Platelet Aggregation in Chinese versus Caucasian Subjects

The figure below shows the IPA to 20 μM ADP following administration of 60-mg prasugrel and 300-mg clopidogrel in Chinese and Caucasian subjects (Part B).

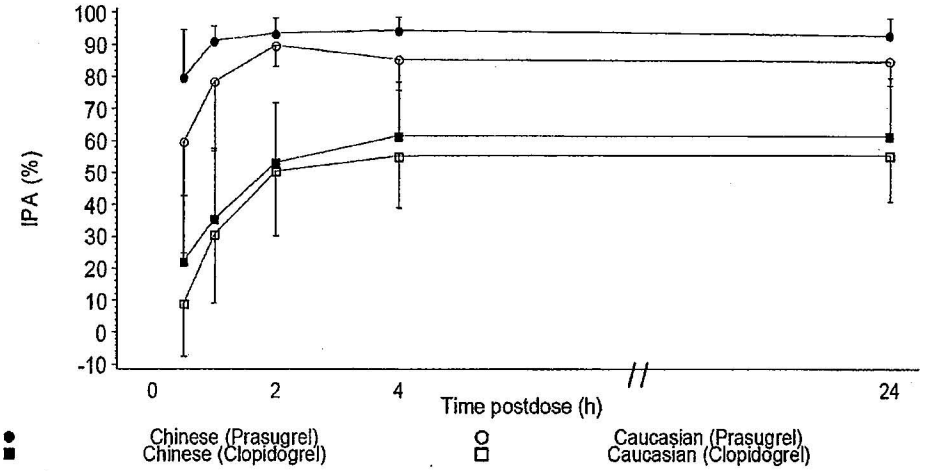


Figure 77. Arithmetic mean IPA to 20 μM ADP following administration of 60 mg prasugrel and 300 mg clopidogrel in Chinese and Caucasian subjects

The sponsor performed a statistical comparison of IPA to 20 μM ADP between Chinese and Caucasian subjects (Parts A and B) following administration of 60-mg prasugrel. Since the variability of the IPA measurement were very high and the curves overlapped, only the difference of 15% (prasugrel treatment, 0.5 hours post-dose) was statistically significant.

Bleeding Time in Chinese Subjects

The mean bleeding time data following administration of 10 to 60 mg prasugrel and placebo in Chinese subjects are shown in the table below.

Table 85. Geometric Mean (CV%) Bleeding Time (s) Following Administration of Single Doses of Prasugrel and Placebo in Chinese Subjects (Parts A and B)

Time (h)	Placebo	10 mg prasugrel	20 mg prasugrel	40 mg prasugrel	60 mg prasugrel
Predose	143 (34.9)	142 (31.5)	131 (34.0)	166 (29.1)	127 (37.4)
24	163 (17.3)	244 (28.8)	353 (59.0)	539 (24.3)	224 (107)

Although bleeding time increased with the dose of prasugrel from the doses of 10 to 40 mg, at 60 mg dose the bleeding time was less than after the 10 mg dose of prasugrel. The sponsor does not explain these changes.

Reviewer' Comments

1. The pharmacokinetics of prasugrel active metabolite was not dose proportional in Chinese subjects in the range of studied dose of 10 to 60 mg. It was more than dose-proportional increase in exposure (both Cmax and AUC values) with the prasugrel dose.

2. The sponsor's Table 85 shows the increase of bleeding time with the prasugrel dose up to 40 mg. The 60 mg dose of prasugrel in Chinese subjects caused the bleeding time similar to the effect of the 10 mg prasugrel dose. The plot of the mean bleeding time at the baseline and 24 hours after the singe dose of prasugrel is shown below.

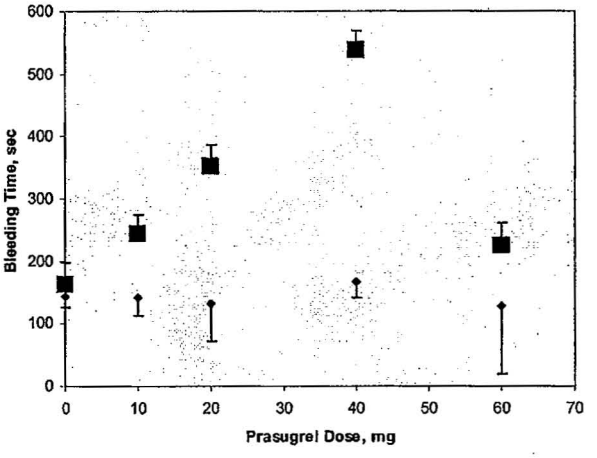


Figure 78. Bleeding time vs. Prasugrel Dose at Baseline (diamonds) and 24 hours post-dose (squares) in Chinese Subjects

It is not explained by the sponsor, what caused so abrupt changes in bleeding time at the highest studied dose of prasugrel. The reviewer inspected the raw data of bleeding time vs. the prasugrel dose (Figure below).

