Table 53. Subject Demographics

Group	Subject number	Gender	Race	Age (years)	Body weight (kg)	Height (cm)	BMI (kg/m²)
Subjects with	101	Male	Caucasian	61	97.2	175	31.7
mild hepatic	102	Male	Afro-Caribbean	59	93.6	178	29.5
impairment	103	Male	Caucasian	57	83.6	173	27.9
(Part 1)	104	Male	Afro-Caribbean	47	79.0	178	24.9
Mean (SD)				56 (6)	88.4 (8.5)	176 (2)	28.5 (2.9)
Subjects with	201	Male	Caucasian	62	89.6	168	31.7
moderate	202	Male	Hispanic	50	65.0	165	23.9
hepatic	203	Female	Caucasian	51	59.5	162	22.7
impairment	204	Female	Afro-Caribbean	50	83.1	165	30.5
(Parts 2 and 3)	205	Female	Caucasian	47	76.8	175	25.1
	206	Female	Caucasian	47	86.4	168	30.6
	207	Female	Caucasian	50	68.0	168	24.1
	208[a]	Female	Caucasian	45	62.2	160	24.3
Mean (SD)				50 (5)	73.8 (11.7)	166 (5)	26.6 (3.7)
Healthy	301	Male	Afro-Caribbean	65	97.3	175	31.8
Subjects	302	Female	Afro-Caribbean	41	70.5	163	26.5
	303	Female	Afro-Caribbean	49	72.7	165	26.7
	304	Male	Afro-Caribbean	42	72.7	175	23.7
	305	Male	Caucasian	53	70.0	170	24.2
	306	Female	Afro-Caribbean	53	79.0	162	30.1
	307	Female	Afro-Caribbean	52	83.3	160	32.5
	308	Female	Hispanic	55	58.1	152	25.1
	309	Male	Afro-Caribbean	53	79.0	175	25.8
	310	Female	Caucasian	47	77.3	168	27.4
Mean (SD				51 (7)	76.0 (10.2)	167 (8)	27.4 (3.1)

Pharmacokinetics:

Mean concentration-time profiles of prasugrel metabolites are illustrated below.

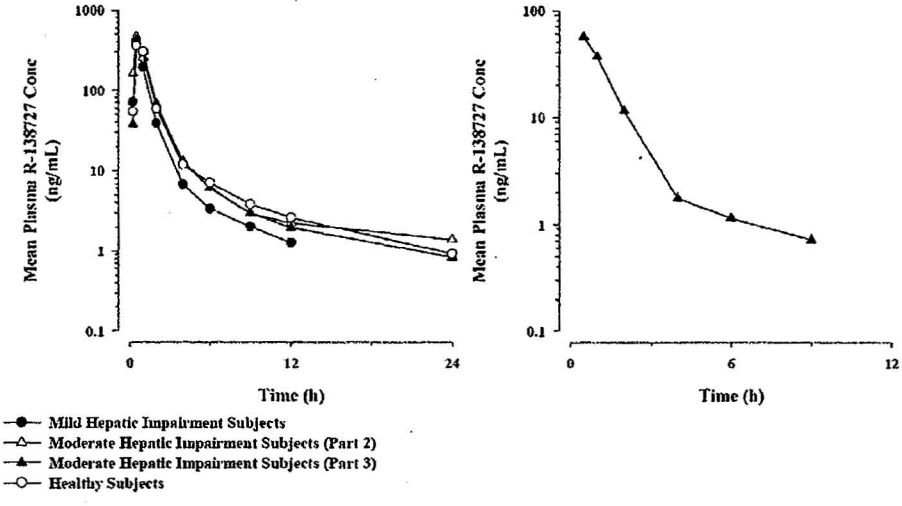

Figure 56. Mean (±SD) plasma R-138727 concentration-time profiles following a prasugrel 60-mg LD (left) and after the fifth daily 10-mg MD (right).

