Table 65. Statistical Comparison of R-95913, R-119251 and R-106583 Pharmacokinetic Parameters Between Subjects with Moderate Hepatic Impairment and Healthy Subjects Following a 60-mg LD and 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-95913	1	AUC(0-t_{last}) (ng•h/mL)	480	571	0.840 (0.683, 1.03)
		C_{max} (ng/mL)	209	260	0.802 (0.617, 1.04)
	6	AUC(0-t_{last}) (ng•h/mL)	88.3	93.5	0.944 (0.689, 1.29)
		C_{max} (ng/mL)	53.2	47.6	1.12 (0.771, 1.62)
R-119251	1	AUC(0-t_{last}) (ng•h/mL)	602	381	1.58 (1.17, 2.14)
		C_{max} (ng/mL)	296	229	1.30 (0.862, 1.95)
	6	AUC(0-t_{last}) (ng•h/mL)	72.7	39.8	1.83 (1.11, 3.02)
		C_{max} (ng/mL)	49.1	29.4	1.67 (1.07, 2.61)
R-106583	1	AUC(0-t_{last}) (ng•h/mL)	1902	2135	0.891 (0.756, 1.05)
		C_{max} (ng/mL)	267	384	0.695 (0.594, 0.814)
	6	AUC(0-t_{last}) (ng•h/mL)	366	403	0.907 (0.702, 1.17)
		C_{max} (ng/mL)	55.6	69.4	0.801 (0.614, 1.04)

The AUC(0-tlast) of R-95913 and R-106583 were not significantly affected by hepatic impairment. The 90% CI (hepatically impaired/healthy) for AUC(0-tlast) and Cmax included 1.0 except for the R-106583 Cmax after a LD, which ranged from 0.594 to 0.814 and indicates a lower LD Cmax in hepatically impaired subjects than in healthy subjects. The R-119251 Cmax and AUC(0-tlast) values were 30% to 83% higher in hepatically impaired subjects than in healthy subjects. In both populations, Tmax values were similar for each of the three inactive metabolites.

Pharmacodynamics

ADP-Induced Platelet Aggregation

The platelet aggregation response to 5 μM ADP at 6 and 24 hours postdose on Days 1 and 6 was similar to the response to 20 μM ADP. The MPA to collagen showed a similar pattern of results to those for ADP and thus are also not presented in this section.

Figure below shows the mean MPA to 20 μM ADP following a 60-mg LD and the fifth daily 10-mg MD of prasugrel in subjects with moderate hepatic impairment and healthy subjects.

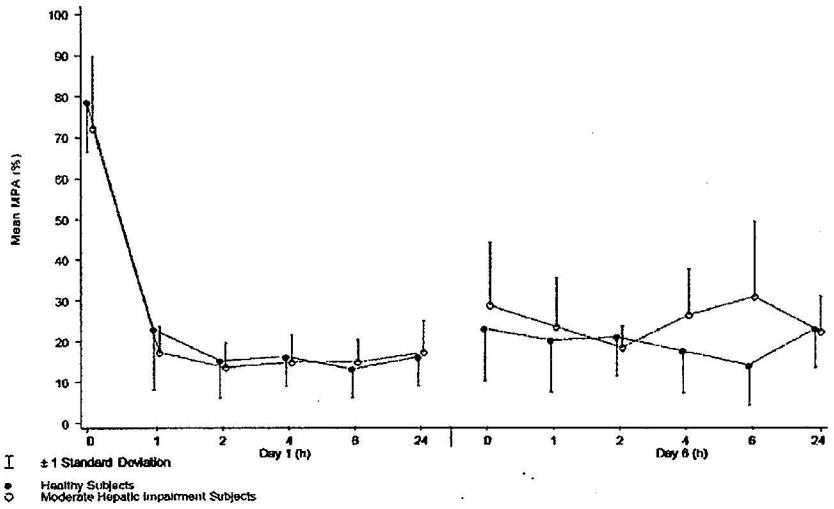


Figure 61 Mean (SD) MPA to 20 μM ADP following a 60-mg LD and the fifth daily 10-mg MD of prasugrel in subjects with moderate hepatic impairment and in healthy subjects.