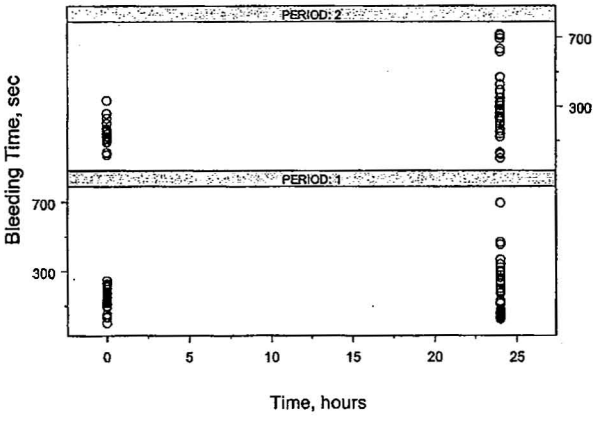


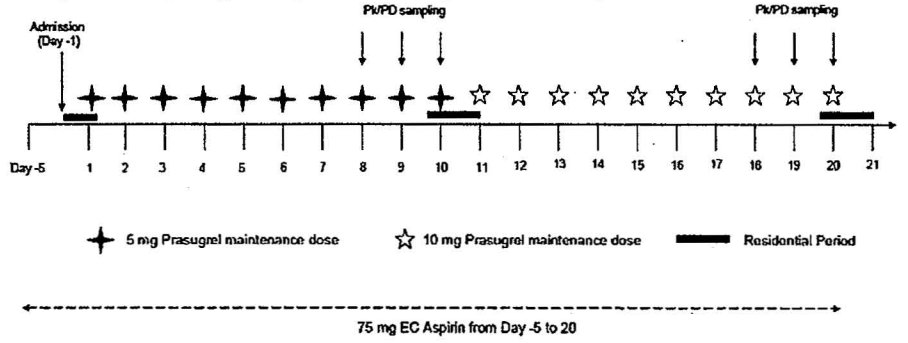
Figure 79. Bleeding Time vs Time post-dose. Period 1 – clopidogrel 300 mg and Period 2 – prasugrel 60 mg

In each treatment arm and population, the raw data contains a number of bleeding time values at 24 hour post-dose which were well below the baseline values, therefore, they may be considered as the outliers. Since the measurements of bleeding time were erroneous, the conclusions regarding the race differences in bleeding time based this study cannot be made.

3. In the studies performed by the sponsor in Japan, there were incidents of severe bleeding after the single 30 mg doses of prasugrel. It is not clear, if that result was due to the small frame of Japanese subjects or possible the race effect. The lower doses in the patients of the Asian descend may be considered.

4.2.13 The Effect of Age on the Pharmacokinetics and Pharmacodynamics of Prasugrel Metabolites in Healthy Subjects (TACG)

Responsible Investigators: Drs D Josa, P Rajagopalan and D Waghorn
Study Centre: Veeda Clinical Research, Old Convent of Notre Dame, 119 Looseleigh Lane, Derriford, Plymouth, PL6 5HH, UK.
Length of Study: 8 January 2007 to 13 April 2007
Phase of Development: 1

Objectives	Primary: to assess the effect of age on platelet aggregation after administration of prasugrel 5 and 10 mg maintenance doses (MDs) in the presence of aspirin. Secondary : to assess the effect of age on the MD pharmacokinetics of the prasugrel active metabolite, R-138727, and the prasugrel inactive metabolites (R-95913, R-106583 and R-119251); to assess the effect of age on bleeding time after administration of prasugrel and aspirin; and to assess the safety and tolerability of prasugrel given to younger and elderly subjects in the presence of aspirin.
Study Design	An open-label, single-sequence, multiple dose study.  Prasugrel: orally as 5- and 10-mg daily MDs. Aspirin EC: orally as a daily 75 mg tablet Duration of Treatment: 5 mg prasugrel: 10 days (Days 1 to 10). 10 mg prasugrel: 10 days (Days 11 to 20). 75 mg aspirin: 25 days (Days -5 to 20).
Population	Thirty-two healthy male and female subjects (17 elderly subjects aged 65 to 80 years and 15 young control subjects aged 20 to 39 years) entered and 31 subjects completed the study.
Investigational Drug	Prasugrel: 5 and 10 mg tablets (as hydrochloride salt), lot numbers CT529112 and CT529114 (Eli Lilly and Co). Commercially available Aspirin EC.
Sampling: Blood	Blood samples: on Days 10 and 20, for the measurement of plasma concentrations of prasugrel's active metabolite (R-138727) and inactive metabolites (R-95913, R-106583, and R 119251). Platelet aggregation was assessed by light transmittance aggregometry (LTA) induced by 5 and 20 μM

