Table 77. Statistical Comparison of R-138727 AUC(0-tlast) Between Chinese, Japanese, Korean, and Caucasian Subjects Following 10-mg MDs of Prasugrel on Day 8

Race	AUC(0-t_{last}) Geometric LS mean (90% CI)	Asian / Caucasian ratio (90% CI)
Caucasian	69.6 (61.1, 79.2)	
Chinese	97.9 (86.8, 111)	1.41 (1.18, 1.68)[a]
Japanese	89.9 (79.3, 102)	1.29 (1.08, 1.55)[a]
Korean	83.9 (73.9, 96.2)	1.21 (1.00, 1.46)[a]

Model : Log(PK) = SUBJECT + SUBJECT*DOSE + RACE + DOSE + RACE*DOSE + RANDOM ERROR

[a] Not equivalent because 90% CIs exceed 0.72 to 1.38 for AUC

Similar to the prasugrel LD, inter-ethnic differences in mean exposure estimates were evident for R-95913 and R-119251 (see Table below for the AUC comparisons). Trends for R-95913 and R-119251 disposition were consistent with the 60 mg LD.

Table 78. Statistical Comparison of Prasugrel Inactive Metabolite AUC(0-tlast) Between Chinese, Japanese, Korean and Caucasian Subjects Following 10-mg MDs of Prasugrel on Day 8

Prasugrel metabolite	Race	AUC(0-t_{last}) Geometric LS means (90% CI)	Asian / Caucasian ratio (90% CI)
R-106583	Caucasian	435 (384, 493)	
	Chinese	460 (411, 516)	1.06 (0.89, 1.25)
	Japanese	442 (389, 503)	1.02 (0.85, 1.22)
	Korean	425 (375, 481)	0.97 (0.81, 1.16)
R-119251	Caucasian	41.1 (35.2, 48.1)	
	Chinese	58.2 (50.4, 67.1)	1.41 (1.14, 1.75)
	Japanese	52.6 (44.9, 61.8)	1.28 (1.02, 1.60)
	Korean	53.9 (46.2, 62.9)	1.31 (1.05, 1.63)
R-95913	Caucasian	73.1 (64.9, 82.3)	
	Chinese	96.2 (86.3, 107)	1.32 (1.12, 1.55)
	Japanese	82.2 (72.2, 93.6)	1.12 (0.94, 1.34)
	Korean	57.0 (50.5, 64.4)	0.78 (0.65, 0.92)

Pharmacokinetics Following 5-mg Prasugrel Maintenance Doses

The figure below illustrates the mean concentration time profiles of R-138727 following daily 5-mg prasugrel MD in Caucasian, Chinese, Japanese, and Korean subjects. As with the other dosing paradigms, mean exposure, especially in the first hour postdose, was higher in Asians compared to Caucasians.

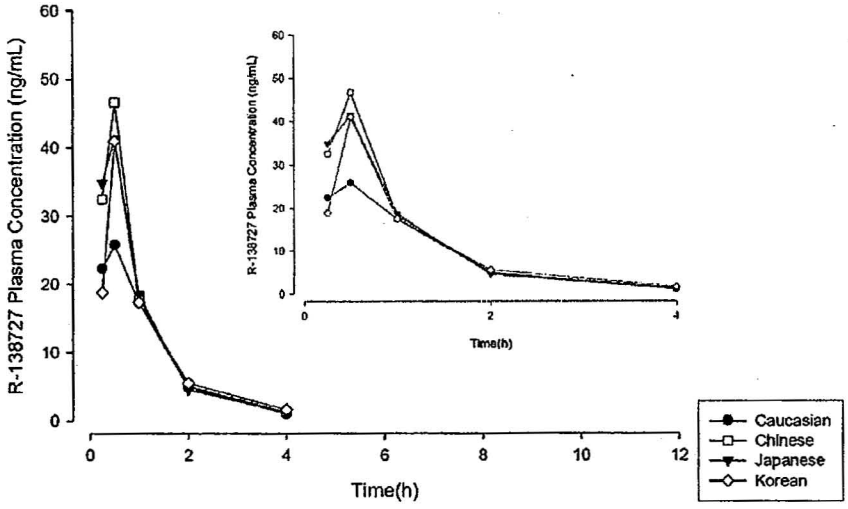


Figure 71. Arithmetic mean plasma concentration- time profiles of R-138727 following 5-mg MDs of prasugrel on Day 18 (upper panel linear with inset 0-4 h; lower panel log-linear).

