

Pharmacodynamics:**Platelet Aggregation Study:**

The mean % IPA induced by 20 μ M ADP following a single LD of a 60 mg prasugrel and following 7 days of 10 mg prasugrel MD was not affected by co-administration with 150 mg aspirin. Co-administration of prasugrel and aspirin increased inhibition of collagen-induced platelet aggregation compared to aspirin alone, with MPA values decreasing from 36% for aspirin alone to between 11% and 16% for prasugrel with aspirin. Aspirin alone decreased the MPA to arachidonic acid from 78% at predose to 7% following 5 days of daily 150 mg aspirin treatment. Following prasugrel dosing, the mean MPA induced by arachidonic acid was significantly higher following prasugrel alone compared to coadministration with aspirin. Adding a 900-mg aspirin dose to the daily treatment regimen of 10 mg prasugrel and 150 mg aspirin did not significantly alter the mean MPA induced by arachidonic acid.

Table 126 compares the IPA response to 20 μ M ADP following administration of 60 mg LD, 10 mg MD prasugrel alone with co-administration of 60 mg LD, 10 mg MD prasugrel and daily dose of 150 mg aspirin. The differences in the % IPA between the two treatment groups were not statistically significant except for the 1 hour post-dose on Day 1.

Table 126 Statistical comparisons of IPA response to 20 μ M ADP following prasugrel administration in the presence of aspirin.

Day	Time (h)	LS mean IPA (90% CI)		Difference (90% CI)	P-value
		Prasugrel (60 mg LD/ 10 mg MD)	Prasugrel (60 mg LD/10 mg MD) + Aspirin (150 mg)		
-1	2		16.3 (13.6, 19.0)		
1	Predose		13.9 (11.1, 16.6)		
	1	80.8 (78.2, 83.4)	77.0 (74.3, 79.7)	-3.77 (-6.22, -1.32)	0.012
	2	81.0 (78.3, 83.6)	81.2 (78.5, 83.9)	0.245 (-2.20, 2.69)	0.869
	4	81.0 (78.4, 83.6)	80.6 (77.9, 83.3)	-0.395 (-2.84, 2.05)	0.789
	24	77.9 (75.3, 80.5)	79.5 (76.8, 82.2)	1.62 (-0.830, 4.07)	0.275
8	Predose	72.2 (69.4, 74.9)	71.5 (68.7, 74.2)	-0.702 (-3.17, 1.77)	0.638
	1	75.5 (72.8, 78.2)	75.7 (72.9, 78.4)	0.194 (-2.28, 2.66)	0.897
	2	75.7 (73.0, 78.4)	75.0 (72.2, 77.7)	-0.716 (-3.19, 1.75)	0.632
	4	75.6 (72.9, 78.4)	78.0 (75.3, 80.8)	2.39 (-0.0790, 4.86)	0.111
	24	70.7 (68.0, 73.4)	71.2 (68.4, 73.9)	0.459 (-2.01, 2.93)	0.759
	96	31.8 (29.1, 34.5)			
	120	24.3 (21.6, 27.0)			
	144	16.6 (13.9, 19.3)			

Table 127 compares the IPA response to 20 μ M ADP for all treatment arms. The differences in the IPA response between the two treatment arms was not statistically significant ($P > 0.5$).

Table 127 Statistical comparisons of IPA response to 20 μ M ADP following a single acute 900-mg dose of aspirin.

Time (h)	LS mean IPA (90% CI)		Difference (90% CI)	P-value
	Prasugrel (60 mg LD/10 mg MD) + Aspirin (150 mg) (Day 8)	Prasugrel (60 mg LD/10 mg MD) + Aspirin (150 mg + 900 mg) (Day 9)		
2*	75.0 (72.2, 77.7)	77.0 (74.3, 79.7)	2.03 (-1.28, 5.33)	0.312
4	78.0 (75.3, 80.8)	76.6 (73.9, 79.3)	-1.43 (-4.74, 1.87)	0.475
6	74.9 (72.2, 77.7)	76.1 (73.3, 78.8)	1.14 (-2.16, 4.45)	0.569
24	71.2 (68.4, 73.9)	70.3 (67.6, 73.0)	-0.847 (-4.15, 2.46)	0.672

* Pre-acute aspirin dose on Day 9

Figure 115 compares the % rIPA (residual inhibitory platelet activity) profiles to 20 μM ADP for all treatment arms. The differences in the IPA response between the two treatment arms was not statistically significant (P>0.5).