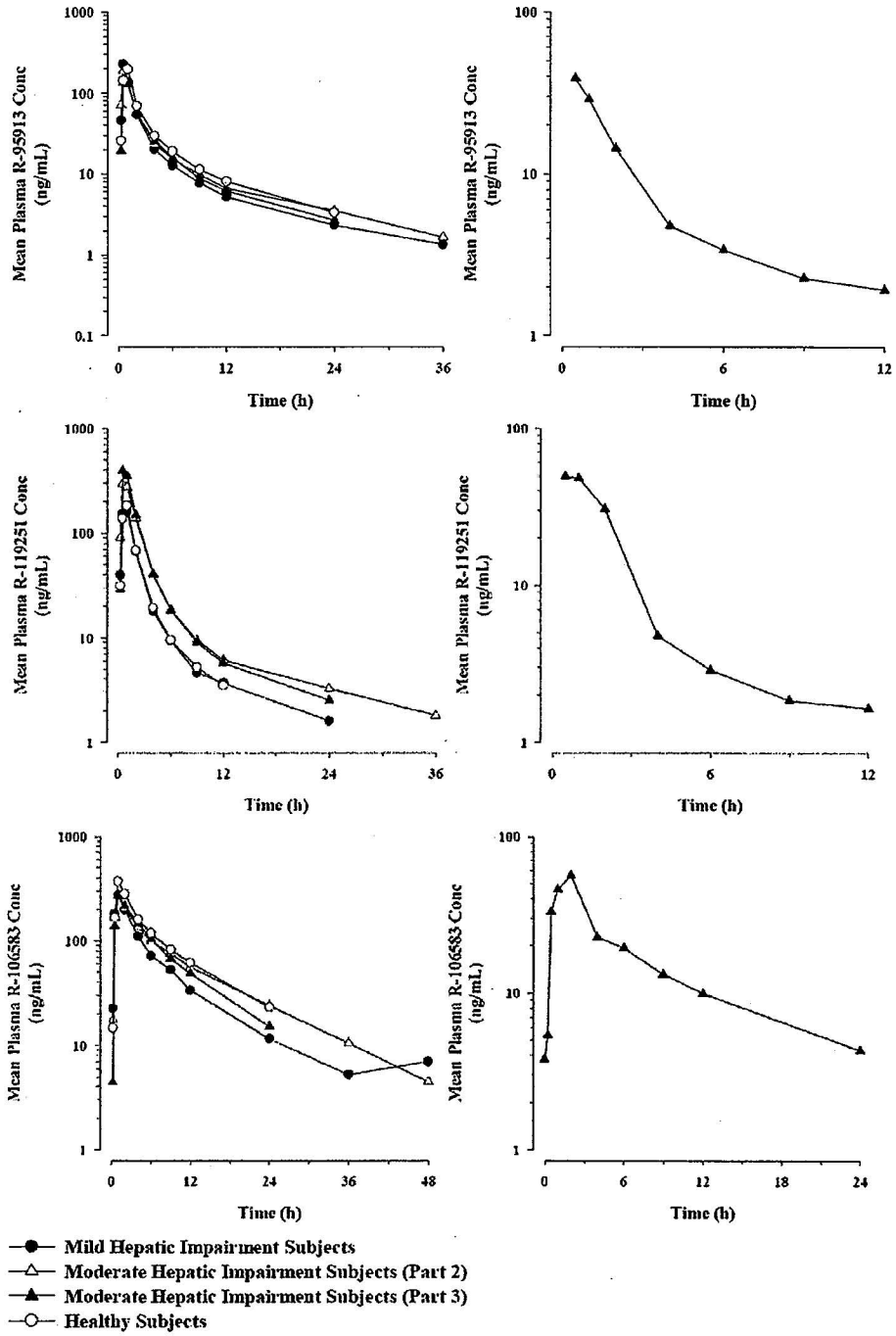

Figure 57. Mean (±SD) plasma R-95913(upper), R-119251 (middle), and R-16583 (lower) concentration-time profiles following a prasugrel 60-mg LD (left) and after the fifth daily 10-mg MD (right)

The PK parameters for all metabolites are listed in the Tables below.