Figure TABZ.7.7 illustrates individual R-138727 Cmax and AUC(0-tlast) estimates stratified by ethnic group. Approximately 24% Chinese, 16% Japanese, and 14% of the Korean subjects exhibited AUC(0-tlast) estimates greater than the range in the Caucasian group.

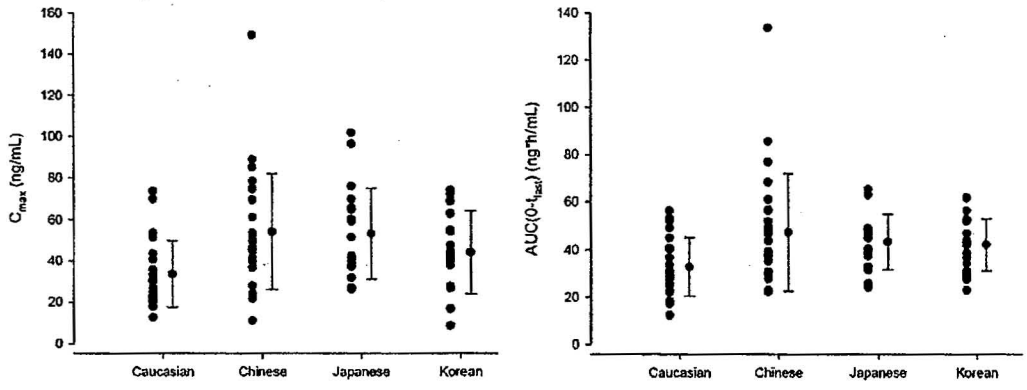


Figure 72. Individual estimates with arithmetic mean ±SD of R-138727 Cmax (left panel) and AUC(0-tlast) (right panel) stratified by ethnic group following 5-mg MDs of prasugrel on Day 18.

Overall, of all Asian subjects, four Chinese subjects and two Japanese subjects consistently demonstrated higher R-138727 exposure in each of the study periods compared to their Caucasian study cohorts.

Table 79 Summary of Geometric Mean (CV%) Pharmacokinetic Parameters of R-138727 Following 5-mg MDs of Prasugrel on Day 18

Parameters	Caucasian	Chinese	Japanese	Korean
N	22	25	19	21
C_{max} (ng/mL)	30.4 (47)	47.9 (56)	49.3 (41)	38.5 (64)
t_{max} [a] (h)	0.50 (0.25-1.00)	0.50 (0.25-1.00)	0.50 (0.25-1.00)	0.50 (0.25-1.00)
AUC(0-t_{last}) (ng•h/mL)	30.3 (42)	42.4 (48)	41.6 (29)	40.6 (28)
AUC(0-2) (ng•h/mL)	25.5 (37)	35.7 (47)	36.1 (28)	32.2 (38)
AUC(0-4) (ng•h/mL)	32.2 [b] (32)	41.4 [c] (46)	41.6 [d] (26)	38.9 (29)

N = Number of subjects
[a] Median (range)
[b] N=19; R-138727 concentrations were only quantifiable up to 2 hours in 3 subjects
[c] N=24; R-138727 concentrations were only quantifiable up to 2 hours in 1 subject
[d] N=18; R-138727 concentrations were only quantifiable up to 2 hours in 1 subject

In the table below a statistical comparison of R-138727 AUC(0-tlast) between the various ethnic groups is shown. LS mean R-138727 AUC(0-tlast) was higher in each of the Asian groups compared to the Caucasian subjects. The upper bound of the 90% CI of the LS mean ratio (each Asian group:Caucasian) exceeded the predefined limits for equivalence.