	adenosine diphosphate (ADP) and the Accumetrics VerifyNow™ P2Y12 (VN-P2Y12) point-of-care device. Bleeding time was assessed using a modified Ivy technique.
Assays	HPLC 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 as the agonists.
PK Assessment	Noncompartmental methods PK for the active (R-138727) and inactive metabolites of prasugrel (R-95913, R-106583, and R 119251)
Statistical	Log-transformed AUC(0-tlast) and Cmax of all four prasugrel metabolites were analyzed separately using a linear mixed effect (LME) model. The 90% CIs for the ratios of geometric LSM between the groups. Tmax estimates: Wilcoxon signed rank test. The effect of MPA to 5 and 20 μM ADP during MD: LME. The effect of prasugrel MD on VN-P2Y12 % inhibition was assessed. Log-transformed bleeding time ratio relative to predose values data: mixed effect model. Geometric LSM ratios of bleeding time ratios, 90% CI (p-values): Day 1 vs Day -5 for each age group, and between age groups following 5 and 10 mg prasugrel MDs on Day 10 and Day 20

Assay:
Determination of the plasma concentration of prasugrel (R138727) and clopidogrel (R361015) active metabolites were performed using the validated methods (Tables below).

Table 86 Assay Characteristics of R138727 in Plasma

Parameter	R138727	
Linearity	0.5 ng/mL to 250 ng/mL	
	Inter-batch	Intra-batch
Precision (CV %)	≤2.8	≤2.6
Accuracy, %	3.0 to 14.8	1.9 to 18.4
LLOQ	0.5ng/mL	
Reviewer Comment	The assay characteristics and specificity are satisfactory, representative mass-chromatograms are shown	

Table 87. 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 %)	≤6.6	≤5.83	≤5.1	≤1.8	≤11.4	≤8.7
Accuracy, %	-1.2 to 1.8	-1.6 to 3.48	-1.9 to 3.4	-3.0 to 2.7	-8.5 to -5.1	-11.6 to 3.6
LLOQ	1ng/mL					
Reviewer Comment	The assay characteristics and specificity are satisfactory, representative mass-chromatograms are shown					

Demographics

Thirty-two Caucasian subjects, aged 20 to 80 years, were enrolled in this study. It was planned to match elderly subjects for gender, weight (±10%), and racial origin to young control subjects. Twenty-six subjects were matched according to these criteria, although for two of these subjects (Subjects 104 and 110) the difference in weight was approximately 11%. In addition, there were six subjects (four elderly females [Subjects 113, 125, 126, and 132] and two young males [Subjects 112 and 131]) for whom a match was not found. The mean demographic parameters are shown below.

Mean (SD)	Age (years)	Body weight (kg)	Height (cm)	BMI (kg/m2)
Elderly (6M/11F)	71 (4.7)	70.2 (8.40)	164 (9.4)	26.0 (2.31)
Young (8M/7F)	28 (6.1)	67.8 (12.82)	168 (7.9)	23.9 (3.53)

Nine (2 males, 7 females) of the 17 subjects in the elderly population were aged 70 years or older.