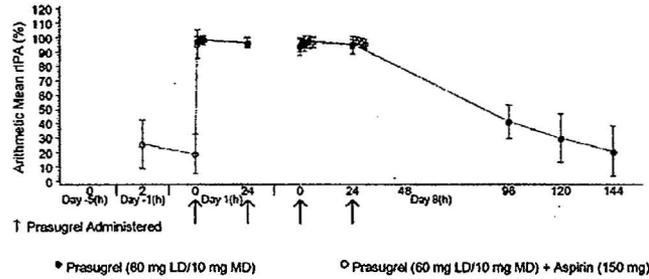


Figure 115 Mean rIPA response to 20 μM ADP following prasugrel administration in the presence of aspirin.

Table 128 Statistical comparisons of VASP phosphorylation following prasugrel administration in the presence of aspirin.

Day	Time (h)	LS mean VASP (90% CI)		Difference (90% CI)	P-value
		Prasugrel (60 mg LD/10 mg MD)	Prasugrel (60 mg LD/10 mg MD) + Aspirin (150 mg)		
-5	Predose		73.3 (70.0, 76.7)		
1	Predose	73.2 (70.4, 75.9)	73.0 (69.7, 76.4)	-0.118 (-4.15, 3.92)	0.961
	2	7.98 (5.21, 10.7)	8.39 (5.07, 11.7)	0.415 (-3.62, 4.45)	0.865
	4	4.84 (2.07, 7.61)	7.65 (4.32, 11.0)	2.81 (-1.23, 6.84)	0.252
	24	11.5 (8.71, 14.2)	8.37 (5.05, 11.7)	-3.10 (-7.14, 0.932)	0.205
8	Predose	22.9 (20.0, 25.8)	24.2 (20.8, 27.5)	1.24 (-2.86, 5.34)	0.617
	4	15.2 (12.3, 18.1)	11.7 (8.37, 15.0)	-3.52 (-7.62, 0.584)	0.158

The statistical comparison of the %VASP phosphorylation for all treatment arms. Both treatment arms demonstrated a very similar VASP response.

Bleeding time:

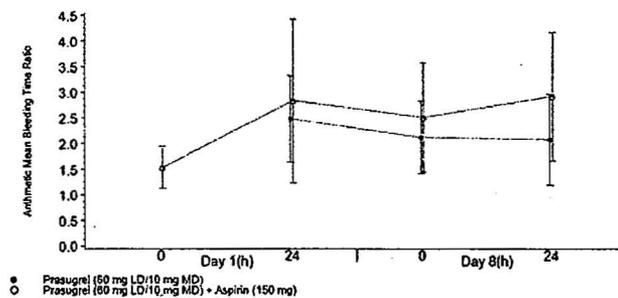


Figure 116 Mean bleeding time ratio following administration of prasugrel alone (N=23) and with aspirin (N=21).

The above figure compares the mean bleeding time ratio profiles of all treatment arms. During the predose of prasugrel while in the treatment with aspirin, the mean bleeding time ratio was

1.5. The mean bleeding time ratio increased at 24 hours post dose from 2.0 to 2.8 (that accounted to 40%) when co-administered with a 60 mg LD, 10 mg MD of prasugrel and a 150 mg of aspirin compared to the subjects administered with 60 mg LD, 10 mg MD of prasugrel on Day 8. The sponsor has not provided the statistical analysis data for the difference in the mean bleeding time ratios. It is possible that the high variability between the two treatment arms in the method is masking the difference.

Table 129 Statistical comparisons of bleeding time ratio following prasugrel administration in the presence of aspirin.

