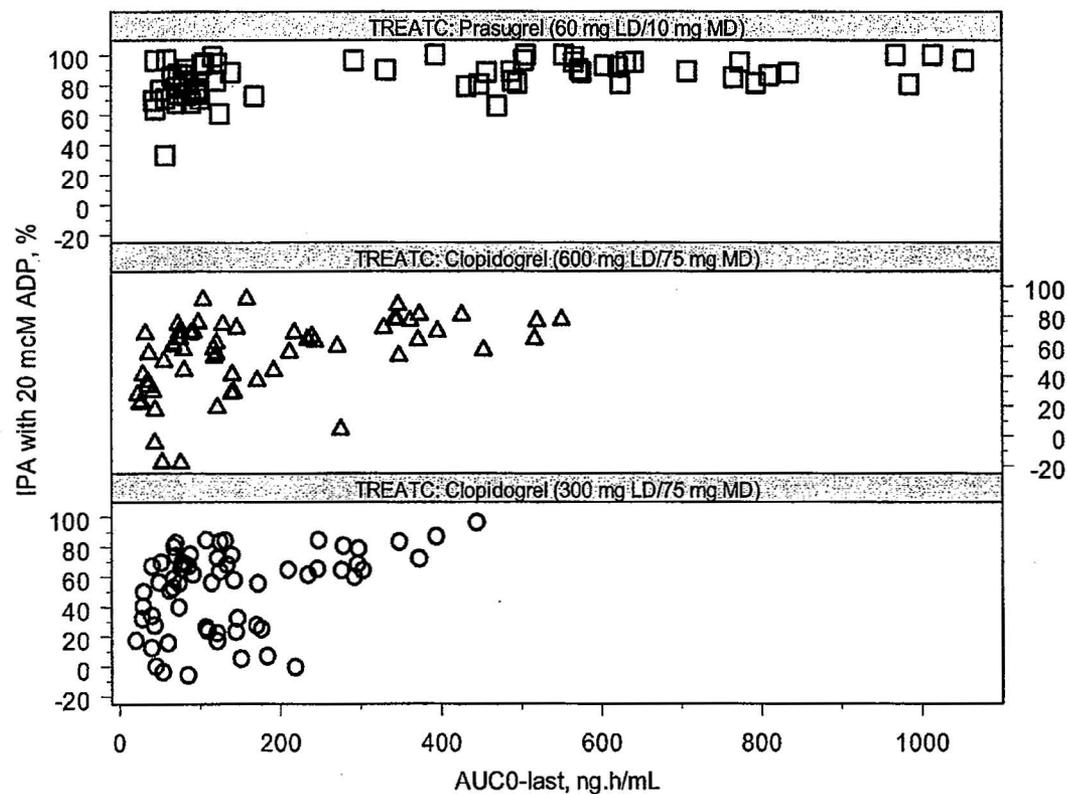


Figure 53. IPA with ADP 20mcM vs AUC of clopidogrel and prasugrel. Blue symbols – LD, Red symbols – MD.

The Figure above shows the IPA response vs AUC0-last for each of the treatments. The IPA response above 80% is observed in each arm of the treatments although the variability lower in the prasugrel arm. The sponsor did not provide the justification of the clinical significance to have platelet aggregation to be suppressed above 80%. However, the strong inhibition of platelet aggregation is well correlated with the prolongation of bleeding time.

Reviewer's Comments:

1. The platelet aggregation in subjects received a loading 60 mg and maintenance 10 mg (60/10) doses of prasugrel was larger, and the variability of this response was smaller that in subjects received clopidogrel 300/75mg or 600/75mg. The sponsor's claim that the AUC0-last values of 600 ng•hr/mL and above provide the best response of the inhibition of platelet aggregation does not deem to be appropriate.
2. The prasugrel treatment also was associated with the prolongation of bleeding time in comparison with the prolongation of bleeding time clopidogrel arms.