Table 54. R-138727

Parameter	Geometric Mean (%CV)			
	Healthy subjects (N=10)	Mild hepatic impairment subjects (N=4)	Moderate hepatic impairment subjects (N=8)	Moderate hepatic impairment subjects (N=7)
		Part 1	Part 2	Part 3
		60 mg prasugrel LD		
C_{max} (ng/mL)	438 (40.7)	384 (35.6)	430 (44.6)	486 (46.7)
t_{max}[a] (h)	0.50 (0.50-1.00)	0.50 (0.48-0.50)	0.50 (0.50-1.00)	0.50 (0.50-1.05)
AUC(0-t_{last}) (ng•h/mL)	464 (34.7)	361 (47.6)	484 (53.3)	470 (41.9)
		10 mg prasugrel MD		
C_{max} (ng/mL)	--[b]	--[b]	--[b]	62.4 (48.8)
t_{max}[a] (h)	--[b]	--[b]	--[b]	0.50 (0.50-2.00)
AUC(0-t_{last}) (ng•h/mL)	--[b]	--[b]	--[b]	67.1 (36.2)

Table 55. R-95913

Parameter	Geometric Mean (%CV)			
	Healthy subjects (N=10)	Mild hepatic impairment subjects (N=4)	Moderate hepatic impairment subjects (N=8)	Moderate hepatic impairment subjects (N=7)
		Part 1	Part 2	Part 3
		60 mg prasugrel LD		
C_{max} (ng/mL)	194 (69.6)	209 (55.0)	199 (24.3)	181 (27.2)
t_{max}[a] (h)	0.75 (0.50-1.00)	0.50 (0.48-1.00)	0.50 (0.25-1.00)	0.50 (0.50-1.05)
AUC(0-t_{last}) (ng•h/mL)	487 (50.7)	416 (34.4)	462 (24.5)	373 (39.0)
		10 mg prasugrel MD		
C_{max} (ng/mL)	--[b]	--[b]	--[b]	45.4 (35.1)
t_{max}[a] (h)	--[b]	--[b]	--[b]	0.50 (0.50-2.00)
AUC(0-t_{last}) (ng•h/mL)	--[b]	--[b]	--[b]	85.5 (36.6)

[a] t_{max}: median (range)
[b] data not collected

Table 56. R-119251

Parameter	Healthy subjects (N=10)	Mild hepatic impairment subjects (N=4)	Moderate hepatic impairment subjects (N=8)	Moderate hepatic impairment subjects (N=7)
	Geometric Mean (%CV)			
		Part 1	Part 2	Part 3
	60 mg LD prasugrel			
C_{max} (ng/mL)	192 (45.6)	170 (51.6)	295 (45.3)	414 (66.5)
t_{max}[a] (h)	1.00 (0.50-1.00)	0.74 (0.50-1.00)	0.78 (0.50-1.00)	0.50 (0.50-1.05)
AUC(0-t_{last}) (ng•h/mL)	345 (51.0)	350 (90.3)	655 (60.5)	708 (58.3)
	10 mg prasugrel MD			
C_{max} (ng/mL)	--[b]	--[b]	--[b]	63.9 (65.8)
t_{max}[a] (h)	--[b]	--[b]	--[b]	0.50 (0.50-2.00)
AUC(0-t_{last}) (ng•h/mL)	--[b]	--[b]	--[b]	107 (59.5)