Table 80. Statistical Comparison of Prasugrel Active Metabolite (R-138727) AUC(0-tlast) Between Chinese, Japanese, Korean and Caucasian Subjects following 5-mg MDs of Prasugrel on Day 18

Race	AUC(0-tlast) Geometric LS means (90% CI)	Asian / Caucasian ratio (90% CI)
Caucasian	30.3 (26.7, 34.5)	
Chinese	42.4 (37.8, 47.6)	1.40 (1.18, 1.66)[a]
Japanese	41.6 (36.7, 47.2)	1.37 (1.15, 1.64)[a]
Korean	40.4 (35.2, 46.3)	1.33 (1.10, 1.61)[a]

For the inactive metabolite disposition trends are similar after a prasugrel 60-mg LD or prasugrel 10-mg MD (data not shown here).

Pharmacodynamics

Platelet Aggregation Using Light Transmittance Aggregometry

The mean baseline (Day 1 predose) MPA to 20 μM ADP was similar for the Caucasian (88%), Chinese (89%), Japanese (86%) and Korean (89%) groups.

The figure below shows the mean IPA to 20 μM ADP following a 60-mg LD (Day 1), 10-mg MD (Day 8), and 5-mg MD (Day 18) of prasugrel in the Caucasian, Chinese, Japanese, and Korean groups. Following a 60-mg LD of prasugrel, each Asian group generally showed higher mean IPA compared to Caucasians, with Korean subjects attaining higher mean IPA more rapidly than all other ethnic groups. Following 10-mg MDs, ethnic differences seemed more pronounced with each Asian group showing higher mean IPA compared to Caucasians. Following 5-mg MDs, ethnic differences were even more pronounced, with Korean subjects showing the highest mean IPA.

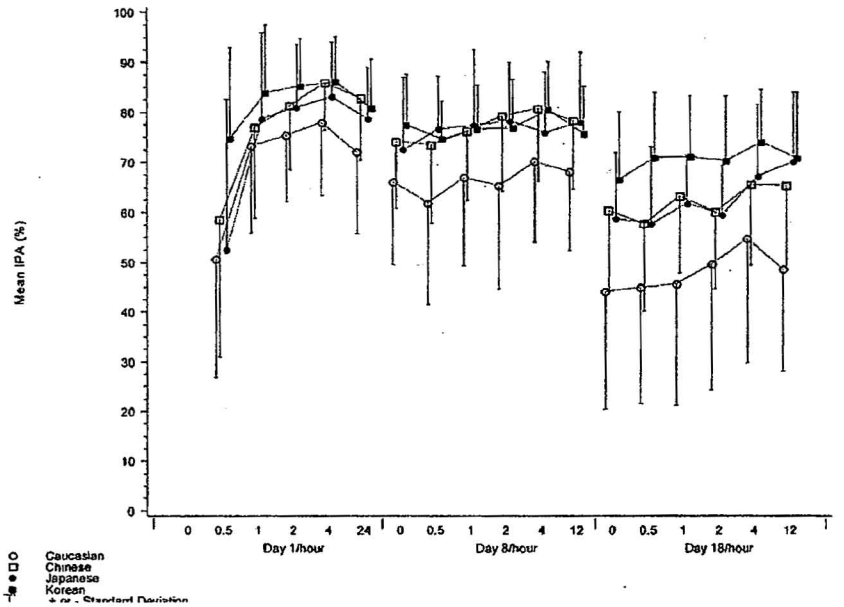


Figure 73.

Mean IPA to 20 μM ADP (LTA) following a 60-mg LD (Day 1), 10-mg MD (Day 8), and 5-mg MD (Day 18) of prasugrel in Caucasian, Chinese, Japanese and Korean subjects.

Following the 60-mg prasugrel LD, mean IPA to 20 μM ADP was higher in the Chinese, Japanese, and Korean groups compared to the Caucasian group from 0.5 to 24 hours after dosing. The difference in IPA was statistically significant between the Chinese and Caucasian groups only at 24 hours postdose, and between the Korean and Caucasian groups at 0.5 and 1 hour postdose.