Pharmacokinetics

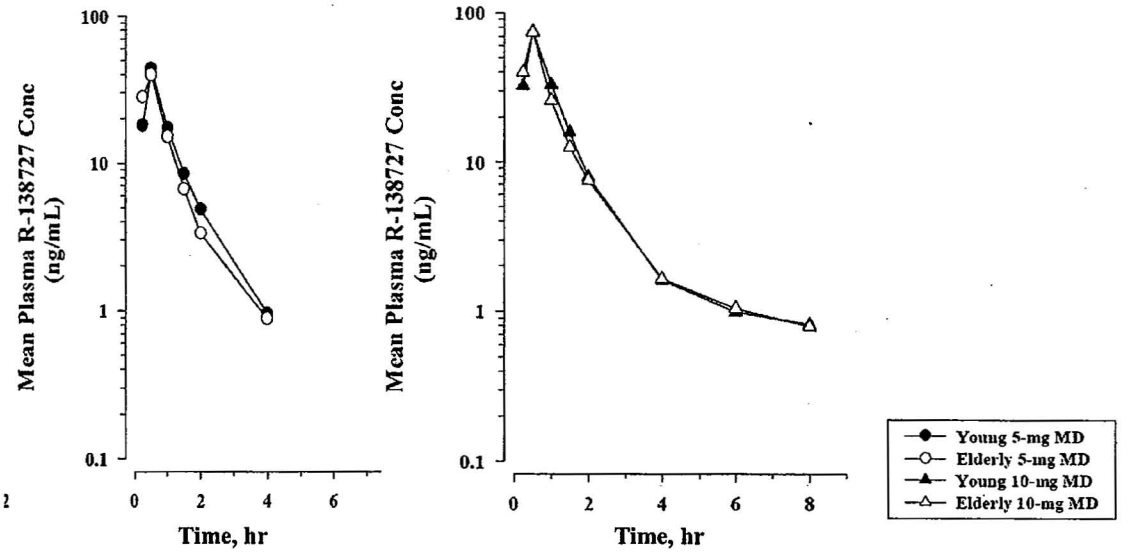


Figure 80. Arithmetic mean plasma concentration-time profiles of R-138727 after 10 days of 5-mg prasugrel MDs and following an additional 10 days of 10-mg prasugrel MDs in young and elderly subjects in the presence of aspirin.

At this low dose, the active metabolite of prasugrel was measurable until 4 and 8 hours post prasugrel multiple doses 5 mg/day and 10 mg/day. The Table 88 below lists the PK parameters of R-138727.

Table 88. PK Parameters of R-138727

	Geometric Mean (%CV)			
	5-mg MD		10-mg MD	
Parameter	Young Subjects (N=15)	Elderly Subjects (N=16)	Young Subjects (N=15)	Elderly Subjects (N=16)
C_{max} (ng/mL)	39.7 (51)	43.7 (43)	77.1 (35)	72.3 (57)
t_{max}[a] (h)	0.50 (0.25-1.50)	0.50 (0.25-0.55)	0.50 (0.25-1.00)	0.50 (0.25-2.00)
AUC(0-t_{last}) (ng•h/mL)	36.7 (33)	35.1 (35)	68.9 (28)	65.8 (32)

Statistical analysis of the effect of age on the pharmacokinetics of the active metabolite is shown in Table 89.

Table 89. Effect of Age on PK of R-138727

			Geometric LS Mean (90% CI)		Elderly vs. Young	
Prasugrel dose	Day	Parameter	Elderly subjects (N=16)	Young subjects (N=15)	Ratio of geometric LS Mean (90% CI)	p-value[a]
5 mg	10	AUC(0-t_{last}) (ng.h/mL)	34.1 (30.0, 38.8)	37.1 (32.5, 42.3)	0.92 (0.79, 1.07)	
		C_{max} (ng/mL)	43.7 (36.3, 52.7)	39.7 (32.8, 48.2)	1.10 (0.84, 1.44)	
		t_{max}[b] (h)	0.500	0.500	-0.125 (-0.250, 0)	0.063
10 mg	20	AUC(0-t_{last}) (ng.h/mL)	64.0 (56.3, 72.8)	69.5 (60.9, 79.4)	0.92 (0.79, 1.07)	
		C_{max} (ng/mL)	72.3 (60.0, 87.1)	77.1 (63.6, 93.5)	0.93 (0.71, 1.22)	
		t_{max}[b] (h)	0.500	0.500	0 (-0.125, 0.250)	0.875

The 90% CI for the ratios of geometric LS means for the comparison of prasugrel active metabolite in healthy young subjects with elderly subjects for AUC(0-tlast) following 5-mg and 10-mg daily doses was contained within the interval of 0.72 to 1.38.
The elderly subjects had lower exposure (AUC0-t) to the active metabolite. The Cmax values were higher in the 5 mg dosing group and lower in the 10 mg dosing group.

Comment:
The proper conclusions regarding effect of age on the Cmax values cannot be made based on this study due to the high variability (CV>45%) of Cmax and a small sample size of this study.

The sponsor also performed analyses of the data for inactive metabolites. In general, trends for disposition of prasugrel inactive metabolites paralleled the active metabolite, and systemic exposures were similar between elderly and young subjects. Although the difference between elderly and young subjects tended to be greatest (33% higher in elderly) in mean plasma R-119251 exposures following 5-mg MDs, this difference appeared to be not clinically meaningful. Since the effect on platelet aggregation occurs only due to the active metabolite, please refer to the study report for the corresponding figures and tables.