Table 57. R-106583

Parameter	Healthy subjects (N=10)	Mild hepatic impairment subjects (N=4)	Moderate hepatic impairment subjects (N=8)	Moderate hepatic impairment subjects (N=7)
	Geometric Mean (%CV)			
		Part 1	Part 2	Part 3
	60 mg prasugrel LD			
C_{max} (ng/mL)	356 (29.9)	265 (36.3)	258 (38.9)	270 (25.6)
t_{max}[a] (h)	1.00 (1.00-1.05)	0.99 (0.50-1.00)	1.00 (1.00-2.00)	1.00 (0.50-2.00)
AUC(0-t_{last}) (ng•h/mL)	2290 (39.9)	1490 (43.6)	1930 (46.9)	1630 (39.7)
	10 mg prasugrel MD			
C_{max} (ng/mL)	--[b]	--[b]	--[b]	58.2 (48.4)
t_{max}[a] (h)	--[b]	--[b]	--[b]	1.00 (1.00-2.00)
AUC(0-t_{last}) (ng•h/mL)	--[b]	--[b]	--[b]	377 (40.5)

The sponsor concluded that the pharmacokinetics of prasugrel metabolites are similar in healthy subjects and subjects with moderate hepatic impairment. Mean concentration-time profiles and exposure estimates are similar, except that exposure to R-119251 appeared to be higher and exposure to R-106583 tended to be lower in subjects with moderate hepatic impairment than in healthy subjects.

Averaged across both parts of the study, the geometric mean exposure to R- 119251, based on Cmax and AUC(0-tlast), was 60% higher in subjects with moderate hepatic impairment than healthy subjects, while exposure to R-106583 appeared to be 24% lower.

Table 58. R-119251

Parameter	Geometric Mean (%CV)			
	Healthy subjects (N=10)	Mild hepatic impairment subjects (N=4)	Moderate hepatic impairment subjects (N=8)	Moderate hepatic impairment subjects (N=7)
		Part 1	Part 2	Part 3
		60 mg LD prasugrel		
C_{max} (ng/mL)	192 (45.6)	170 (51.6)	295 (45.3)	414 (66.5)
t_{max}[a] (h)	1.00 (0.50-1.00)	0.74 (0.50-1.00)	0.78 (0.50-1.00)	0.50 (0.50-1.05)
AUC(0-t_{last}) (ng•h/mL)	345 (51.0)	350 (90.3)	655 (60.5)	708 (58.3)
		10 mg prasugrel MD		
C_{max} (ng/mL)	--[b]	--[b]	--[b]	63.9 (65.8)
t_{max}[a] (h)	--[b]	--[b]	--[b]	0.50 (0.50-2.00)
AUC(0-t_{last}) (ng•h/mL)	--[b]	--[b]	--[b]	107 (59.5)

[a] t_{max}: median (range)
[b] data not collected

Table 59. R-106583

Parameter	Geometric Mean (%CV)			
	Healthy subjects (N=10)	Mild hepatic impairment subjects (N=4)	Moderate hepatic impairment subjects (N=8)	Moderate hepatic impairment subjects (N=7)
		Part 1	Part 2	Part 3
		60 mg prasugrel LD		
C_{max} (ng/mL)	356 (29.9)	265 (36.3)	258 (38.9)	270 (25.6)
t_{max}[a] (h)	1.00 (1.00-1.05)	0.99 (0.50-1.00)	1.00 (1.00-2.00)	1.00 (0.50-2.00)
AUC(0-t_{last}) (ng•h/mL)	2290 (39.9)	1490 (43.6)	1930 (46.9)	1630 (39.7)
		10 mg prasugrel MD		
C_{max} (ng/mL)	--[b]	--[b]	--[b]	58.2 (48.4)
t_{max}[a] (h)	--[b]	--[b]	--[b]	1.00 (1.00-2.00)
AUC(0-t_{last}) (ng•h/mL)	--[b]	--[b]	--[b]	377 (40.5)

The study was terminated early due to extensive damage at the study site caused by a hurricane in August 2005. Parts 1 and 2 of the study were completed as planned. Seven subjects from Part 2 were enrolled into Part 3 and completed the multiple dosing phase; no other subjects were recruited into Part 3. The data for only 10 healthy subjects was analyzed.