Table below presents the results of statistical comparisons of MPA to 20 μM ADP between subjects with moderate hepatic impairment and healthy subjects. The mean baseline (predose) MPA to 20 μM ADP for subjects with moderate hepatic impairment and healthy subjects was similar. There was no significant difference in MPA to 20 μM ADP in subjects with moderate hepatic impairment compared to healthy subjects after a 60 mg LD on Day 1 or after the final 10 mg MD on Day 6, except at 4 and 6 hours after the final MD when MPA was higher in hepatically impaired subjects than in healthy subjects. The reason for the significant difference in MPA at 4 and 6 hours after the last MD—but not immediately before or 1, 2, or 24 hours after the last MD is unknown.

Table 66. Statistical Comparison of MPA to 20 μM ADP Between Subjects with Moderate Hepatic Impairment and Healthy Subjects After a 60-mg LD and After the Fifth Daily 10-mg MD of Prasugrel

		LS mean MPA (%) (90% CI)		Hepatic impairment - Healthy	
Day	Time (h)	Moderate hepatic impairment subjects	Healthy subjects	Difference (90% CI)	p-value
1	Predose	72.3 (64.7, 79.9)	78.5 (73.1, 83.9)	-6.20 (-15.51, 3.11)	0.267
	1	17.5 (12.1, 22.8)	22.9 (18.3, 27.4)	-5.40 (-12.12, 1.32)	0.184
	2	13.9 (8.5, 19.2)	15.2 (10.6, 19.7)	-1.30 (-8.02, 5.42)	0.747
	4	15.1 (9.7, 20.4)	16.2 (11.6, 20.7)	-1.10 (-7.82, 5.62)	0.785
	6	15.1 (9.7, 20.4)	13.1 (8.6, 17.6)	1.95 (-4.77, 8.67)	0.628
	24	17.4 (12.0, 22.7)	16.1 (11.6, 20.6)	1.25 (-5.47, 7.97)	0.756
6	Predose	29.0 (23.6, 34.3)	23.0 (18.4, 27.5)	6.00 (-0.72, 12.72)	0.141
	1	23.8 (18.4, 29.1)	20.2 (15.7, 24.7)	3.55 (-3.17, 10.27)	0.379
	2	18.7 (13.3, 24.0)	21.0 (16.4, 25.5)	-2.30 (-9.02, 4.42)	0.568
	4	26.8 (21.4, 32.1)	17.6 (13.1, 22.1)	9.15 (2.43, 15.87)	0.027
	6	31.2 (25.8, 36.5)	14.1 (9.6, 18.6)	17.05 (10.33, 23.77)	<0.001
	24	22.6 (17.2, 27.9)	23.0 (18.5, 27.5)	-0.45 (-7.17, 6.27)	0.911

Sponsor's Conclusions:

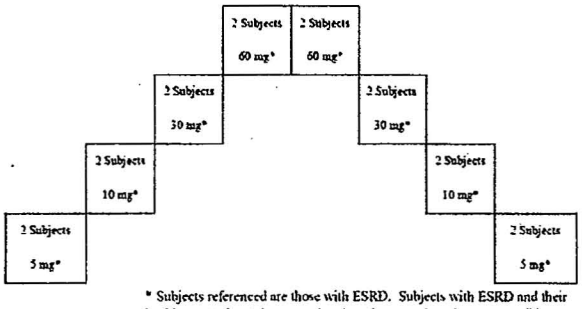
1. Exposure to prasugrel's active metabolite R-138727 was similar between hepatically impaired subjects and their healthy matches. Point estimates for the ratios of geometric LS means for AUC(0-tlast) and Cmax after the LD and after the last MD ranged from 0.91 to 1.14, and the 90% CIs for these parameters included 1.0. Variability in AUC(0-tlast) and Cmax was high in both populations.
2. The AUC(0-tlast) of R-95913 and R-106583 were not significantly affected by hepatic impairment. The 90% CI (hepatically impaired/healthy) for AUC(0-tlast) and Cmax included 1.0 except for the R-106583 Cmax after a LD, which ranged from 0.594 to 0.814 and indicates a lower LD Cmax in hepatically impaired subjects than in healthy subjects. R-119251 Cmax and AUC(0-tlast) were 30% to 83% higher in hepatically impaired subjects than in healthy subjects.
3. The mean baseline (predose) MPA to 20 μM ADP for subjects with moderate hepatic impairment and healthy subjects was similar.
4. There was no statistically significant difference in MPA to 20 μM ADP in subjects with moderate hepatic impairment compared to healthy subjects after a 60 mg prasugrel LD on Day 1 or after the final 10-mg prasugrel MD on Day 6, except at 4 and 6 hours after the final MD when MPA was higher in hepatically impaired subjects than in healthy subjects. This difference between healthy and hepatically impaired subjects at 4 and 6 hours, if real, would not affect safety in hepatically impaired subjects.
5. There was no statistically or clinically significant difference in exposure to prasugrel's active metabolite when prasugrel was given as a 60-mg LD followed by daily 10-mg MDs to healthy subjects and to subjects with moderate hepatic impairment.
6. There was no statistically or clinically significant difference in MPA when prasugrel was given as a 60-mg LD to healthy subjects and to subjects with moderate hepatic impairment.
7. There was no clinically meaningful difference in MPA when prasugrel was given as daily 10-mg MDs, although the MPA at 4 and 6 hours after the final MD was statistically significantly higher in subjects with moderate hepatic impairment compared to healthy subjects.
8. Exposure to prasugrel's inactive metabolite R-119251 was about 70% higher in subjects with moderate hepatic impairment than in healthy subjects.

Reviewer Comments

1. This study was performed to add the information for the comparison of the maintenance doses of prasugrel in subjects with moderate hepatic impairment vs. healthy subjects. The sponsor repeated the same study design as in study TAAN, namely: a 60-mg loading dose and five daily 10-mg maintenance doses of prasugrel and compared the pharmacokinetics of prasugrel's active and inactive metabolites.
2. There was no statistically or clinically significant difference in exposure to prasugrel's active metabolite when prasugrel was given as a 60-mg LD followed by daily 10-mg MDs to healthy subjects and to subjects with moderate hepatic impairment.
3. A dose adjustment of prasugrel in the hepatically impaired patients is not required.

4.2.9 Pharmacokinetics and Pharmacodynamics of Prasugrel Metabolites After Single Doses of 5 to 60 mg in Subjects with Normal Renal Function and Subjects with End Stage Renal Disease on Haemodialysis (TACJ)

Principal Investigator: Dr. Gilbert Weiner,
Study Centre: Allied Research International Inc., 1405 NW 167th Street, Miami Gardens, Florida 33169, USA. Publications
Duration of Study: 27 November 2006 through 17 May 2007
Phase of Development: 1

Objectives	Primary: to characterize the pharmacokinetic/pharmacodynamic relationship of active metabolite in subjects with end stage renal disease (ESRD) and use that relationship to predict a dosage regimen that produces a profile of maximum platelet aggregation (MPA) versus time similar to that produced by a 60-mg loading dose and daily 10-mg maintenance dosing in healthy subjects. Secondary: to assess the safety and tolerability of prasugrel in ESRD subjects; determine the effects of ESRD on the pharmacokinetics of prasugrel's inactive metabolites after single doses in ESRD subjects; assess platelet aggregation using traditional methodology and the Accumetrics VerifyNow™ P2Y12 (VNP2Y12) point-of-care device.
Study Design	Sequential dose escalation, open label, single-dose study.  * Subjects referenced are those with ESRD. Subjects with ESRD and their healthy control matches were dosed on the same day wherever possible, otherwise, they were to follow the same schedule for pharmacodynamic blood sampling.
Population	Thirty-two subjects (16 subjects with ESRD and 16 healthy subjects) received single doses of prasugrel. One subject was withdrawn following a single dose of 60-mg prasugrel. Test group: male or female subjects with ESRD (stable on haemodialysis for at least 3 months), aged between 25 and 75 years, inclusive. Control group: healthy male and female subjects with normal renal function matched by age, gender, body weight, and race (where possible) to subjects with ESRD.
Investigational Drugs	Prasugrel: a single 5, 10, 30, and 60-mg doses, provided as 5 and 10-mg tablets from lot numbers CT528570 and CT528571, respectively
Sampling: Blood	Blood samples were collected on Day 1, up to 24 hours postdose, for the measurement of plasma concentrations of prasugrel's active metabolite (R-138727) and inactive metabolites (R-95913, R-106583, and R-119251). Blood samples for measurement of platelet aggregation by LTA, induced by 5 and 20 μM ADP, and using the VNP2Y12 point-of-care device were collected at predose and 2, 4, and 24 hours postdose. The duration of the pharmacodynamic