Following the last 10-mg prasugrel MD on Day 8, mean IPA to 20 μM ADP was statistically significantly higher in the Chinese, Japanese, and Korean groups compared to the Caucasian groups at most time points from predose to 12 hours postdose.

Following the final 5-mg prasugrel MD on Day 18, the mean IPA to 20 μM ADP was statistically significantly higher in each Asian group compared to the Caucasian group at most time points from predose to 12 hours postdose.

The mean IPA to 20 μM ADP from 0.5 to 12 hours following the final 5-mg MD in Korean subjects appeared to be similar to the mean IPA achieved following the last 10-mg MD in Caucasian subjects, although this was no confirmed by formal statistical analysis. In Chinese and Japanese subjects, the mean IPA to 20 μM ADP up to 12 hours following the 5-mg MD was slightly below the mean IPA achieved following the 10-mg MD in Caucasian subjects.

Comparison of Platelet Aggregation Using the Turbidometric Method and Accumetrics VerifyNow™ Assay

The sponsor compared the same measurement of IPA by two method, and concluded that the results are similar.

Pharmacokinetic/Pharmacodynamic Evaluations

The sponsor attempted to graphically explore the relationship between MPA to 20 μM ADP and R-138727 exposure across different ethnicities. The sponsor showed (Figure below) the MPA to 20 μM ADP as a function of R-138727 AUC(0-tlast) following a 60-mg prasugrel LD (upper panel) and daily 5- and 10-mg prasugrel MDs (lower panel).

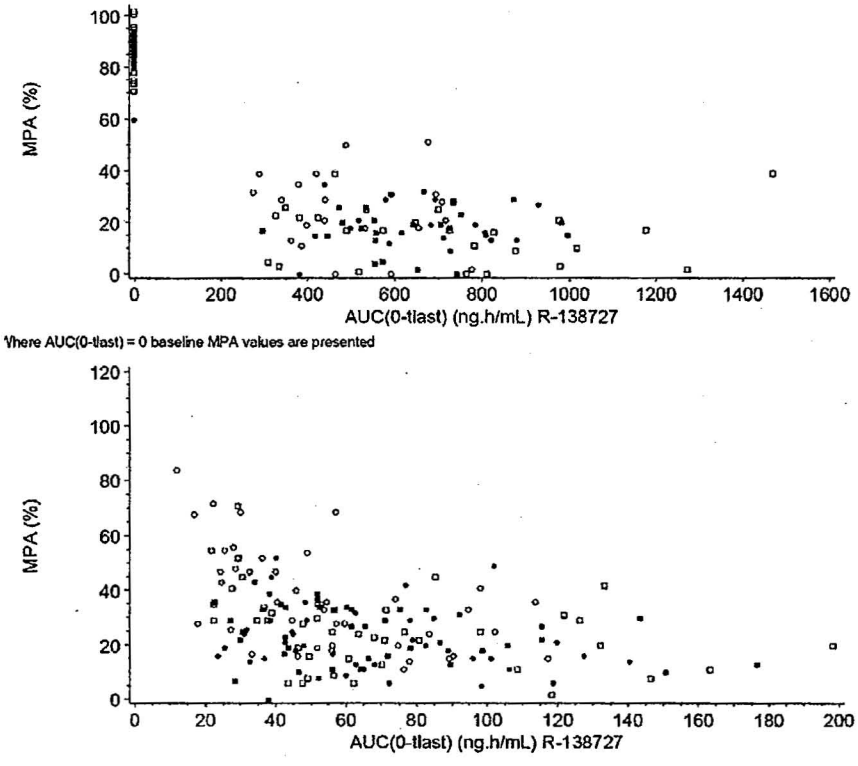


Figure 74. Relationship between R-138727 AUC(0-tlast) and MPA to 20 μM ADP following 60-mg prasugrel LD (upper panel) and daily 5- and 10-mg prasugrel MDs combined (lower panel).