Pharmacodynamics
ADP-Induced Platelet Aggregation
Table below presents the results of the pre- and post-aspirin baseline statistical comparisons of MPA to 20 μM ADP in young and elderly subjects.

Table 90. Statistical Comparison of Pre- and Post-Aspirin Baseline MPA to 20 μM ADP in Healthy Young Subjects and Elderly Subjects

	LS mean MPA (%) (90% CI)		Day 1 vs Day -5	
Age group	Day -5	Day 1	Difference (90% CI)	p-value
Elderly	77.5 (73.0, 82.0)	72.7 (68.2, 77.2)	-4.76 (-11.0, 1.42)	0.203
Young	76.4 (71.7, 81.2)	68.3 (63.5, 73.1)	-8.13 (-14.7, -1.55)	0.044

Mean MPA to 20 μM ADP was significantly (8 percentage points) lower following 75 mg aspirin administration for 5 days in the young group, but the difference was not statistically significant in the elderly group.

The statistical comparison of baseline MPA to 20 μM ADP between young and elderly subjects on Days 1 and 11 is shown in the Table below.

Table 91. Statistical Comparison of Baseline MPA to 20 μM ADP between Healthy Young Subjects and Elderly Subjects

	LS mean MPA (%) (90% CI)		Elderly vs Young	
	Elderly	Young	Difference (90% CI)	p-value
Day 1[a]	72.8 (68.9, 76.7)	68.2 (64.0, 72.4)	4.56 (-1.13, 10.3)	0.184
Day 11[b]	42.6 (38.4, 46.7)	33.1 (28.8, 37.4)	9.50 (3.53, 15.5)	0.011

On Day 1, the mean predose MPA to 20 μM ADP was similar for the young and elderly subjects. On Day 11, the mean MPA to 20 μM ADP prior to 10 mg prasugrel maintenance dosing was significantly lower for the young subjects compared with the elderly subjects.

Figure below shows the arithmetic mean (standard deviation [SD]) MPA to 20 μM ADP prior to dosing, following 75 mg aspirin MDs for 5 days (Day 1), and during 5 and 10 mg prasugrel MDs + aspirin for 10 days in young and elderly subjects.

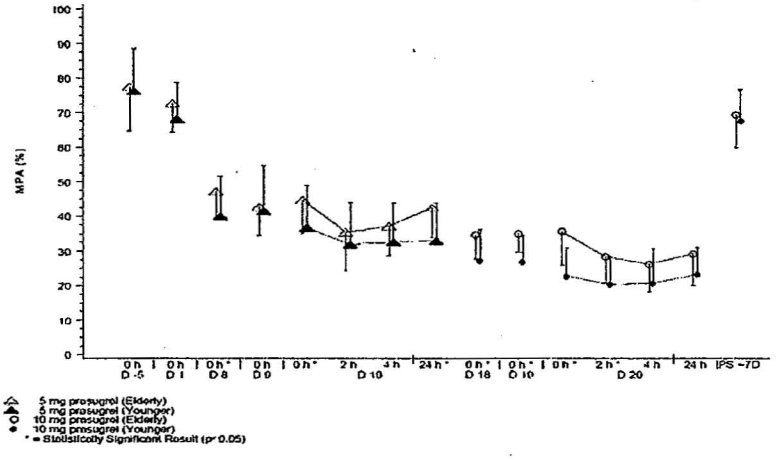


Figure 81. Arithmetic mean (1-sided SD) MPA to 20 μM ADP following 75 mg aspirin MDs, and 5 and 10 mg prasugrel MDs with 75 mg aspirin MD in healthy young and elderly subjects.

Visual examination confirms that steady-state MPA to 20 μM ADP was achieved by the eighth dose of 5 and 10 mg prasugrel on Days 8 and 18, respectively. The variability in MPA to 20 μM ADP was similar in each age group.

Mean MPA to 20 μM ADP was higher in elderly subjects compared to young subjects following 5 mg prasugrel MDs on Days 8, 9, and 10 (up to 24 hours postdose), and following 10 mg prasugrel MDs on Days 18, 19, and 20 (up to 24 hours postdose), although not all differences were statistically significant. Where the differences were statistically significant, a difference of less than 10% was generally observed (Table below).