	effect was also assessed after discharge. A blood sample was collected from all subjects every 2 to 3 days for up to 3 weeks following dosing, for assessment of MPA by both LTA and using the VNP2Y12 device.
Assay	HPLC with LC/MS/MS detection, chromatograms were shown. Platelet aggregation was assessed by light transmittance aggregometry (LTA) induced by 5 and 20 μM adenosine diphosphate (ADP) and the Accumetrics VerifyNow™ P2Y12 point-of-care device.
PK Assessment	Plasma concentrations of the active CS-747 metabolite (R138727), the three inactive CS-747 metabolites (R95913, R119251, R106583). 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.

Assay

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

Table 67. 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 %)	3.5 to 7.0	2.2 to 4.9	3.2 to 7.6
Accuracy, %	-5.8 to 2.1	-6.8 to 3.8	-3.7 to 2.3
LLOQ	1ng/mL		
Reviewer Comment	The assay characteristics and specificity are satisfactory, representative mass-chromatograms are shown		

Table 68. 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 6.8
Accuracy, %	-2.8 to 4.0
LLOQ	0.5ng/mL
Reviewer Comment	The assay characteristics and specificity are satisfactory, representative mass-chromatograms are shown

Demographics:

A total of 32 subjects, aged 24 to 68 years, were enrolled in this study. Sixteen subjects (12 males, 4 females) had ESRD requiring haemodialysis for at least three months, and 16 subjects (12 males, 4 females) were healthy with normal renal function (creatinine clearance, CLcr =80 mL/min). Of the subjects with ESRD, four subjects were Caucasian and 12 subjects were of Afro-Caribbean origin. Thirteen subjects in the healthy control group were Caucasian, one

subject was Afro-Caribbean, one subject was native Indian, and one subject was of mixed race (Hispanic/Latin). Both groups were matched for age (±15 years) and weight (±10%). Only five subjects with ESRD were matched with healthy subjects of the same racial origin.

Pharmacokinetics

The mean concentration-time profiles of R-138727 after prasugrel administration to healthy and ESRD subjects are shown in the figure below.

