

4.2.10 Pharmacokinetics of Prasugrel Metabolites in Subjects with Moderate Renal Impairment, Subjects with End Stage Renal Disease Requiring Haemodialysis and Healthy Subjects with Normal Renal Function (TABW)

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Duration of Study: 17 January 2006 to 06 June 2007

Phase of Development: 1

Objectives	<p>Primary: To evaluate the pharmacokinetics of the prasugrel active metabolite in subjects with moderate renal impairment (MRI) and subjects with end stage renal disease (ESRD) requiring haemodialysis, compared to those in healthy subjects with normal renal function (NR), after a single oral 60-mg loading dose of prasugrel.</p> <p>Secondary: to evaluate the inhibition of platelet aggregation produced by prasugrel in healthy subjects, in MRI subjects, and in subjects with ESRD requiring haemodialysis;</p> <p>to determine the effects of MRI and ESRD on the pharmacokinetics of prasugrel inactive metabolites in subjects with MRI and subjects requiring haemodialysis;</p> <p>to assess the safety and tolerability of prasugrel in healthy subjects, in MRI subjects and in subjects with ESRD requiring haemodialysis; and</p> <p>to assess platelet aggregation in MRI subjects and their healthy matched controls.</p>
Study Design	A parallel-design, open-label, single-dose study. Forty-three subjects (five - ESRD, ten - MRI, and 28 healthy subjects) received single 60-mg doses of prasugrel.
Study Population	Male or female subjects with ESRD (who had required dialysis for at least 3 months) and male or female subjects with MRI function (Cockcroft-Gault creatinine clearance of 30 to 50 mL/min), 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 to subjects with ESRD and MRI.
Investigational Drug	Prasugrel provided as 10-mg tablets from lot number CT524157 (SFBC International) and CT526934 (_____)
Sampling	Blood samples up to 48 hours postdose (ESRD subjects), 36 hours postdose (healthy matches to ESRD subjects), or 24 hours postdose (MRI and their healthy matches).
Pharmacokinetics	Plasma concentrations of prasugrel active metabolite (R-138727) and inactive metabolites (R-95913, R-106583, and R-119251).
Pharmacodynamics	Platelet aggregation was assessed up to 144 hours postdose
Assays	HPLC with LC/MS/MS detection, chromatograms were shown. Platelet aggregation in platelet-rich plasma by light transmittance aggregometry (LTA) induced by 5 and 20 μ M adenosine diphosphate (ADP) and collagen (subjects with ESRD, moderate renal impairment and healthy subjects), and by the VNP2Y12 point-of-care device (subjects with MRI

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	and their healthy matches only)
PK Assessment	A non-compartmental PK analysis
Statistical methods	Log-transformed AUC(0-tlast) and Cmax of R-138727 were analyzed using a linear mixed effect model. The 90% confidence intervals (CI) for the ratios of geometric least squares (LS) means between the subjects with ESRD and healthy matches, and between subjects with moderate renal impairment and healthy matches, are presented. A comparison of tmax estimates was performed using the Wilcoxon signed-rank test (for subjects MRI and healthy matches only). The effect of prasugrel on MPA to 5 and 20 μ M ADP in subjects with ESRD, subjects with MRI, and in healthy subjects was assessed using a linear mixed-effect model at each scheduled time point. The least squares (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.

Results:**Assay**

Plasma samples were analyzed for R-138727, R-119251, R-106583, and R-95913 at Advion BioServices, Inc., (Advion), a subsidiary of Advion BioSciences, Inc., Ithaca, NY, USA, using validated liquid chromatography with tandem mass spectrometric detection (LC/MS/MS) methods. The lower limit of quantitation was 0.5 ng/mL for R-138727 and 1 ng/mL for R-119251, R-106583, and R-95913. The upper limit of quantitation was 250 ng/mL for R-138727 and 500 ng/mL for R-119251, R-106583, and R-95913. Samples above the limit of quantitation were diluted and reanalyzed to yield results within the calibrated range. The inter-batch and intra-batch values for accuracy and precision were similar to the once reported in Table 51, and acceptable, chromatograms were shown.