Table 92. Statistical Comparison of MPA to 20 μM ADP between Healthy Young Subjects and Elderly Subjects Following 5 mg Prasugrel MDs and 10 mg Prasugrel MDs

			LS mean MPA (%) (90% CI)		Elderly - young	
Prasugrel dose	Day	Time (h)	Elderly subjects	Young subjects	Difference (90% CI)	p-value
5 mg[a]	8	Predose	44.1 (40.0, 48.3)	38.2 (34.1, 42.3)	5.95 (1.30, 10.6)	0.035
	9	Predose	39.7 (35.6, 43.8)	39.7 (35.6, 43.8)	0.0414 (-4.60, 4.68)	0.988
	10	Predose	41.6 (37.5, 45.8)	34.9 (30.8, 39.0)	6.71 (2.07, 11.4)	0.018
		2	32.4 (28.3, 36.6)	30.1 (26.0, 34.2)	2.32 (-2.32, 6.97)	0.409
		4	34.1 (30.0, 38.3)	30.2 (25.9, 34.4)	3.96 (-0.765, 8.68)	0.168
		24	39.5 (35.4, 43.6)	31.2 (27.1, 35.3)	8.32 (3.68, 13.0)	0.003
10 mg[b]	18	Predose	36.2 (32.2, 40.1)	30.6 (26.3, 34.9)	5.62 (0.920, 10.3)	0.049
	19	Predose	36.5 (32.6, 40.4)	30.3 (26.0, 34.6)	6.20 (1.50, 10.9)	0.030
	20	Predose	37.1 (33.2, 41.1)	26.1 (21.8, 30.4)	11.0 (6.32, 15.7)	<0.001
		2	29.7 (25.8, 33.7)	23.7 (19.3, 28.0)	6.09 (1.39, 10.8)	0.033
		4	27.7 (23.7, 31.7)	24.1 (19.8, 28.4)	3.63 (-1.15, 8.41)	0.211
		24	30.6 (26.7, 34.6)	26.6 (22.3, 30.9)	4.06 (-0.643, 8.76)	0.155
		Poststudy[c]	67.5 (63.7, 71.3)	69.7 (65.8, 73.7)	-2.24 (-8.00, 3.52)	0.514

Platelet Aggregation Using Accumetrics VerifyNow™ P2Y12 Assay

Figure below shows the arithmetic mean (SD) VN-P2Y12 % inhibition prior to dosing and following 75 mg aspirin MDs for 5 days (Day 1), and during 5 and 10 mg prasugrel MDs for 10 days in young and elderly subjects.

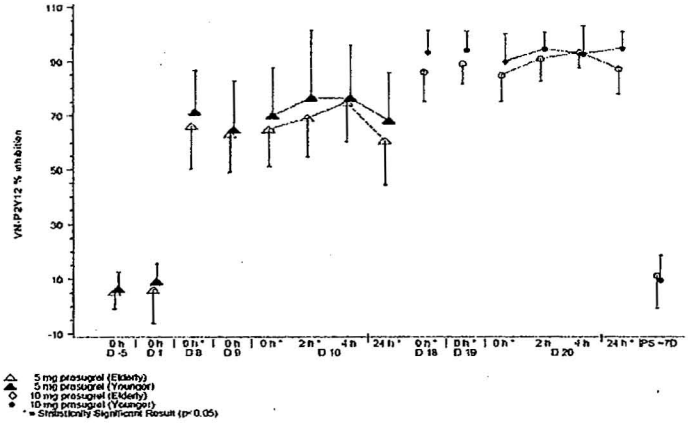


Figure 82. Arithmetic mean (1-sided SD) VN-P2Y12 % inhibition following 75 mg aspirin MDs, and 5 and 10 mg prasugrel MDs with 75 mg aspirin MDs in healthy young and elderly subjects.

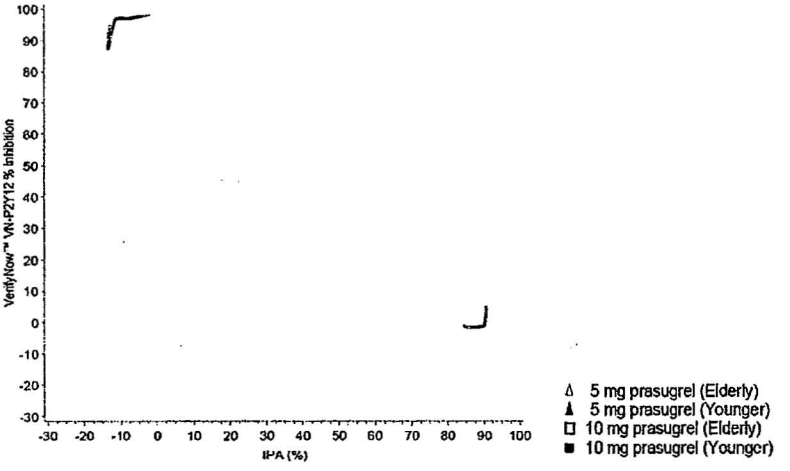
The sponsor compared statistical comparison of VN- P2Y12 % inhibition between young and elderly subjects are presented in the table below. Mean VN- P2Y12 % inhibition was consistently higher in young compared to elderly subjects following both 5 and 10 mg prasugrel MDs. The differences between young and elderly subjects were statistically significant at approximately 2 and 24 hours post 5 mg dose and at 24 hours post 10 mg dose.