3. The lower doses of prasugrel (both loading and maintenance) should be considered more appropriate to diminish the prolongation of bleeding time and the number of the major bleeding events.

Comment to the MO:

The necessity to reach the total inhibition of platelet aggregation in the clinical setting should be carefully evaluated since it is directly correlated with the increase of incidence of bleeding events and the prolongation of bleeding time.

4.2.6 Comparative Bioavailability Assessment of CS-747.base and CS-747.HCl with a Pilot CS-747.HCl Food Effect Assessment in Healthy Subjects (TAAF)

Study number: H7T-EW-TAAF

Principal Investigators: Michael Turik, MD

Study Centre: Lilly Laboratory for Clinical Research, Indianapolis, Indiana, US

Dates of Study: 12 April 2003 through 06 June 2003

Clinical Phase: Phase 1

Objectives	<p>Primary: To assess the relative bioavailability of the base and hydrochloride salt forms of CS-747 in terms of the relative exposure to the active metabolite of CS-747 (R-138727), after administration of a single 15 mg dose</p> <p>Secondary:</p> <ul style="list-style-type: none"> - to assess the safety and tolerability of CS-747.base and CS-747.HCl; - to further define the concentrations of three inactive metabolites of CS-747 (R-95913, R-119251 and R-106583); - to perform an initial assessment of the effect of food on the bioavailability of CS-747.HCl 																												
Study Design	A single centre, open-label, randomized, three period crossover study. Subjects were randomized to one of six treatment sequences to receive 15 mg CS-747.base (fasted), CS-747.HCl (fasted) or CS-747.HCl (fed)																												
Study Population	Total participated and analyzed: 25 subjects CS-747.base (fasted): Male 20, Female 5, Total 25; CS-747.HCl (fed or fasted) : Male 20, Female 5																												
Diagnosis and Inclusion Criteria	Healthy male or female subjects between the ages of 18 and 65 years, inclusive, BMI 19-32 kg/m ² , ECG results within the normal reference range																												
Investigational Drug	CS-747: 5, 10, 15 mg tablets. Lots: CT503392: 5 mg CS-747.base CT503393: 10 mg CS-747.base CT503396: 15 mg CS-747.HCl																												
Dosage and Administration	A single oral dose was given to each subject on Day 1 of each of the three dosing periods. A washout period of approximately 14 days separated each dosing occasion. Treatment sequences: <table border="1" style="margin-left: 20px;"> <thead> <tr> <th></th> <th>Period 1</th> <th>Period 2</th> <th>Period 3</th> </tr> </thead> <tbody> <tr> <td>Sequence 1</td> <td>CS-747.HCl with food</td> <td>CS-747.base</td> <td>CS-747.HCl</td> </tr> <tr> <td>Sequence 2</td> <td>CS-747.HCl with food</td> <td>CS-747.HCl</td> <td>CS-747.base</td> </tr> <tr> <td>Sequence 3</td> <td>CS-747.base</td> <td>CS-747.HCl with food</td> <td>CS-747.HCl</td> </tr> <tr> <td>Sequence 4</td> <td>CS-747.base</td> <td>CS-747.HCl</td> <td>CS-747.HCl with food</td> </tr> <tr> <td>Sequence 5</td> <td>CS-747.HCl</td> <td>CS-747.HCl with food</td> <td>CS-747.base</td> </tr> <tr> <td>Sequence 6</td> <td>CS-747.HCl</td> <td>CS-747.base</td> <td>CS-747.HCl with food</td> </tr> </tbody> </table>		Period 1	Period 2	Period 3	Sequence 1	CS-747.HCl with food	CS-747.base	CS-747.HCl	Sequence 2	CS-747.HCl with food	CS-747.HCl	CS-747.base	Sequence 3	CS-747.base	CS-747.HCl with food	CS-747.HCl	Sequence 4	CS-747.base	CS-747.HCl	CS-747.HCl with food	Sequence 5	CS-747.HCl	CS-747.HCl with food	CS-747.base	Sequence 6	CS-747.HCl	CS-747.base	CS-747.HCl with food
	Period 1	Period 2	Period 3																										
Sequence 1	CS-747.HCl with food	CS-747.base	CS-747.HCl																										
Sequence 2	CS-747.HCl with food	CS-747.HCl	CS-747.base																										
Sequence 3	CS-747.base	CS-747.HCl with food	CS-747.HCl																										
Sequence 4	CS-747.base	CS-747.HCl	CS-747.HCl with food																										
Sequence 5	CS-747.HCl	CS-747.HCl with food	CS-747.base																										
Sequence 6	CS-747.HCl	CS-747.base	CS-747.HCl with food																										
Sampling: Blood	A total of 33 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	2 validated LC-MS/MS methodologies, chromatograms were shown.																												
PK Assessment	Pharmacokinetic—plasma concentrations of the three inactive CS-747 metabolites (R-95913, R-119251, R-106583) and of the active CS-747 metabolite (R-138727). PK parameters: C _{max} , AUC(0-∞) and AUC(0-t _{last}) using WinNonlin). Statistical—Appropriate linear mixed effect model which																												