The inactive thiolactone prasugrel metabolite (R-95913) was unstable in the plasma of subjects with ESRD and did not provide reliable estimates of plasma concentrations. The plasma concentrations or pharmacokinetic parameters of R-95913 were reported for subjects with ESRD.

Platelet aggregation was performed at each research unit on a PAP-4 optical aggregometer, with temperature maintained at 37°C. Platelet aggregation in platelet rich plasma was measured using LTA with 5 and 20 μ M ADP, and 2 μ g/mL collagen as the agonists. Platelet counts of the platelet rich plasma were adjusted using autologous platelet poor plasma only where counts were greater than 400,000/ μ L. For subjects with moderate renal impairment and their healthy matches, platelet aggregation was also assessed with the VNP2Y12 device according to the manufacturer's guidance approximately 10 minutes after sample collection.

Demographics:

A total of 43 subjects, aged 38 to 75 years, were enrolled in this study. Five subjects (1 male, 4 females) had ESRD requiring haemodialysis for at least three months, 10 subjects (4 males, 6 females) had moderate renal impairment with an estimated CGCL of 30 to 50 mL/min, and 28 subjects (10 males, 18 females) were healthy with normal renal function (assessed by estimated creatinine clearance >80 mL/min). Of the subjects with ESRD, three subjects were Afro-Caribbean, one subject was Hispanic and one subject was Black. Six subjects with moderate renal impairment were Caucasian, two subjects were Asian, one subject was Hispanic and one

subject was a Pacific Islander. Of the 28 subjects in the healthy control, 13 subjects were Caucasian, 10 subjects were Hispanic, four subjects were Asian, and one subject was of Afro-Caribbean origin.

Pharmacokinetics.

The figure below shows mean concentration-time profiles of prasugrel’s active metabolite in healthy subjects, subjects with moderate renal impairment, and subjects with ESRD.

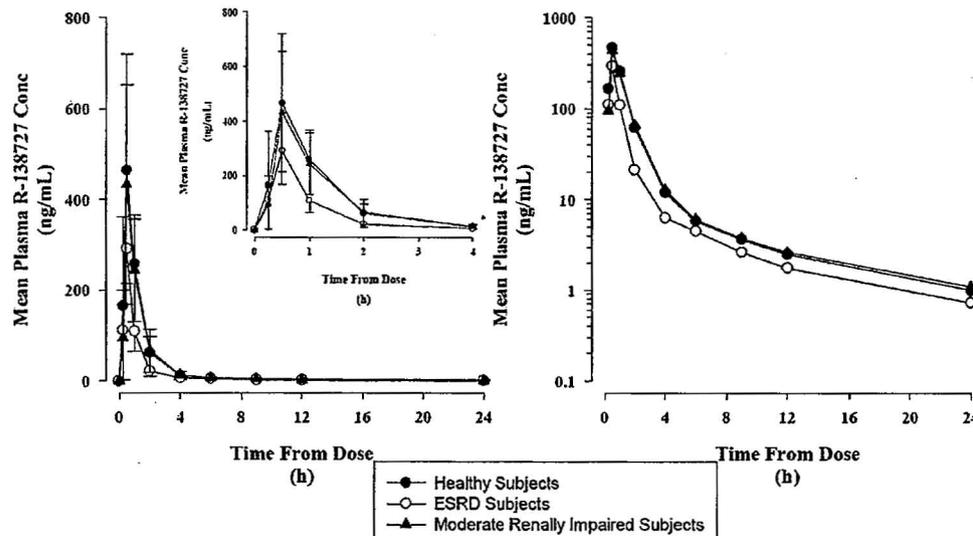


Figure 64. Arithmetic mean (±SD) plasma concentrations-time profiles of R-138727 after a single 60-mg prasugrel dose in healthy subjects, ESRD subjects and moderate renal impairment subjects.

The table below summarizes the noncompartmental pharmacokinetic parameter estimates for R-138727 in these three subject groups.