Since only 4 subjects with mild hepatic impairment were evaluated, a direct comparison of geometric means between subjects with mild hepatic impairment and healthy subjects was not possible and the study was been inconclusive.

Pharmacodynamics:

The sponsor compared MPA to 20 μM ADP following a single 60-mg LD of prasugrel in subjects with mild and moderate hepatic impairment (Parts 1 and 2) and healthy subject (Figure below).

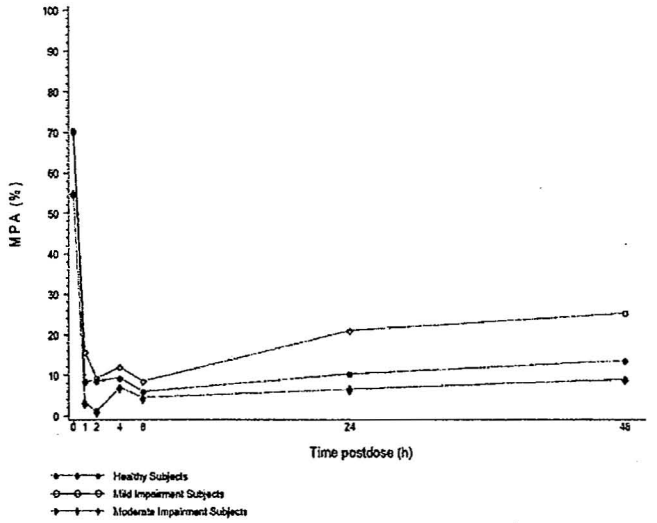

Figure 58. Mean MPA to 20 μM ADP following a single 60-mg LD of prasugrel in subjects with mild and moderate hepatic impairment (Parts 1 and 2) and healthy subjects

Also, a more detailed comparison of MPA to 20 μM ADP at 6 and 24 hours following a single 60-mg LD of prasugrel is shown below.

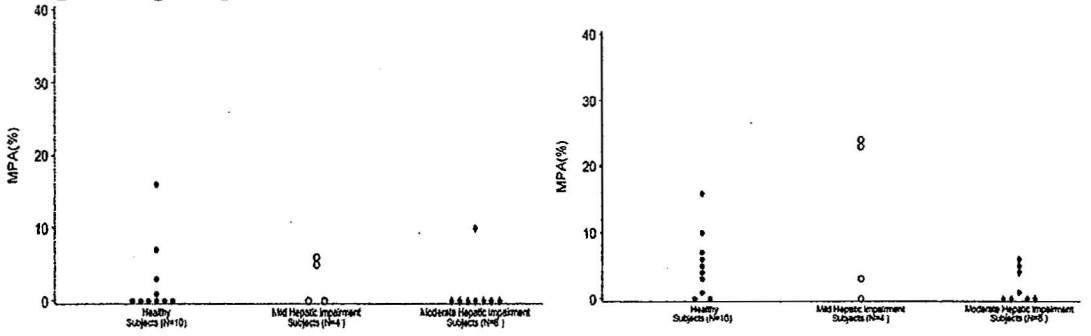

Figure 59. MPA to 20 μM ADP at 6 (left) and 24 hours (right) following a single 60-mg LD of prasugrel in subjects with mild and moderate hepatic impairment and healthy subjects.

The mean baseline (predose) MPA to 20 μM ADP for subjects with mild hepatic impairment and healthy subjects was about 70% (Table below). The mean baseline MPA was approximately 15% lower in subjects with moderate hepatic impairment in Part 2 compared to healthy subjects and subjects with mild hepatic impairment. In Part 3, the baseline MPA in subjects with moderate hepatic impairment was comparable to healthy subjects and subjects with mild hepatic impairment. A similar profile was observed for mean MPA following administration of a 60-mg LD of prasugrel to healthy subjects and subjects with mild and moderate hepatic impairment.