	assumes that the derived PK parameters, AUC and Cmax, are log-normally distributed was used to construct 90% confidence intervals for the ratios of mean PK parameters among treatments.
PD Safety	Safety data (including adverse events, vital signs, ECG tracings, clinical laboratory values) were tabulated and summarized using descriptive methodology.

Results

Assay

The active and 3 inactive metabolites were measured in plasma. The assays characteristics are shown below. The assay validation was acceptable.

Table 46: Assay Characteristics of Inactive Metabolites in Plasma

Parameter	R119251		R106583		R95913	
Linearity	1 ng/mL to 500 ng/mL					
	Inter-batch	Intra-batch	Inter-batch	Intra-batch	Inter-batch	Intra-batch
Precision (CV %)	2.4 to 6.6	1.4 to 10.9	2.7 to 3.6	1.6 to 5.2	4.0 to 12.5	2.8 to 3.5
Accuracy, %	-0.3 to -10.5	-10.7 to 1.3	-9.9 to 3.9	-11.0 to 5.6	4.6 to 4.7	6.2 to 14.1
LLOQ	1ng/mL					
Reviewer Comment	The assay characteristics and specificity are satisfactory, representative mass-chromatograms are shown					

Table 47 Assay Characteristics of an Active Metabolite in Plasma

Parameter	R138727	
Linearity	0.5 ng/mL to 250 ng/mL	
	Inter-batch	Intra-batch
Precision (CV %)	0.98 to 3.39	0.72 to 3.14
Accuracy, %	-7.0 to -5.98	-9.0 to 6.72
LLOQ	0.5ng/mL	
Reviewer Comment	The assay characteristics and specificity are satisfactory, representative mass-chromatograms are shown	

Demographics:

There were 26 subjects randomized to this study, 25 subjects completed the study, see the table below.

Table 48. Demographic Characteristics

Parameter	Mean (SD) (N=25)	Range (N=25)
Age (years)	41 (13.9)	19 – 65
Body weight (kg)	81.1 (12.76)	55.3 – 103.2
Height (cm)	173 (10.8)	150 – 191
Body mass index (kg/m ²)	27.0 (2.83)	20.3 – 30.9

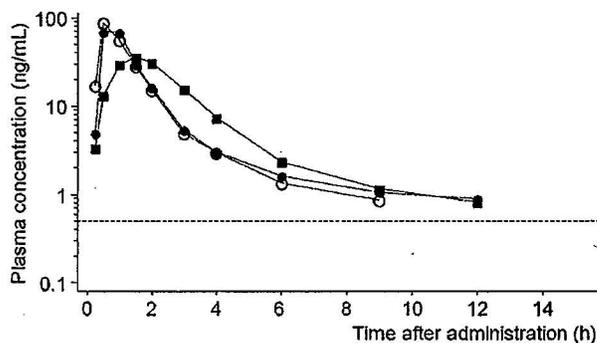


Figure 54. Geometric mean plasma concentrations of R-138727.