Table 71. PK Parameter Estimates for R-138727

Parameter	Geometric Mean (%CV)		
	Healthy Subjects (N=28)	ESRD Subjects (N=5)	Moderate Renally Impaired Subjects (N=10)
C _{max} (ng/mL)	441 (64.9)	274 (39.9)	385 (71.1)
t _{max} ^a (h)	0.50 (0.25-2.07)	0.50 (0.50-0.50)	0.50 (0.50-1.00)
AUC(0-t _{last}) (ng.h/mL)	499 (34.7)	259 (42.4)	464 (57.5)
AUC(0-24) (ng.h/mL)	498 (34.7)	257 (40.8)	464 (57.5)
AUC(0-∞) (ng.h/mL)	512 (34.0)	267 (41.7)	476 (56.3)

The statistical analyses of pharmacokinetic parameter estimates are shown below. The active metabolite AUC(0-t_{last}) was 47% lower in ESRD subjects than in the matching healthy subjects. In subjects with moderate renal impairment, the mean AUC(0-t_{last}) and C_{max} were not statistically different from that in the matching healthy subjects.

Table 72. Statistical Analysis of Pharmacokinetic Parameters for R-138727

Parameter	Units	Geometric LS Mean		Ratio of geometric LS Mean	p-value ^c
		ESRD subjects (N=5)	Healthy subjects (N=8)	ESRD:Healthy (90% CI)	
AUC(0-t _{last})	ng.h/mL	259	487	0.53 (0.32, 0.86)	
C _{max}	ng/mL	274	460	0.59 (0.29, 1.19)	
t _{max} ^a	h	0.500	0.500	0 (-0.250, 0.125)	NC ^b

Parameter	Units	Subjects with moderate renal impairment (N=10)	Healthy subjects (N=20)	Moderate renal impairment:Healthy (90% CI)	p-value ^c
		AUC(0-t _{last})	ng.h/mL	464	
C _{max}	ng/mL	385	433	0.88 (0.67, 1.28)	
t _{max} ^a	h	0.500	0.638	-0.125 (-0.513, 0.062)	0.219

^a t_{max}: analyzed nonparametrically; median and median difference (minimum difference, maximum difference) of ESRD-healthy subjects

^b Not calculated due to low number of subjects

^c Wilcoxon Signed-Rank p-value for t_{max}

Plots of individual estimates of C_{max} and AUC(0-t_{last}) in healthy subjects, subjects with ESRD, and subjects with moderate renal impairment show considerable overlap between the populations.

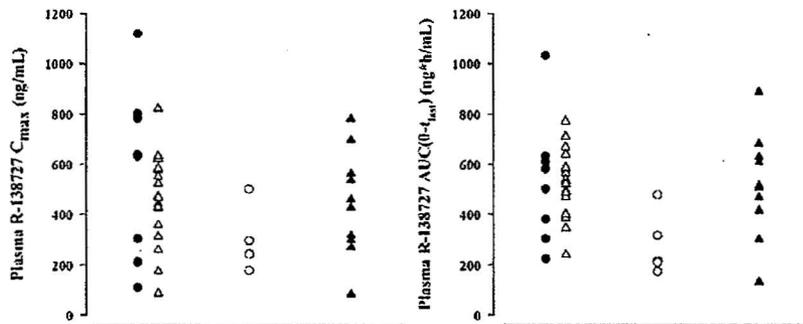


Figure 65. Individual estimates of R-138727 C_{max} and AUC(0-t_{last}) Circles represent ESRD subjects (open) with healthy matched subjects (closed); Triangles represent moderate renally impaired subjects (closed) with healthy matched subjects (open)

The exposures to each of the inactive metabolites were similar among populations except for the following:

- 1) For R-95913, exposures could not be assessed in ESRD subjects because concentrations could not be quantified in plasma collected from this population;
- 2) For R-119251, C_{max} and AUC(0-t_{last}) tended to be higher in subjects with either degree of renal impairment than in healthy subjects; and
- 3) C_{max} of R-106583 appeared to be lower in ESRD subjects and subjects with moderate renal impairment than in healthy subjects.

Pharmacodynamics

The mean MPA to 20 μ M ADP following a single 60-mg dose of prasugrel in subjects with moderate renal impairment, subjects with ESRD and healthy matched subjects shown below.