Table 60. Mean (±SD) MPA to 20 µM ADP Following a 60-mg LD and the Fifth Daily 10-mg MD of Prasugrel in Subjects with Mild and Moderate Hepatic Impairment (Parts 1 to 3) and Healthy Subjects

		Mean (±SD) MPA (%)					
Day	Time (h)	Healthy subjects (N=10)	Mild hepatic impairment subjects (Part 1) (N=4)	Moderate hepatic impairment subjects (Part 2) (N=8)	Moderate hepatic impairment subjects (Part 3) (N=7)		
				60 mg prasugrel LD			
1	Predose	70.2 (14.5)	70.5 (18.4)	54.9 (15.9)	66.1 (15.8)		15.0 (9.3)
	1	8.5 (8.1)	15.8 (10.6)	3.1 (4.4)	3.9 (5.2)		14.1 (9.7)
	2	8.6 (7.5)	9.3 (7.4)	1.0 (2.1)	5.3 (7.2)		12.6 (8.5)
	4	9.3 (7.4)	12.0 (13.8)	7.0 (8.5)	8.7 (8.2)		9.0 (7.4)
	6	6.0 (7.9)	8.5 (5.5)	4.5 (6.2)	6.4 (4.9)		7.1 (5.8)
	24	10.3 (6.4)	21.0 (15.0)	6.6 (5.8)	13.6 (8.1)		15.9 (10.4)
	48	13.6 (10.2)	25.3 (15.4)	9.0 (8.4)	—[a]	day 5	21.0 (17.8)

COMMENTS

1. The comparison of the PK parameters between the groups of subjects with different hepatic function was performed by the sponsor only for a loading 60 mg dose of prasugrel (including the data obtained in part 3, after a week of dosing prasugrel with 10 mg/day). The effect of the severely impaired hepatic function on the pharmacokinetics of prasugrel at chronic dosing has not been assessed.
2. The PK parameters estimated for the active metabolite R-138727 in healthy subjects and in subjects with moderate hepatic impairment were very similar. The group of subjects with mild hepatic impairment had 12% lower Cmax values and 22% lower AUC(0-last) values in comparison with healthy subjects. Since this group included the data from only 4 subjects, the comparison is not statistically solid.
3. Since other metabolites are inactive, the differences in their exposure would not be of clinical importance. Briefly, the exposure (both Cmax and AUC) of the least abundant metabolite, R119251 was about 60% higher in subjects with moderate hepatic impairment, while the exposure to R106583 was about 24% lower and the exposure to R95913 was similar in all groups.
4. The PD response measure as MPA to 20 mcM ADP was similar in the groups of healthy subjects, and subjects with mild and moderate hepatic impairment.
5. The effect of hepatic impairment on the prolongation of bleeding time and the frequency of the bleeding events was not evaluated in this study.
6. Although the effect of the impaired hepatic function on the pharmacokinetics of prasugrel at chronic dosing has not been assessed, the differences in the pharmacokinetics of the active metabolite and in the inhibition of platelet aggregation after the prasugrel loading dose were very minor. A dose adjustment for the hepatically impaired subjects is not required.

4.2.8 Pharmacokinetics and Pharmacodynamics of Prasugrel Metabolites after Multiple Dosing in Subjects with Moderate Liver Disease and Healthy Subjects with Normal Hepatic Function (TABV)

Investigators: Drs. S. Oberstein and G. Weiner
Study Centers: SFBC International, 11190 Biscayne Blvd, Miami, Florida 33181, USA, and Allied Research International, 1405 NW 167th Street, Miami Gardens, Florida 33169, USA.
Duration of Study: 8 Febuary 2006 to 5 October 2006
Phase of Development: 1