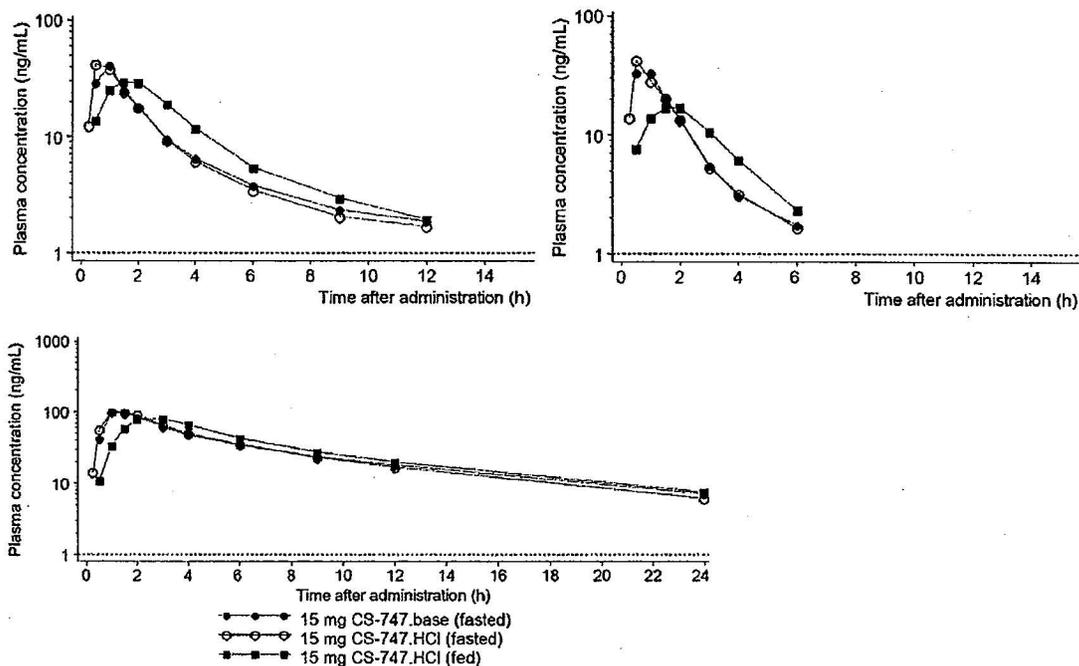


Figure 55. Geometric mean plasma concentrations of R95913 (upper left), R119251 (upper right), and R106583 (lower panel)

The comparison of the 15 mg CS-747.base formulation to the 15 mg CS-747.HCl formulation in the fasted state is shown in the table below. For each of the metabolites, the two CS-747 formulations meet standard bioequivalence criteria with respect to AUC(0-∞) and AUC(0-tlast). However, with respect to observed peak exposure (Cmax), the two formulations were not bioequivalent for the active metabolite (R-138727) and two out of the three inactive metabolites measured (R-95913 and R-119251). For metabolite R-106583, Cmax is equivalent between the two formulations. The sponsor concluded that the salt formulation was absorbed more rapidly than the base formulation after the single 15 mg dose.