Based on the superposition of the AUC values for all groups shown on this figure, the sponsor concluded that the IPA response did not depend on the ethnicity.

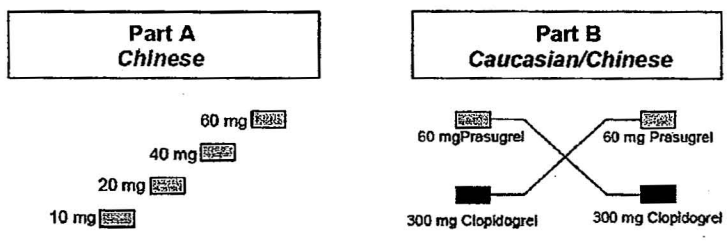
Reviewer's Comments

1. Mean R-138727 exposure following a 60-mg LD or daily 10- or 5-mg MDs of prasugrel was higher in each of the Asian groups compared to Caucasians.
2. Following a 60-mg prasugrel LD, mean IPA to 20 μM ADP was generally higher in Chinese, Japanese and Korean subjects compared to Caucasian subjects up to 24 hours postdose, however, the differences between each Asian group and Caucasian subjects did not consistently achieve statistical significance, probably due to the high variability of the IPA measurements.

3. Following daily MDs of 10- and 5-mg prasugrel, IPA to 20 μM ADP was statistically significantly higher in each Asian group compared to Caucasian subjects at the majority of time points from predose up to 12 hours after each MD.
4. In this study, the Asian race differences in the IPA response were not conclusive.
5. The most frequently reported adverse events during the study were bleeding-related events. The highest incidence of bleeding-related adverse events was reported by Korean subjects 20 out of 33, and the lowest incidence reported by Japanese subjects, 9 out of 10. For each ethnic group, the bleeding-related events were most frequently reported following the 10-mg MDs. The bleeding events analyses are performed in the clinical review.

4.2.12 A study to evaluate the safety and tolerability of prasugrel in healthy Chinese subjects, and to compare effects of prasugrel and clopidogrel in Chinese and Caucasian subjects (TAAQ).

Principal investigator: Dr R Kelly
Study Centre: Lilly-NUS Centre for Clinical Pharmacology Pte Ltd., Level 6 Clinical Research Centre (MD 11), National University of Singapore, 10 Medical Drive, Singapore 117597.
Study Duration: 11 July 2005 to 14 June 2006
Phase of Development: 1

Objectives	Primary: to evaluate the safety and tolerability of prasugrel when given as single doses up to 60 mg in healthy Chinese subjects. Secondary: to evaluate the effects of different doses of prasugrel on the inhibition of platelet aggregation (IPA) and bleeding times in healthy Chinese subjects; to compare the effects of prasugrel and clopidogrel on the IPA and bleeding times in Chinese and Caucasian subjects; and to evaluate the pharmacokinetics of prasugrel metabolites in Chinese and Caucasian subjects.
Study Design	This was a two-part study. Part A was a blind, placebo-controlled, ascending single oral dose, sequential group study in Chinese subjects. In Part A, escalating doses of prasugrel were administered to four cohorts of Chinese subjects. Within each cohort, six subjects were randomly assigned to receive prasugrel and two subjects were randomly assigned to receive placebo. The prasugrel dose escalation was 10 mg, 20 mg, 40 mg and 60 mg. Part B was an investigator-blind, randomized, single oral dose, two-period cross-over study in Chinese and Caucasian subjects. In Part B, subjects received a 60-mg dose of prasugrel and a 300-mg dose of clopidogrel in two separate periods. There was a minimum of 14 days washout between treatments in Part B.  Part A = Prasugrel dose escalation safety study in Chinese subjects. Part B = Randomised, cross-over study of prasugrel and clopidogrel in Chinese and Caucasian subjects.
Population	Part A: 24 Chinese subjects Part B: 14 Chinese and 14 Caucasian subjects.
Investigational Drug	Part A, prasugrel: oral single 10-, 20-, 40-, and 60-mg doses. Part B, prasugrel: oral single 60-mg dose. Prasugrel: 10-mg tablets, lot numbers CT520560, CT522055, and CT524928. Part A, placebo: tablets from lot number CT520561.
Reference	Part B, clopidogrel: oral a single 300-mg dose, 75-mg tablets, lot #1418.