Table 93. Statistical Comparison of VN-P2Y12 % Inhibition Between Healthy Elderly Subjects and Young Subjects Following 5 mg Prasugrel MDs and 10 mg Prasugrel MDs

			LS mean % inhibition (90% CI)		Elderly - young	
Prasugrel dose	Day	Time (h)	Elderly subjects	Young subjects	Difference (90% CI)	p-value
5 mg[a]	8	Predose	66.4 (60.3, 72.5)	73.9 (67.9, 79.9)	-7.48 (-13.5, -1.46)	0.041
	9	Predose	63.5 (57.3, 69.6)	67.3 (61.3, 73.3)	-3.88 (-9.90, 2.14)	0.288
	10	Predose	65.1 (59.0, 71.3)	72.5 (66.5, 78.5)	-7.33 (-13.3, -1.31)	0.045
		2	69.3 (63.1, 75.6)	79.7 (73.5, 85.8)	-10.3 (-16.5, -4.14)	0.006
		4	75.1 (68.9, 81.2)	79.6 (73.5, 85.7)	-4.52 (-10.6, 1.58)	0.223
		24	61.0 (54.8, 67.1)	70.7 (64.7, 76.7)	-9.71 (-15.7, -3.70)	0.008
10 mg[b]	18	Predose	83.0 (76.8, 89.1)	93.2 (86.6, 99.7)	-10.2 (-16.4, -3.96)	0.007
	19	Predose	85.9 (79.9, 91.9)	93.1 (86.7, 99.5)	-7.22 (-13.2, -1.19)	0.049
	20	Predose	81.7 (75.7, 87.7)	89.4 (82.9, 96.0)	-7.71 (-13.8, -1.59)	0.038
		2	87.7 (81.7, 93.7)	93.5 (86.7, 100)	-5.84 (-12.3, 0.569)	0.134
		4	90.6 (84.5, 96.7)	93.9 (86.8, 101)	-3.29 (-10.1, 3.55)	0.428
		24	84.2 (78.2, 90.2)	93.9 (87.4, 100)	-9.70 (-15.7, -3.67)	0.008
		Poststudy[c]	11.8 (7.17, 16.4)	9.13 (4.31, 13.9)	2.67 (-3.52, 8.87)	0.462

Comparison of Platelet Aggregation Using Light Transmission Aggregometry and Accumetrics VerifyNow™ P2Y12 Assay

The sponsor compared graphically both methods for the measuring of platelet aggregation (the LTA and VN-P2Y12 methods) and found them to give similar results.



b(4)

Figure 83. Scatter plot of IPA to 20 µM ADP (LTA) versus VN-P2Y12% inhibition following 5 and 10 mg prasugrel MDs.

Bleeding Time

The baseline bleeding times were similar on Day -5, prior to aspirin administration, for young and elderly subjects, with geometric mean values of 109 and 101 seconds, respectively. On Day 1, predose bleeding times were similar for young and elderly subjects, but longer than on Day -5 (130 seconds for the young subjects and 124 seconds for the elderly subjects).
The figure below shows the mean bleeding time ratios following 10 days of 5 and 10 mg prasugrel MDs in young and elderly subjects.

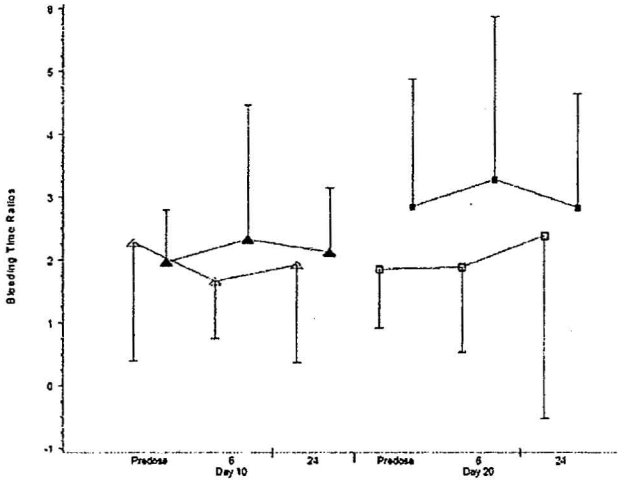


Figure 84. Arithmetic mean (1-sided SD) bleeding time ratios following the tenth daily 5 mg prasugrel MDs and tenth daily 10 mg prasugrel MDs in healthy young and elderly subjects.