Table 49 Formulation comparison between 15 mg CS-747.base (Fasted) vs. 15 mg CS-747.HCl (Fasted)

Metabolites	PK Parameter (unit)	Geometric mean ^a (90% CI) [CS747.HCl (fasted)]	Geometric mean ^a (90% CI) [CS747.base (fasted)]	Ratio of Geometric mean ^a (90% CI) [CS-747.HCl (fasted) vs CS-747.base (fasted)]
R-138727	AUC (0-∞) (ng·h/ml)	129 (114, 146)	124 (110, 140)	1.04 (0.977, 1.11)
	AUC (0-t _{last}) (ng·h/ml)	124 (110, 141)	117 (103, 132)	1.07 (0.996, 1.14)
	C _{max} (ng/ml)	124 (105, 147)	105 (88.9, 125)	1.18 (0.987, 1.41)^b
R-95913	AUC (0-∞) (ng·h/ml)	117 (103, 133)	116 (103, 132)	1.00 (0.924, 1.09)
	AUC (0-t _{last}) (ng·h/ml)	107 (93.8, 121)	105 (92.1, 119)	1.02 (0.933, 1.11)
	C _{max} (ng/ml)	62.8 (54.5, 72.4)	49.6 (43.1, 57.2)	1.27 (1.07, 1.49)^b
R-119251	AUC (0-∞) (ng·h/ml)	75.1 (65.4, 86.3)	70.5 (61.4, 81.0)	1.07 (0.988, 1.15)
	AUC (0-t _{last}) (ng·h/ml)	70.8 (61.3, 81.7)	65.6 (56.9, 75.8)	1.08 (0.996, 1.17)
	C _{max} (ng/ml)	53.6 (45.3, 63.4)	44.5 (37.6, 52.7)	1.20 (1.01, 1.44)^b
R-106583	AUC (0-∞) (ng·h/ml)	741 (645, 852)	745 (648, 857)	0.994 (0.951, 1.04)
	AUC (0-t _{last}) (ng·h/ml)	660 (577, 755)	645 (564, 738)	1.02 (0.976, 1.07)
	C _{max} (ng/ml)	121 (106, 139)	108 (94.6, 123)	1.12 (1.03, 1.23)

The fed versus fasted comparison for the 15 mg CS-747.HCl formulation is presented in Table below.

Table 50. Food effect comparison between 15 mg CS-747.HCl (Fed) vs 15 mg CS-747.HCl (Fasted)

Metabolites	PK Parameter (unit)	Geometric mean ^a (90% CI) [CS-747.HCl (Fed)]	Geometric mean ^a (90% CI) [CS-747.HCl (Fasted)]	Ratio of Geometric mean ^a (90% CI) [CS-747.HCl (fed) vs CS-747.HCl (fasted)]
R-138727	AUC (0-∞) (ng·h/ml)	122 (108, 138)	129 (114, 146)	0.949 (0.893, 1.01)
	AUC (0-t _{last}) (ng·h/ml)	118 (105, 134)	124 (110, 141)	0.952 (0.890, 1.02)
	C _{max} (ng/ml)	63.6 (53.7, 75.4)	124 (105, 147)	0.512 (0.428, 0.612)^b
R-95913	AUC (0-∞) (ng·h/ml)	144 (127, 163)	117 (103, 133)	1.23 (1.13, 1.34)^b
	AUC (0-t _{last}) (ng·h/ml)	133 (117, 151)	107 (93.8, 121)	1.25 (1.14, 1.36)^b
	C _{max} (ng/ml)	50.4 (43.8, 58.1)	62.8 (54.5, 72.4)	0.803 (0.680, 0.948)^b
R-119251	AUC (0-∞) (ng·h/ml)	69.0 (59.9, 79.4)	75.1 (65.4, 86.3)	0.918 (0.849, 0.993)
	AUC (0-t _{last}) (ng·h/ml)	63.4 (54.9, 73.1)	70.8 (61.3, 81.7)	0.896 (0.827, 0.970)
	C _{max} (ng/ml)	27.3 (23.1, 32.3)	53.6 (45.3, 63.4)	0.510 (0.427, 0.609)^b
R-106583	AUC (0-∞) (ng·h/ml)	789 (686, 907)	741 (645, 852)	1.06 (1.02, 1.11)
	AUC (0-t _{last}) (ng·h/ml)	691 (604, 791)	660 (577, 755)	1.05 (0.998, 1.10)
	C _{max} (ng/ml)	98.2 (86.0, 112)	121 (106, 139)	0.810 (0.741, 0.885)^b

For three subjects in the CS-747.HCl fed period, the terminal half-life, and hence AUC(0-∞), of R-119251 was not calculated.