Sampling: Blood	PK Blood samples were collected for the determination of plasma concentrations of prasugrel active (R-138727) and inactive metabolites (R-95913, R-106583 and R-119251) in both Parts A and B of the study. Blood samples for analysis of the clopidogrel active metabolite (R-130964) were collected in Part B of the study only. Samples were collected during each treatment period at 0.25, 0.5, 1, 1.5, 2, 4, 8, 12, and 24 hours postdose. In Parts A and B, blood samples (9 mL), for measurement of platelet aggregation induced by 5 and 20 μM ADP, were collected predose and at 0.5, 1, 2, 4, and 24 hours postdose. Blood samples for measurement of VASP phosphorylation were collected during Part B only, at predose and 0.5, 1, 2, 4, and 24 hours post-dose.
Assay	HPLC with LC/MS/MS detection, chromatograms were shown. See Table 51 and Table 52 for the assay characteristics
PK Assessment	Noncompartmental methods
PD Assessment	Bleeding times were measured using a modified Ivy technique.
Statistics	(1) A comparison of IPA between prasugrel doses at each time point for Chinese subjects (Parts A and B). A mixed effects model was used for this analysis with baseline (predose) MPA as a continuous covariate, dose, time, and dose by time as fixed effects, and subject, subject by dose, and subject by time as random effects. (2) A comparison of IPA between Chinese (Parts A and B) and Caucasian (Part B) subjects at each time point following a 60-mg prasugrel dose. A mixed effects model was used for this analysis with baseline (predose) MPA values as a continuous covariate, race, time, and ethnic group by time as fixed effects, and subject, and subject by time as random effects. (3) A comparison of IPA in each ethnic group between arms (Part B) at each time point. A mixed effects model was used with baseline (predose) MPA values as a continuous covariate, treatment, time, race, treatment by time, treatment by race, and treatment by time by race as fixed effects, and subject, subject by race, subject by treatment and subject by time as random effects. (4) A comparison of bleeding time ratio (BTR), ratio of the geometric mean bleeding time at a given time to the geometric mean bleeding time at predose (BTt/BT0), within prasugrel doses in Chinese subjects (Parts A and B). A mixed effect model was used with log transformed geometric mean baseline bleeding time as a covariate, dose as a fixed effect, and subject and subject by dose as random effects. (5) A comparison of BTR between Chinese (Parts A and B) and Caucasian (Part B) subjects following a 60-mg prasugrel dose. A mixed effects model was used with geometric mean baseline values as a continuous covariate, race, time, and ethnic group by time as fixed categorical effects, and subject, and subject by time as random effects. (6) A comparison of BTR between 60-mg prasugrel and 300-mg clopidogrel in each ethnic group (Part B). A mixed effects model was used with geometric mean baseline values as a covariate, treatment, race, treatment by time, and treatment by race as fixed effects, and subject, and subject by dose as random effects.

Results

Demographics

A total of 61 healthy subjects participated in this study, with 32 subjects in Part A and 29 subjects in Part B. In Part A, all subjects were Chinese (30/2 m/f, aged 21 to 55 years). In Part B, 14 subjects were Chinese (12/2 m/f, aged 21 to 38 years), and 15 subjects were Caucasian (13/3 m/f, aged 21 to 34 years).

Pharmacokinetics

In Part A, the sponsor studied the PK of prasugrel ascending doses in Chinese subjects. The PK parameters increased more than dose-proportional in the studied prasugrel dose range of 10 to 60 mg (same conclusion was made previously for the Caucasian subjects). The variability of the parameters estimated after the 60 mg dose of prasugrel was very high.