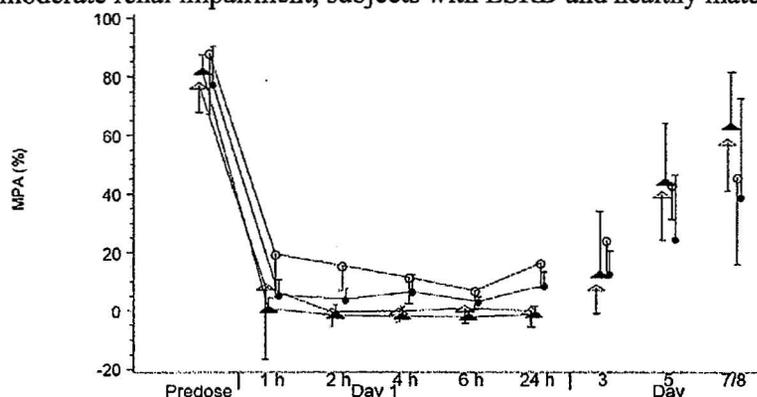


Figure 66. Mean MPA to 20 μ M ADP following a 60-mg dose of prasugrel in subjects with ESRD (●), subjects with moderate renal impairment (▲) and healthy matched subjects to each group (○, Δ).

The inhibition of platelet aggregation was achieved in each group of subjects after a 60-mg prasugrel and was maintained above 80% up to 24 hours post-dose period. The sponsor compared at the 5% significance level the mean MPA values at each time point between subjects with moderate renal impairment and healthy matched subjects and between subjects with ESRD and healthy matched subjects and concluded that the differences were not statistically significant (with the exception of the 96-hour time point, healthy- ESRD).

REVIEWER COMMENTS:

1. The active metabolite AUC(0-tlast) was 47% lower in ESRD subjects than in matching healthy subjects.
2. The exposure to the active metabolite was similar between healthy subjects and subjects with moderate renal impairment.
3. The sponsor concluded that the differences in mean MPA values at each time point between subjects with moderate renal impairment and healthy matched subjects and between subjects with ESRD and healthy matched subjects were not statistically significant ($\alpha=5\%$). However, at each time point, including the baseline, ESRD subjects had less maximum platelet aggregation values (vs. healthy) with the differences between 3 and 19%. It is not clear if this is an indication of the increased IPA due to the low baseline MPA values in ESRD group. Finally, since there were only 5 subjects with ESRD in this study, the statistical conclusions about the MPA response in patients with the severe renal impairment is difficult to make.
4. There were two of five ESRD subjects with a possible prolonged pharmacodynamic effect than in healthy matched subjects. However, the enrolment of subjects with ESRD was terminated early and this study did not complete evaluating subjects with ESRD as planned. The sponsor did not reach a conclusion regarding potential dose adjustment in this group.

5. Since recommendations regarding dose adjustment in the severely renally impaired (ESRD) cannot be made, the label should contraindicate prasugrel administration to ESRD patients.

Investigational Drug	Prasugrel: orally as a 60-mg LD, and 5-mg and 10-mg daily MDs. Supplied as 10-mg tablets from lot numbers CT527095 and CT527099, and 5-mg tablets from lot number CT527097.
Sampling: Blood	60-mg LD: on Day 1, 10-mg MD on Day 8, and 5-mg MD on Day 18. Measurement of plasma concentrations of R-138727 and R-95913, R-106583, and R-119251. The platelet aggregation by LTA (5 and 20 μ M ADP) and the Accumetrics VN-P2Y12 point-of-care device: Days 1, 8, and 18.
Assay	HPLC with LC/MS/MS detection, chromatograms were shown. Please see Table 51 and Table 52 for the assay characteristics. Platelet aggregation in platelet-rich plasma was measured using LTA with 5 and 20 μ M ADP as the agonists, and using the Accumetrics VN- P2Y12 device.
PK Assessment	PK parameter estimates for R-138727, R-95913, R-106583, and R-119251 were calculated using noncompartmental methods following the 60-mg LD and 5-mg and 10-mg MDs of prasugrel. Additionally partial AUCs up to 2 and 4 hours postdose [AUC(0-2) and AUC(0-4)] were calculated.
Statistical	Log-transformed AUC(0-tlast) and Cmax of all four prasugrel metabolites were analyzed using a linear mixed effect model. The 90% confidence intervals (CI) for the ratios of geometric least squares (LS) means between each Asian group and Caucasian subjects were presented. A comparison of tmax estimates was performed using the Kruskal-Wallis test. A linear mixed effect model was used to assess the effect of ethnicity on IPA and maximum platelet aggregation (MPA) to 5 and 20 μ M ADP during LD and MDs. The 90% CIs for the difference of geometric LS means between each Asian group and Caucasian subjects were presented.
PK/PD	Exploratory graphical evaluations were conducted to compare the relationship between R-138727 AUC(0-tlast) and 24 hours postdose MPA to 20 μ M ADP following a 60-mg LD across ethnicities. Similarly, the relationship between R-138727 AUC(0-tlast) and 12 hours postdose MPA (on Days 8 and 18 combined) were evaluated after daily 5- and 10-mg prasugrel MDs.