Objectives	Primary: to evaluate the pharmacokinetics of prasugrel's active metabolite in subjects with moderate hepatic impairment after a 60-mg loading dose and five daily 10-mg maintenance doses. Secondary: to evaluate the inhibition of platelet aggregation produced by prasugrel in subjects with moderate hepatic impairment; to evaluate the safety and tolerability of prasugrel in subjects with moderate hepatic impairment; and to 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, multiple oral dose study in subjects with moderate hepatic impairment, with a control group of subjects with normal hepatic function. All 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.
Study Population	Thirty subjects (10 with moderate hepatic impairment and 20 with normal hepatic function) received multiple doses of prasugrel. Male and female subjects with stable liver cirrhosis classified as Child-Pugh Class B (moderate hepatic impairment), aged 46 to 74 years. The control group included 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 numbers: CT524123 (SFBC International) and CT527501 (Allied Research International)
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 μM 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 μM adenosine diphosphate [ADP], and 2 μg/mL collagen)
Statistical methods	Summary statistics are presented for the pharmacokinetic and pharmacodynamic data. A linear mixed-effect model was used to compare the pharmacokinetic parameters of prasugrel's metabolites between subjects with moderate hepatic impairment and healthy subjects following the LD and final MD. Least squares (LS) geometric means for each group, the ratio of geometric means of the two groups, and the corresponding 90% confidence intervals (CI) were estimated separately for each metabolite following the LD and final MD. Values of tmax were analyzed non-parametrically using the Wilcoxon sign rank test. The effect of prasugrel on maximum platelet aggregation (MPA) to 20 μM ADP in subjects with moderate hepatic impairment and in healthy subjects was assessed using a linear mixed-effect model at each scheduled time point. The LS mean for each group at each time point, the LS mean difference between groups, and corresponding 90% CI, along with the p-values, were calculated. The same analysis was performed for MPA to 5 μM ADP and 2 μg/mL collagen, and inhibition of platelet aggregation (IPA) to 5 and 20 μM ADP and 2 μg/mL collagen.

Results

Assay

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

Table 61. 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 %)	3.54 to 5.2	3.0 to 4.9	1.8 to 5.6
Accuracy, %	-2.3 to 2.1	-3.3 to 1.1	-1.25 to 0.3
LLOQ	1ng/mL		
Reviewer Comment	The assay characteristics and specificity are satisfactory, representative mass-chromatograms are shown		

Table 62. Assay Characteristics of an Active Metabolite in Plasma

Parameter	R138727
Linearity	0.5 ng/mL to 250 ng/mL
	Intra-batch
Precision (CV %)	2.4 to 6.1
Accuracy, %	-4.4 to 3.8
LLOQ	0.5ng/mL
Reviewer Comment	The assay characteristics and specificity are satisfactory, representative mass-chromatograms are shown

Demographics

Nineteen subjects were enrolled at SFBC International, and 11 subjects were enrolled at Allied Research International. Ten of the subjects (7 males, 3 females) had stable liver cirrhosis classified as moderate (Child-Pugh Class B, 7-9 points), and 20 subjects (14 males, 6 females) were healthy without apparent hepatic disease. Most subjects were Hispanic or Caucasian.

Pharmacokinetics

The mean plasma concentration vs time profiles for both studied groups were practically superimposed (Figure below).

A summary of noncompartmental pharmacokinetic estimates is contained in Table below.

Exposure to prasugrel's active metabolite R-138727 was similar between hepatically impaired subjects and their healthy matches.