For the active metabolite (R-138727), fed vs fasted treatments were bioequivalent with respect to AUC(0-∞) and AUC(0-t_{last}). In the presence of food, the C_{max} values of R-138727 were decreased by 48.8%.

For the inactive metabolite R-95913, food intake increased AUC(0-∞) between 13% and 34% (90% CI) and similarly for AUC(0-tlast). For the active and other inactive metabolites measured (R-119251 and R-106583), both AUC(0-∞) and AUC(0-tlast) are bioequivalent in the fed and fasted condition. For all metabolites, food intake decreased the Cmax values, and increased median tmax from 0.5 to 1.5 hours.

Sponsor's Conclusions

CS-747.base and CS-747.HCL demonstrated comparable fasted bioavailability for the active metabolite in terms of AUC(0-∞) and AUC(0-tlast).

The ratio of Cmax of the active metabolite (R-138727) between CS-747.HCl to CS-747.base was 1.18 (90% CI 0.987-1.41), reflecting an improved absorption profile of the HCL salt.

For the inactive metabolites, a similar trend was observed for Cmax, AUC(0-∞) and AUC(0-tlast).

According to standard bioequivalence criteria, food had no effect on AUC(0-∞) and AUC(0-tlast) of the active metabolite of CS-747.HCl, however, Cmax was reduced by 48.8% (90% CI 38.8-57.2%) with a delay of median tmax from 0.5 to 1.5 hours.

REVIEWER COMMENTS:

1. The sponsor compared the bioavailability of 2 formulations (base vs. salt) measuring the active and 3 inactive metabolites of prasugrel. The two formulations were bioequivalent with respect to the exposure to the active metabolite (both AUC(0-∞) and AUC(0-tlast)) but not in respect to its Cmax. The absorption of the salt formulation was faster than the base formulation.
2. The sponsor evaluated the food effect after a single 15 mg dose of CS-747.HCL. For the active metabolite, the fed vs. fasted condition was bioequivalent with respect to the exposure (both AUC(0-∞) and AUC(0-tlast)). The intake of a high-fat breakfast decreased the absorption of the active metabolite for 48.8% with a delay of median tmax from 0.5 to 1.5 hours. The importance of this difference at the chronic administration of 10 mg/day of prasugrel is not known.
3. The loading dose of prasugrel is 60 mg. The effect of food on the administration of the loading (highest recommended) dose was not assessed in this study, therefore, this study is not considered to be the definitive food effect study.

4.2.7 A Pharmacokinetics and pharmacodynamics of prasugrel metabolites after single and multiple dosing in subjects with liver disease and healthy subjects with normal hepatic function. (TAAN)

Principal Investigator: Dr. Ramon Vargas

Study Centre: MDS Pharma Services, 2237 Poydras Street, New Orleans, LA70119, USA.