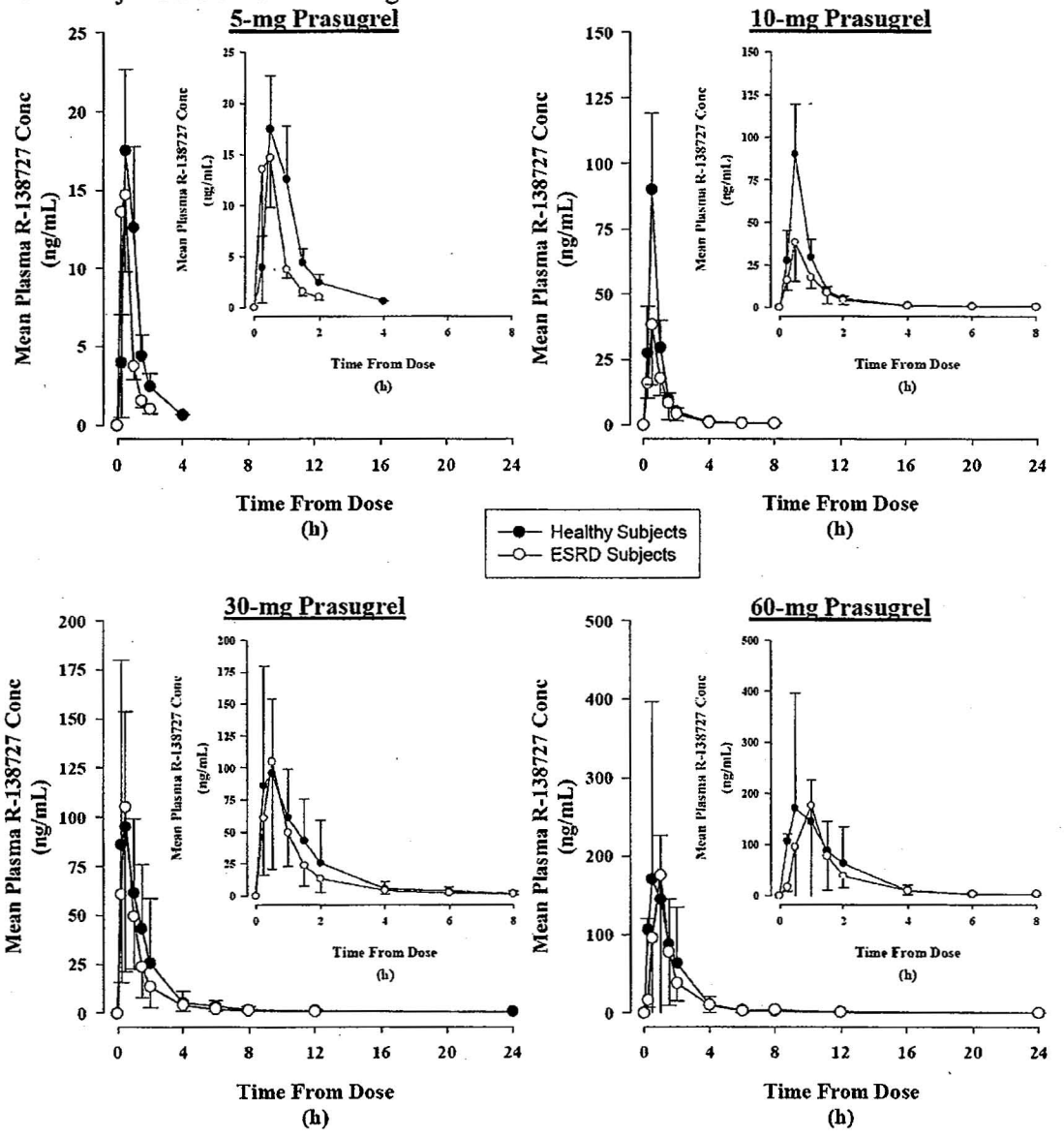


Figure 62 Arithmetic mean (±SD) plasma concentrations-time profiles of R-138727 after a single 5-, 10-, 30- or 60-mg prasugrel dose in healthy subjects and ESRD subjects

Following a single prasugrel dose from 5 to 60-mg, peak R-138727 plasma concentrations were achieved in approximately 0.5 hours in both groups. Typically, mean R-138727 concentration-time profiles appeared to be lower in ESRD subjects compared to healthy subjects following prasugrel administration across the dose range. The table below provides summary statistics for pharmacokinetic parameters of R-138727.

Table 69 Noncompartmental Pharmacokinetic Parameter Estimates for R-138727 after a Single 5-, 10-, 30- or 60-mg Prasugrel Dose in Healthy Subjects and ESRD Subjects

	Geometric Mean (%CV)			
	5-mg		10-mg	
Parameter	Healthy Subjects (N=4)	ESRD Subjects (N=4)	Healthy Subjects (N=4)	ESRD Subjects (N=4)
C_{max} (ng/mL)	19.6 (9.30)	15.9 (57.5)	85.9 (38.1)	42.4 (31.5)
t_{max}[a] (h)	0.50 (0.50-1.00)	0.50 (0.25-0.50)	0.50 (0.50-0.50)	0.50 (0.50-1.00)
AUC(0-t_{last}) (ng•h/mL)	17.1 (13.1)	10.3 (46.5)	64.5 (25.3)	34.7 (16.4)
	30-mg		60-mg	
Parameter	Healthy Subjects (N=4)	ESRD Subjects (N=4)	Healthy Subjects (N=4)	ESRD Subjects (N=4)
C_{max} (ng/mL)	131 (31.1)	93.7 (76.7)	229 (55.1)	110 (177)
t_{max}[a] (h)	0.62 (0.25-1.50)	0.50 (0.25-1.00)	0.75 (0.50-1.50)	1.00 (1.00-1.50)
AUC(0-t_{last}) (ng•h/mL)	154 (32.4)	107 (66.4)	295 (29.9)	197 (78.5)