Table 81. Pharmacokinetic Parameter Estimates [Geometric Mean (%CV)] for Prasugrel Active Metabolite (R-138727) after Single Prasugrel Doses of 10, 20, 40 and 60 mg in Chinese Subjects (Parts A and B)

Prasugrel dose (mg)	10	20	40	60
N	6	6	6	20
C_{max} (ng/mL)	82.5 (34.4)	194 (28.4)	493 (16.4)	569 (55.0)
t_{max}[a] (h)	0.50 (0.50-0.55)	0.50 (0.25-0.50)	0.50 (0.50-0.50)	0.50 (0.25-2.00)
AUC(0-t_{last}) (ng*hr/mL)	86.0 (40.1)	189 (18.9)	453 (12.4)	726 (32.1)
AUC(0-8h) (ng*hr/mL)	97.1[b] (24.2)	186 (18.9)	432 (12.6)	694 (32.9)

median (range)

N=5, prasugrel concentrations were only quantifiable up to 4 hours postdose in one subject

The pharmacokinetics of R-138727 are not dose proportional. The graphic assessment of dose proportionality is shown in the figure below.

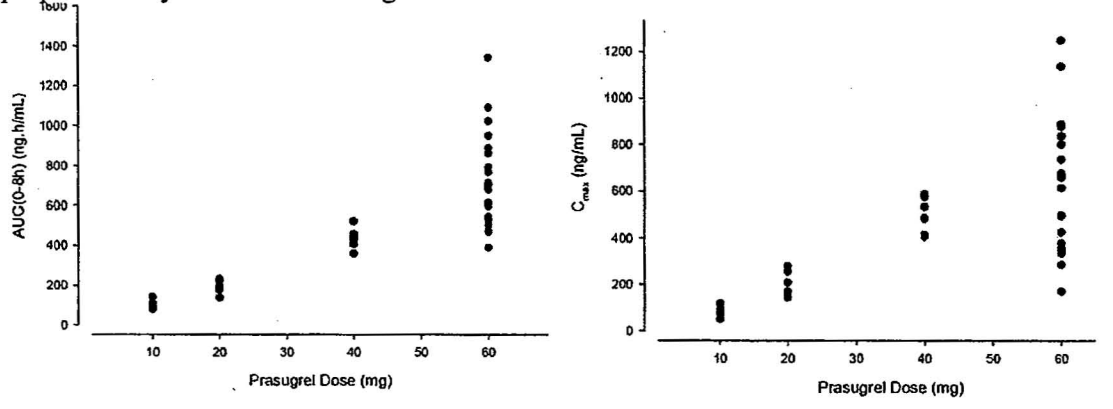


Figure 75 Prasugrel active metabolite AUC(0-8h) (upper panel) and Cmax (lower panel) after single doses of 10, 20, 40 and 60 mg prasugrel in Chinese subjects (Parts A and B).

The statistical evaluation of the dose proportionality was not performed.

Prasugrel Pharmacokinetics in Chinese versus Caucasian Subjects

Table 82. Pharmacokinetic Parameter Estimates for Prasugrel Active Metabolite after a Single 60-mg Prasugrel Dose in Chinese and Caucasian Subjects

Race	Chinese	Caucasians
N	20	14
C_{max} (ng/mL)	569 (55.0)	436 (52.7)
Weight normalised C_{max} (ng/mL/kg)	8.83 (66.2)	6.43 (65.0)
t_{max}[b] (h)	0.50 (0.25-2.00)	0.53 (0.50-1.50)
AUC(0-t_{last}) (ng*hr/mL)	726 (32.1)	609 (28.6)
Weight normalised AUC(0-t_{last}) (ng*hr/mL/kg)	11.3 (45.9)	9.00 (41.4)

The sponsor compared PK parameters of all prasugrel metabolites estimated in both populations (Table below). The geometric mean parameters shown in this table differ from the same geometric mean parameters listed in the table above. The parameters shown in the table below have less difference (Cmax 30%, AUC 20%, weight normalized AUC 25%) than in the table above (Cmax 20%, AUC 11%). No explanation is given by the sponsor.