Results

Demographics

A total of 89 subjects, aged 20 to 56 years, were enrolled in this study. Twenty-two subjects were Caucasian (12 males and 10 females aged 20 to 56 years); 25 subjects were Chinese (20 males and 5 females aged 20 to 48 years); 20 subjects were Japanese (16 males and 4 females aged 21 to 33 years); and 22 subjects were Korean (12 males and 10 females aged 21 to 33 years). All Asian subjects were first generation and the majority had lived in the UK for less than 1 year. Mean age and BMI were similar across the ethnic groups.

Pharmacokinetics

Prasugrel Loading 60-mg Dose

The figure below illustrates the mean concentration time profiles of prasugrel active metabolite (R-138727) following administration of a 60-mg prasugrel LD to groups of Caucasian, Chinese, Japanese, and Korean subjects. All ethnic groups achieved peak concentrations approximately a half hour after dosing. Mean plasma concentrations of R-138727 in the Asian groups tended to be higher than those in the Caucasian group. These mean differences were most evident in the early portions of the pharmacokinetic profile (up to ~4 hours postdose).

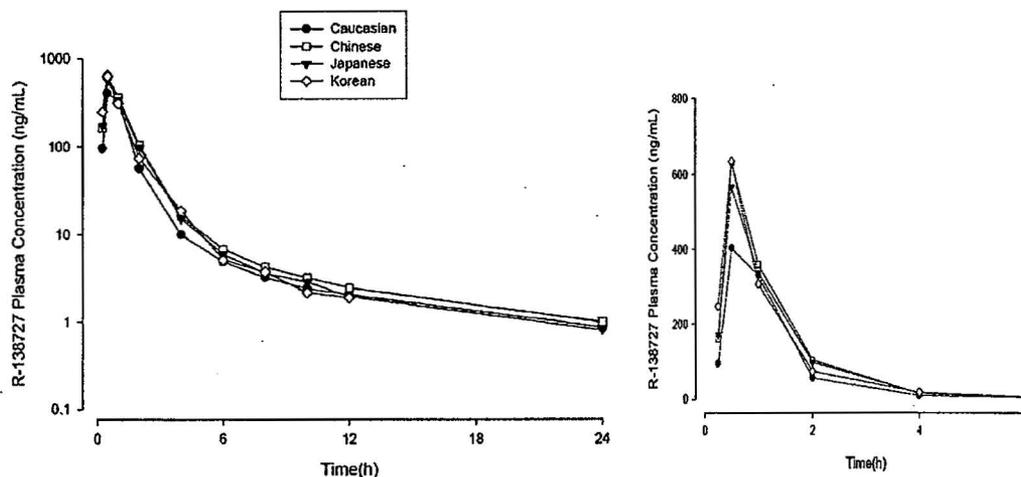


Figure 67. Arithmetic mean plasma concentration-time profiles of R-138727 following a 60-mg LD of prasugrel on Day 1 (right panel linear with from 0-6 h)

Individual estimates of R-138727 C_{max} and AUC(0-tlast) for each of the Asian groups overlapped to some degree with the estimates for the Caucasian group (Figure below). Approximately 48%, 37%, and 50% of individual Chinese, Japanese, and Korean C_{max} estimates, respectively, were higher than the maximum Caucasian C_{max} estimate. Further, approximately 40%, 32%, and 14% of individual Chinese, Japanese, and Korean AUC(0-tlast) estimates, respectively, were greater than the maximum Caucasian AUC(0-tlast) estimate.