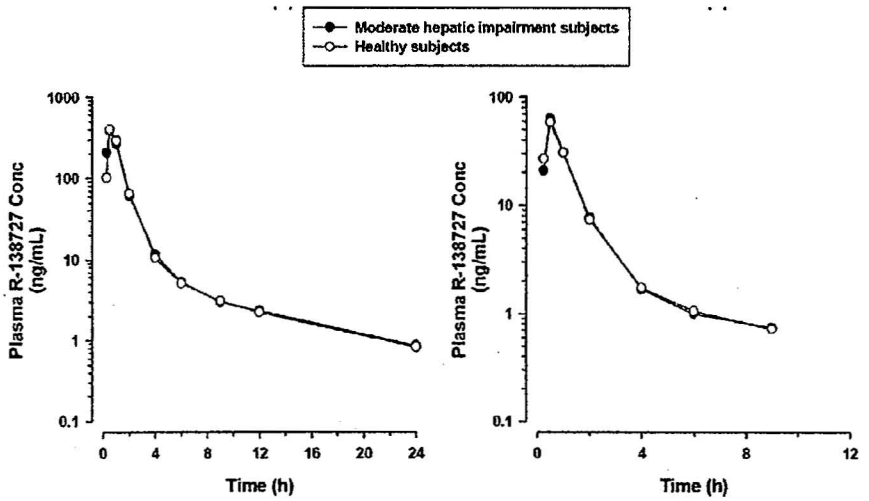

Figure 60 Plasma concentrations (arithmetic mean ± SD) of R-138727 after a single 60-mg LD (A) and after the fifth daily 10-mg MD (B) of prasugrel in healthy subjects and moderate hepatic impairment subjects.

Table 63. PK Parameters in healthy subjects and in subjects with moderate hepatic impairment.

	Geometric Mean (%CV)	
Parameter	Healthy subjects (N=20)	Moderate hepatic impairment subjects (N=10)
	60-mg prasugrel LD	
AUC(0-t_{last}) (ng•h/mL)	477 (29.5)	466 (38.7)
C_{max} (ng/mL)	403 (62.1)	368 (49.8)
t_{max}[a] (h)	0.50 (0.50-1.00)	0.50 (0.25-0.50)
	10-mg prasugrel MD	
AUC(0-t_{last}) (ng•h/mL)	56.9 (66.3)	61.5 (43.2)
C_{max} (ng/mL)	51.8 (90.3)	59.3 (62.9)
t_{max}[a] (h)	0.50 (0.25-2.00)	0.50 (0.50-1.00)

Statistical comparisons of pharmacokinetic parameter estimates in hepatically impaired subjects and their healthy matches are listed below.

Table 64. Statistical Comparison of R-138727 Pharmacokinetic Parameters Between Subjects with Moderate Hepatic Impairment and Healthy Subjects After a 60-mg LD and After the Fifth Daily 10-mg MD of Prasugrel

Prasugrel metabolite	Day	Parameter	Geometric LS means: Moderate hepatic impairment subjects	Geometric LS means: Healthy subjects	Ratio of geometric LS means (90% CI) Hepatic impaired / healthy
R-138727	1	AUC(0-t_{last}) (ng•h/mL)	466	477	0.917 (0.836, 1.14)
		C_{max} (ng/mL)	368	403	0.912 (0.664, 1.25)
	6	AUC(0-t_{last}) (ng•h/mL)	61.5	56.9	1.08 (0.760, 1.54)
		C_{max} (ng/mL)	59.3	51.8	1.14 (0.779, 1.68)
R-138727	1	t_{max} (h)	0.500	0.625	-0.125 (-0.500, 0)
	6	t_{max} (h)	0.500	0.500	0 (0, 0.125)

Point estimates for the ratios of geometric LS means for AUC(0-tlast) and Cmax after the LD and after the last MD ranged from 0.91 to 1.14, and the 90% CIs for these parameters included 1.0. Variability in Cmax after a LD and in AUC(0-tlast) and Cmax during MD ranged from 43% to 90%, considerably higher than the 33% upper CV limit assumed when powering the study. R-138727 tmax was similar between the two populations.

Since the pharmacokinetics of the inactive metabolites is not of clinical importance, here is only brief statistical comparison of the two studied groups. The plots and tables are in the study report.