Table 83. Statistical Comparison of Prasugrel Metabolite Pharmacokinetic Parameters in Chinese and Caucasian Subjects after a Single 60-mg Prasugrel Dose

Prasugrel metabolite	Parameters (units)	Race	Least Squares geometric means	Chinese / Caucasian ratio (90% CI)
R-138727	AUC(0-t_{last}) (ng.h/mL)	Caucasian	634	1.11
		Chinese	707	(0.98, 1.27)
	C_{max} (ng/mL)	Caucasian	457	1.20
		Chinese	550	(0.92, 1.57)
R-95913	AUC(0-t_{last}) (ng.h/mL)	Caucasian	376	0.99
		Chinese	374	(0.80, 1.23)
	C_{max} (ng/mL)	Caucasian	160	1.04
		Chinese	167	(0.81, 1.34)
R-106583	AUC(0-t_{last}) (ng.h/mL)	Caucasian	3484	0.90
		Chinese	3137	(0.78, 1.04)
	C_{max} (ng/mL)	Caucasian	537	0.95
		Chinese	508	(0.84, 1.07)
R-119251	AUC(0-t_{last}) (ng.h/mL)	Caucasian	664	0.75
		Chinese	496	(0.64, 0.87)
	C_{max} (ng/mL)	Caucasian	343	0.73
		Chinese	252	(0.57, 0.94)

Although exposure to R-138727 (both Cmax and AUC values) in Chinese subjects was larger than in Caucasians, the high variability of parameters did not allow to conclude the statistical difference.

Clopidogrel Pharmacokinetics in Chinese versus Caucasian Subjects

Figure below shows the mean plasma concentration-time profiles of clopidogrel active metabolite (R-130964) following administration of 300-mg clopidogrel in Chinese and Caucasian subjects.

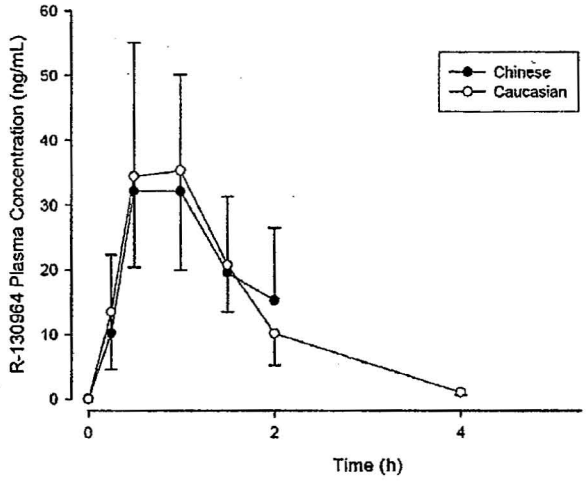


Figure 76 Arithmetic mean plasma concentration-time profiles of R-130964 in Chinese and Caucasian subjects following a single oral 300-mg clopidogrel dose

The sponsor presented the pharmacokinetic parameters of R-130964 in Chinese and Caucasian subjects. In the table below the AUCt-last values were measured up to 2 hours post-dose for Chinese subjects and up to 4 hours post-dose for Caucasians.

Table 84. Geometric Mean (CV%) Clopidogrel Active Metabolite Pharmacokinetic Parameters after a Single 300-mg Dose between Chinese and Caucasian Subjects

Metabolite	R-130964	
Race	Chinese	Caucasian
N	14	14
C_{max} (ng/mL)	38.6 (46.8)	36.1 (46.5)
Weight normalised C_{max} (ng/mL/kg)	0.605 (55.5)	0.533 (46.6)
t_{max}[a] (h)	1.00 (0.50-2.00)	1.00 (0.50-1.50)
AUC(0-t_{last}) (ng*h/mL)	46.6 (48.8)	48.7 (46.0)
Weight-normalised AUC(0-t_{last}) (ng*h/mL/kg)	0.729 (61.3)	0.719 (44.1)

The sponsor performed a statistical comparisons of the R-130964 PK parameters. The comparison of AUC values is not appropriate. The sponsor concluded that the differences were not statistically significant. However, the PK variability was very high, and probably this study was not properly powered to detect the differences between both populations.