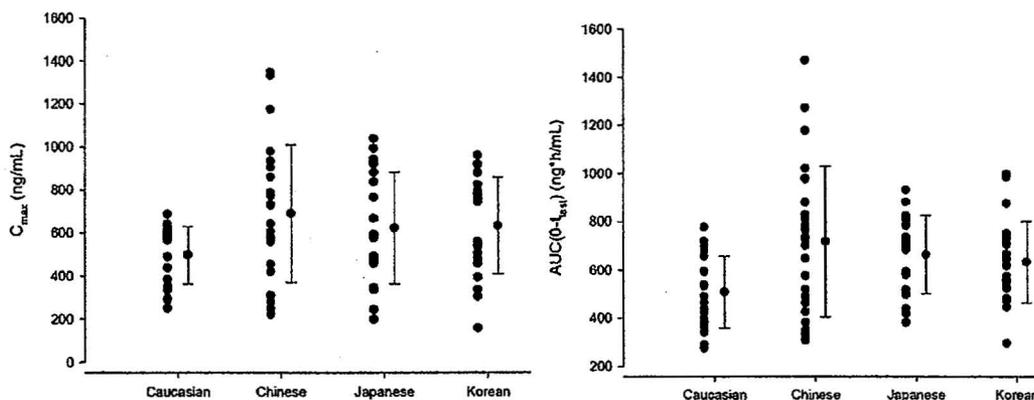


Figure 68. Individual estimates with arithmetic mean ± SD of R-138727 C_{max} (upper panel) and AUC(0-tlast) (lower panel) stratified by ethnic group following a 60-mg LD of prasugrel on Day 1

Mean ethnic differences were observed in various measures of R-138727 exposure (C_{max} and AUC) as well as partial areas [AUC(0-2) and AUC(0-4)] consistent with trends in the concentration time profiles (Table below).

Table 73. Summary of Geometric Mean (CV%) Pharmacokinetic Parameters of R-138727 following a 60-mg LD of Prasugrel on Day 1

Parameters	Caucasian	Chinese	Japanese	Korean
N	22	25	19	22
C _{max} (ng/mL)	476 (31)	614 (55)	565 (51)	586 (47)
t _{max} ^a (h)	0.54 (0.25-1.02)	0.50 (0.25-2.02)	0.50 (0.25-2.00)	0.50 (0.25-1.00)
AUC(0-t _{last}) (ng•h/mL)	486 (31)	653 (48)	643 (27)	611 (28)
AUC(0-2) (ng•h/mL)	393 (32)	499 (56)	495 (36)	477 (40)
AUC(0-4) (ng•h/mL)	444 (31)	594 (48)	590 (28)	563 (28)

Statistical comparisons of key R-138727 exposure estimates [C_{max} and AUC(0-t_{last})] demonstrated higher mean exposures in Asian subjects compared to Caucasians (Table below).

Table 74. Statistical Comparison of Prasugrel Active Metabolite (R-138727) Pharmacokinetic Parameters Between Chinese, Japanese, Korean, and Caucasian Subjects Following a 60-mg LD of Prasugrel on Day 1

Parameters (units)	Race	Geometric LS means (90% CI)	Asian / Caucasian ratio (90% CI)
AUC(0-t _{last}) (ng.h/mL)	Caucasian	486 (427, 553)	
	Chinese	653 (583, 733)	1.34 (1.13, 1.60) ^a
	Japanese	643 (567, 730)	1.32 (1.10, 1.58) ^a
	Korean	611 (533, 700)	1.26 (1.04, 1.52) ^a
C _{max} (ng/mL)	Caucasian	476 (405, 560)	
	Chinese	614 (531, 710)	1.29 (1.04, 1.60) ^a
	Japanese	565 (478, 668)	1.19 (0.94, 1.49) ^a
	Korean	586 (477, 719)	1.23 (0.94, 1.59) ^a