Study period: 09 February 2005 through 26 August 2005

Phase of Development: 1

Objectives	Primary: to evaluate the pharmacokinetics of prasugrel's active metabolite in subjects with mild and moderate hepatic impairment during single and multiple oral prasugrel dosing. Secondary objectives: (1) evaluate the inhibition of platelet aggregation produced by prasugrel in subjects with mild and moderate hepatic impairment, (2) evaluate the safety and tolerability of prasugrel in subjects with mild and moderate hepatic impairment, (3) and characterize the pharmacokinetics of prasugrel's inactive metabolites in subjects with moderate hepatic impairment during multiple oral prasugrel dosing
Study Design	This was a parallel-design, open-label, single and multiple dose, three-part study in subjects with mild and moderate hepatic impairment, with a control group of subjects with normal hepatic function. Part 1: single 60 mg doses to 4 subjects with mild hepatic impairment. Part 2, single 60 mg doses to 8 with moderate hepatic impairment. Part 3: 10 subjects received a single dose of 60-mg LD of prasugrel on Day 1 followed by 5 daily MDs of 10 mg prasugrel on Days 2 to 6. The control group of 11 subjects with normal hepatic function received a single dose of 60 mg prasugrel on Day 1.
Study Population	Male and female subjects with stable liver cirrhosis classified as Child-Pugh Class A or B (mild or moderate hepatic impairment), aged 25 to 75 years, inclusive. Control group: healthy male and female subjects matched by age, gender, and body weight to subjects with moderate hepatic impairment.
Investigational Drug	Prasugrel was provided as 10 mg tablets from lot number CT518165.
Sampling: Blood	Blood samples were collected from all subjects in Parts 1 and 2 at 0.25, 0.5, 1, 2, 4, 6, 9, 12, 24, 36, and 48 hours postdose following a 60-mg LD. Blood samples were collected during MD from subjects with moderate hepatic impairment (Part 3) at 0.25, 0.5, 1, 2, 4, 6, 9, 12, and 24 hours postdose on Day 1, and predose and 0.25, 0.5, 1, 2, 4, 6, 9, 12, 24, 36, and 48 hours postdose on Day 6.
Assays	2 validated HPLC methods with LC/MS/MS detection, chromatograms were shown. Platelet aggregation in platelet-rich plasma was measured using the turbidometric method with 5 and 20 μ M ADP and collagen as the agonists.
PK Assessment	Measurement of plasma concentrations of prasugrel active metabolite (R-138727) and inactive metabolites (R-95913, R-106583, and R-119251). PK parameter estimates for R-138727, R-95913, R-106583, and R-119251: noncompartmental methods.

PD Assessment	Platelet aggregation (induced by 5 and 20 μ M adenosine diphosphate [ADP], and 2 μ g/mL collagen)
Statistical methods	Summary statistics are presented for the pharmacokinetic and pharmacodynamic data.

Results:**Assay:**

The performance of the bioanalytical method during study sample analysis is documented in the tables that follow.

Table 51. Assay Characteristics of Inactive Metabolites in Plasma

Parameter	R119251		R106583		R95913	
Linearity	1 ng/mL to 500 ng/mL					
	Inter-batch	Intra-batch	Inter-batch	Intra-batch	Inter-batch	Intra-batch
Precision (CV %)	2.5 to 4.6	1.4 to 10.9	2.5 to 5.0	1.6 to 5.2	3.1 to 5.1	2.8 to 3.5
Accuracy, %	-2.3 to -1.7	-10.7 to 1.3	-1.2 to 1.8	-11.0 to 5.6	-2.2 to 1.4	6.2 to 14.1
LLOQ	1ng/mL					
Reviewer Comment	The assay characteristics and specificity are satisfactory, representative mass-chromatograms are shown					

Table 52. Assay Characteristics of an Active Metabolite in Plasma

Parameter	R138727	
Linearity	0.5 ng/mL to 250 ng/mL	
	Inter-batch	Intra-batch
Precision (CV %)	1.48 to 3.85	0.72 to 3.14
Accuracy, %	-4.1 to -4.3	-9.0 to 6.72
LLOQ	0.5ng/mL	
Reviewer Comment	The assay characteristics and specificity are satisfactory, representative mass-chromatograms are shown	

Demographics

Twenty-two subjects, aged 41 to 65 years, were enrolled in this study. Four of the subjects (all males) had stable liver cirrhosis classified as mild (Child-Pugh Class A, 5-6 points), 8 subjects (6 females, 2 males) had stable liver cirrhosis classified as moderate (Child-Pugh Class B, 7-9 points), and 10 subjects (6 females, 4 males) were healthy without apparent hepatic disease. Subject demographics shown in the table below.