The time to peak plasma concentration was similar between the studied groups. The systemic exposure was generally lower in subjects with ESRD compared to healthy subjects.
The sponsor attempted to statistically analyze these data. Since there were only 4 subjects in each dosing group, a conclusion about the statistical significance of the differences cannot be made.

Table 70 Statistical Analysis of Pharmacokinetic Parameters for R-138727 after a Single 5-, 10-, 30- or 60-mg Prasugrel Dose in Healthy Subjects and ESRD Subjects

				Ratio of geometric LS Mean
	Prasugrel	Geometric LS Mean (90% CI)		ESRD:Healthy
Parameter	Dose	ESRD subjects	Healthy subjects	(90% CI)
AUC(0-t_{last}) (ng.h/mL)	5-mg	10.3 (7.25, 14.6)	17.1 (12.1, 24.3)	0.60 (0.37, 0.96)
	10-mg	34.7 (24.5, 49.2)	64.5 (45.5, 91.5)	0.53 (0.33, 0.86)
	30-mg	107 (75.6, 152)	154 (109, 219)	0.69 (0.43, 1.11)
	60-mg	197 (139, 279)	295 (208, 418)	0.66 (0.41, 1.07)
Cmax (ng/mL)	5-mg	15.9 (9.60, 26.2)	19.6 (11.9, 32.5)	0.80 (0.39, 1.65)
	10-mg	42.4 (25.6, 70.1)	85.9 (52.0, 142)	0.49 (0.24, 1.00)
	30-mg	93.7 (56.7, 155)	131 (79.0, 216)	0.71 (0.35, 1.46)
	60-mg	110 (66.4, 182)	229 (138, 378)	0.48 (0.23, 0.97)
t_{max}[a] (h)	5-mg	0.500	0.500	-0.125 (-0.500, 0)
	10-mg	0.500	0.500	0 (0, 0.500)
	30-mg	0.500	0.625	-0.250 (-1.00, 0.750)
	60-mg	1.00	0.750	0.250 (-0.500, 1.00)

The trends for disposition of R-106583 paralleled the active metabolite and geometric mean estimates of AUC(0-tlast) and Cmax were lower in ESRD subjects compared to healthy subjects. The geometric mean estimates of R-119251 AUC(0-tlast) appeared to be slightly higher in ESRD compared to healthy subjects with no conclusive evidence of dose-dependent increases. Since the information about the inactive metabolites is not critical for this review, the reader is referred to the study report for the information pertaining to the inactive metabolites.

Pharmacodynamics: Platelet Aggregation Using Light Transmittance Aggregometry

The mean baseline MPA to 20 μM ADP was lower in subjects with ESRD compared to healthy subjects (58-73 vs. 69-76%).

The MPA values plotted vs time after a 5 and 60 mg dose of prasugrel are shown in the figure below. In general, the MPA response was similar in both healthy and renally impaired subjects