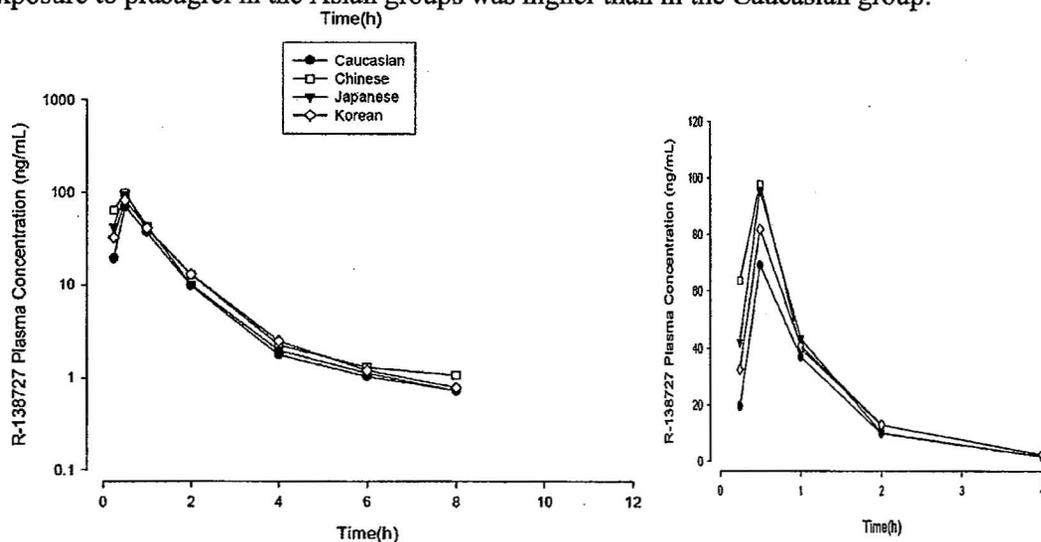
The sponsor also reported the minor inter-ethnic differences in mean profiles for the inactive metabolites especially proximal to peak concentrations. Statistical comparison of R-95913, R-106583, and R-119251 PK parameters for all races is shown in Table below.

Table 75. Statistical Comparison of R-95913, R-106583, and R-119251 Pharmacokinetic Parameters Between Chinese, Japanese, Korean, and Caucasian Subjects Following a 60-mg LD of Prasugrel on Day 1

Prasugrel metabolite	Parameter (units)	Race	Geometric LS means (90% CI)	Asian / Caucasian ratio (90% CI)
R-106583	AUC(0-t _{last}) (ng.h/mL)	Caucasian	2689 (2375, 3044)	
		Chinese	2836 (2532, 3177)	1.05 (0.89, 1.25)
		Japanese	2868 (2522, 3262)	1.07 (0.89, 1.28)
		Korean	2779 (2457, 3144)	1.03 (0.86, 1.23)
	C _{max} (ng/mL)	Caucasian	494 (444, 550)	
		Chinese	477 (432, 527)	0.96 (0.83, 1.12)
		Japanese	454 (406, 507)	0.91 (0.78, 1.07)
		Korean	443 (395, 497)	0.89 (0.76, 1.05)
R-119251	AUC(0-t _{last}) (ng.h/mL)	Caucasian	361 (308, 422)	
		Chinese	430 (373, 496)	1.19 (0.96, 1.47)
		Japanese	411 (350, 482)	1.14 (0.91, 1.42)
		Korean	480 (411, 560)	1.33 (1.07, 1.66)
	C _{max} (ng/mL)	Caucasian	244 (205, 291)	
		Chinese	262 (226, 304)	1.07 (0.85, 1.35)
		Japanese	234 (196, 279)	0.95 (0.74, 1.23)
		Korean	316 (262, 381)	1.29 (1.00, 1.67)
R-95913	AUC(0-t _{last}) (ng.h/mL)	Caucasian	427 (379, 480)	
		Chinese	539 (483, 600)	1.26 (1.07, 1.48)
		Japanese	427 (377, 489)	1.01 (0.84, 1.20)
		Korean	350 (310, 395)	0.81 (0.69, 0.97)
	C _{max} (ng/mL)	Caucasian	221 (187, 260)	
		Chinese	260 (225, 302)	1.18 (0.94, 1.47)
		Japanese	217 (181, 261)	0.98 (0.77, 1.26)
		Korean	175 (147, 209)	0.79 (0.62, 1.01)