Due to the very high variability of the measurements, the differences in bleeding time ratio between the young and elderly population were not pronounced.
The statistical comparison of bleeding time ratios between young and elderly subjects following prasugrel administration is shown in the table below.

Table 94. Statistical Comparison of Bleeding Time Ratios between Healthy Elderly Subjects and Young Subjects Following the Tenth Daily 5 mg Prasugrel MDs and the Tenth Daily 10 mg Prasugrel MDs

			Geometric LS mean Bleeding Time ratios (90% CI)[a]		Elderly vs young	
Prasugrel dose	Day	Time (h)	Elderly subjects	Young subjects	Ratio (90% CI)	p-value
5 mg	10	Predose	1.62 (1.25, 2.10)	1.62 (1.24, 2.12)	1.00 (0.737, 1.36)	0.998
		6	1.28 (0.987, 1.66)	1.59 (1.22, 2.07)	0.805 (0.593, 1.09)	0.244
		24	1.38 (1.06, 1.78)	1.72 (1.32, 2.25)	0.800 (0.589, 1.09)	0.231
10 mg	20	Predose	1.65 (1.27, 2.13)	2.45 (1.86, 3.22)	0.673 (0.491, 0.921)	0.038
		6	1.52 (1.17, 1.96)	2.85 (2.18, 3.72)	0.533 (0.392, 0.726)	<0.001
		24	1.73 (1.34, 2.24)	2.45 (1.87, 3.20)	0.708 (0.520, 0.963)	0.065

At the end of the 5-mg MD phase on Day 10 (predose, and at 6 and 24 hours postdose), mean bleeding times in young subjects were prolonged by approximately 60% to 70% compared to baseline, and in older subjects by approximately 30% to 60%, although statistical analysis showed no significant difference between age groups. At the end of the 10 mg prasugrel MD phase on Day 20 (predose, and 6 and 24 hours postdose), young subjects showed further

prolongation from baseline (Day 1, predose) in mean bleeding time of 145% to 185% whereas elderly subjects experienced only slight further prolongation, resulting in significant difference of 67% and 53% between age groups at predose and 6 hours postdose, respectively.

Sponsor's Conclusions

Following 10 days administration of 5 and 10 mg prasugrel MDs on a background of aspirin, mean MPA to 20 μM ADP was generally similar in elderly subjects compared to young subjects, based on a priori statistical criteria.

Mean bleeding times in both young and elderly subjects were prolonged compared to baseline, with no statistically significant differences between the two populations following 5 mg prasugrel MDs. Following 10 days administration of 10 mg prasugrel MDs, mean bleeding times were significantly longer (up to 67%) in young compared to elderly subjects.

There was no significant difference in the pharmacokinetics of prasugrel active metabolite between elderly and young subjects following 10 mg MDs, as the 90% CI for the geometric LS mean ratios for AUC(0-tlast) and Cmax were fully contained within the predefined limits of 0.72 to 1.38 and 0.70 to 1.43, respectively.

The systemic exposure (AUC(0-tlast)) of prasugrel active metabolite was equivalent between elderly and young subjects following 5 mg MDs. Although, the upper limit of the 90% CI for the ratio of geometric LS means (0.84 to 1.44) marginally exceeded the predefined limits of 0.70 to 1.43 for Cmax following 5 mg MDs and was influenced by a single subject, this excursion is not deemed to be clinically meaningful.

Generally, mean exposures for the prasugrel inactive metabolites were comparable between young and elderly subjects.

Oral doses of prasugrel were considered to be safe and well tolerated when administered to elderly and young subjects as 5 mg MDs for 10 days, immediately followed by 10 days of 10 mg MDs, on a background of 75-mg daily aspirin. Minor bleeding events related to study procedures, such as localized minor bleeding at venipuncture, intravenous cannula, and Ivy bleeding time sites, were more common in elderly compared to young subjects.

Reviewer's Comments

1. In the studied populations, the chronic doses of 5 mg and 10 mg of prasugrel led to a similar exposure to the active metabolite. The PK differences between the younger and elderly subjects were not statistically significant, however, the variabilities for both Cmax and AUC were very high, from 30 to 70% therefore masking the differences.
2. The age differences in the large population (Study TAAL) were assessed during the population PK and PK/PD data analyses. Please see the pharmacometics review for the recommendation regarding the prasugrel dose adjustment in elderly.