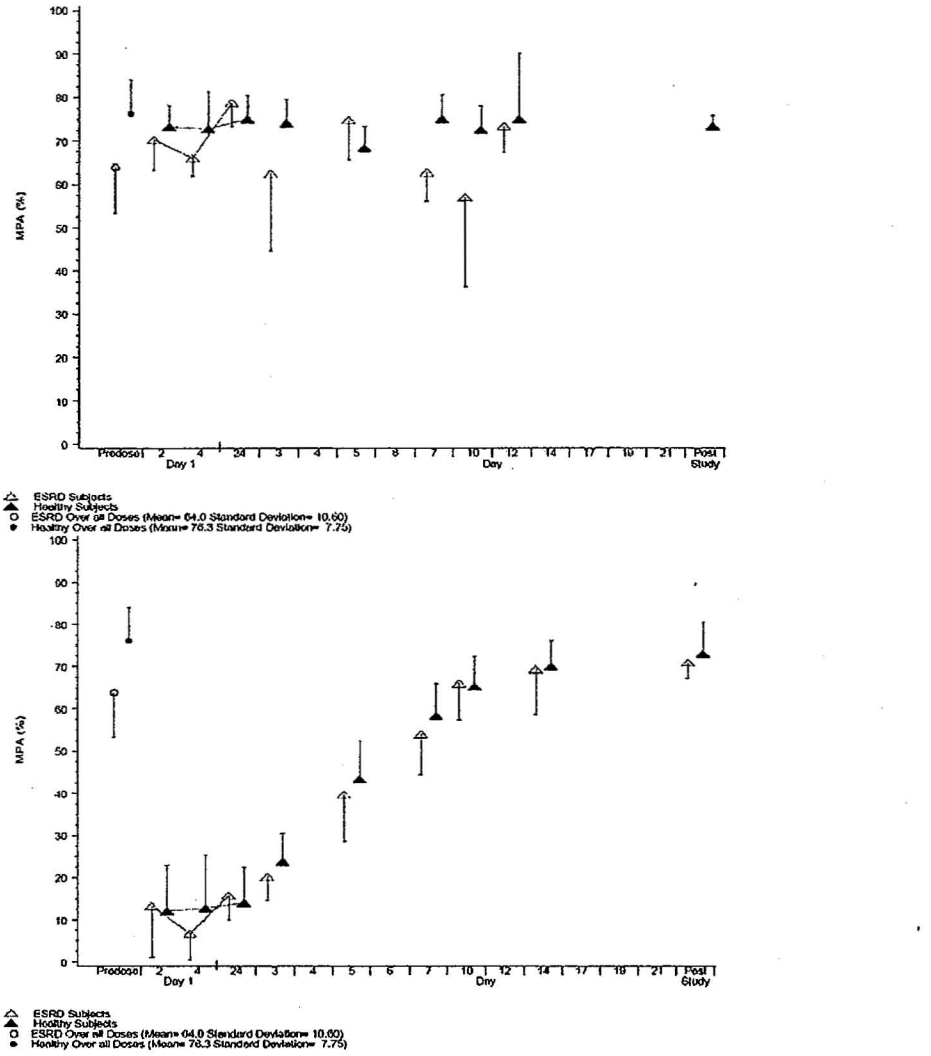


Figure 63 Mean (± SD) MPA to 20 μM ADP following a single oral dose of 5-mg (upper panel) and 60 mg (lower panel) prasugrel in subjects with ESRD and healthy matched subjects.

The sponsor also compared the MPA values for both groups at each time point and after every dose of prasugrel. The sponsor concluded that the differences between study groups were not statistically significant besides the few occasions. Since the comparison was made for the data obtained in 4 subjects per group of dosing, it is not statistically solid to make a final conclusion regarding the whole population of subjects with ESRD.

Sponsor's Conclusions:

1. Generally, systemic exposure of R-138727 (AUC0-tlast) tended to be lower in subjects with ESRD compared to that in healthy subjects.

2. The magnitude and time course of the mean MPA response to 20 μM ADP were similar for subjects with ESRD and healthy matched subjects following single doses of 5 to 60-mg prasugrel.
3. The recovery in platelet aggregation response was similar for subjects with ESRD and healthy matched subjects following single doses of 10 to 60-mg prasugrel. The recovery in platelet aggregation response was not assessed at the 5-mg prasugrel dose level.

Reviewer's Comments

1. The sponsor designed the study to assess the differences in the prasugrel PK and PD between the healthy subjects and subjects with ESRD. Since the sponsor included in each dosing group only 4 subjects, the statistical conclusions of this study are not solid and the results may be used only for descriptive purposes.
2. Despite of the tendency of the lower exposure (both by AUC and Cmax) to prasugrel in ESRD subjects compared to the healthy subjects, the pharmacodynamic response measured as MPA to 20 mcM ADP was similar between the compared groups.
3. This result may be is one of the confirmations that this pharmacodynamic marker does not properly correlate with the exposure to the drug.