Prasugrel Maintenance 10-mg Doses

The figure below shows the PK profiles of R-138727 following multiple daily administration of 10 mg prasugrel (Day 8) in Caucasian, Chinese, Japanese, and Korean groups. The mean exposure to prasugrel in the Asian groups was higher than in the Caucasian group.

**Figure 69. Arithmetic mean plasma concentration- time profiles of R-138727 following 10-mg MDs of prasugrel on Day 8 (right panel linear with inset 0-4 h).**

The individual estimates of C_{max} and AUC(0-t_{last}) for R-138727 across ethnicities are shown below.

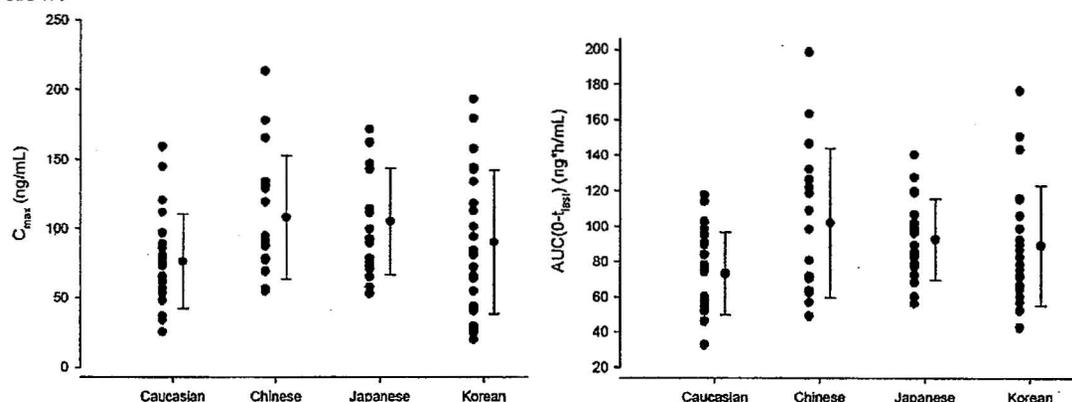


Figure 70. Individual estimates with arithmetic mean \pm SD of R-138727 C_{max} and AUC(0-t_{last}) stratified by ethnic group following 10-mg MDs of prasugrel on Day 8

Approximately 41% Chinese, 21% Japanese, and 14% Korean subjects exhibited higher R-138727 AUC(0-t_{last}) than the maximum range of AUC(0-t_{last}) for Caucasians.

The Table 76 summarizes the pharmacokinetic parameters and Table 77- a comparison of AUC(0-t_{last}) of each of the Asian groups to the Caucasian group for R-138727. The LS mean R-138727 AUC(0-t_{last}) was higher in each of the Asian groups compared to the Caucasian group. The 90% CI of the LS mean ratio of R-138727 AUC(0-t_{last}) (each Asian group:Caucasian group) exceeded predefined equivalence limits.

Table 76. Summary of Geometric Mean (CV%) Pharmacokinetic Parameters of R-138727 Following 10-mg MDs of Prasugrel on Day 8

Parameters	Caucasian	Chinese	Japanese	Korean
N	22	17	19	22
C _{max} (ng/mL)	69.3 (48)	101 (41)	98.7 (38)	74.4 (76)
t _{max} ^a (h)	0.50 (0.25-1.00)	0.50 (0.25-2.00)	0.50 (0.25-1.00)	0.50 (0.25-2.00)
AUC(0-t _{last}) (ng·h/mL)	69.6 (34)	94.7 (43)	89.9 (26)	83.9 (37)
AUC(0-2) (ng·h/mL)	55.4 (35)	76.7 (40)	75.0 (25)	62.9 (51)
AUC(0-4) (ng·h/mL)	64.6 (34)	87.8 (41)	84.8 (25)	76.5 (41)