Day	Time (h)	LS mean ratio (90% CI)		(Prasugrel + Aspirin) : Prasugrel	
		Prasugrel (60 mg LD/ 10 mg MD)	Prasugrel (60 mg LD/10 mg MD) + Aspirin (150 mg)	Ratio (90% CI)	P-value
1	Predose		1.47 (1.25, 1.73)		
	24	2.34 (2.06, 2.67)	2.46 (2.06, 2.90)	1.05 (0.863, 1.28)	0.673
8	Predose	2.01 (1.76, 2.31)	2.28 (1.93, 2.68)	1.13 (0.925, 1.38)	0.312
	24	1.89 (1.65, 2.16)	2.67 (2.25, 3.16)	1.41 (1.15, 1.73)	0.006

Table 129 compares the mean bleeding time ratio for all treatment arms. The mean bleeding time ratio increased by 41% at 24 hours post dose when co-administered with a 60/10 mg doses of prasugrel and 150 mg of aspirin compared to the subjects administered after 60/10 mg doses of prasugrel on Day 8.

Table 130 Statistical comparisons of bleeding time ratio following a single acute 900-mg dose of aspirin.

Time (h)	LS mean ratio (90% CI)		Day 9 : Day 8	
	Prasugrel (60 mg LD/10 mg MD) + Aspirin (150 mg) (Day 8)	Prasugrel (60 mg LD/10 mg MD) + Aspirin (150 mg + 900 mg) (Day 9)	Ratio (90% CI)	P-value
Predose ^a	2.01 (1.76, 2.31)	2.67 (2.25, 3.16)	1.17 (0.926, 1.48)	0.2643
24	2.67 (2.25, 3.16)	2.49 (2.11, 2.94)	0.934 (0.738, 1.18)	0.630

^a Pre-acute aspirin dose on Day 9

Table 130 compares the mean bleeding time ratio for all treatment arms. The mean bleeding time ratio was not statistically significant between the treatment arms.

COMMENTS:

- The IPA response to 20 μ M ADP was similar between the combination treatment with 10 mg MD of prasugrel with daily dose of 150 mg aspirin and to prasugrel treatment alone.
- The mean bleeding time ratio increased by 41% at 24 hours post dose when co-administered with a 60/10 mg dosing of prasugrel and 150 mg of aspirin compared to the subjects administered with a 60/10 mg dosing of prasugrel on Day 8.

Comment to MO:

In patients who received a 150 mg dose of aspirin daily, the addition of the proposed regimen of prasugrel may lead to the prolongation of bleeding time by 41%.

4.2.22 Effect of Prasugrel on the Pharmacodynamics and Pharmacokinetics of Single Dose Warfarin in Healthy Subjects (H7T-EW-TAAR)

Principal Investigator: Joseph Chiesa, MD FFPM
 Study center: Phase 1 Clinical Trials Unit Ltd., Old Convent of Notre Dame, 119 Looseleig Lane, Derriford, Plymouth, PL6 5HH, UK.
 Study period: 16 February 2005 to 25 April 2005.
 Phase of development: Phase I

<p>Objectives</p>	<p>Primary: To determine the effect of prasugrel on the anticoagulant response of warfarin. Secondary: To determine the effect of prasugrel on the pharmacokinetics of R- and S-warfarin. To determine the degree of platelet aggregation after dosing prasugrel alone and in combination with warfarin To explore the effect of warfarin on inhibition of platelet aggregation. To assess the safety and tolerability of co-administration of prasugrel and warfarin.</p>
<p>Study Design</p>	<p>This was a single-centre, open-label, randomized, two-period crossover study.</p> <p>Sequence 1</p> <p>Treatment 1: Day -1 (Residential), Day 1 (Single 15 mg warfarin), Day 2-6 (Residential), Day 7 (Washout), Day 8-13 (10 mg prasugrel)</p> <p>Treatment 2: Day -1 (Residential), Day 1 (60 mg prasugrel), Day 2-11 (10 mg prasugrel), Day 12-13 (Residential)</p> <p>Sequence 2</p> <p>Treatment 2: Day -1 (Residential), Day 1-13 (10 mg prasugrel), Day 14 (Washout), Day 15-20 (Single 15 mg warfarin), Day 21-26 (Residential)</p> <p>Treatment 1: Day -1 (Residential), Day 1-6 (Single 15 mg warfarin), Day 7-20 (Residential)</p> <p>Legend: ↓ 60 mg prasugrel ↑ 10 mg prasugrel ◆ Single 15 mg warfarin ■ Residential period ★ Approximately 14 days washout between Treatments</p>
<p>Study Population</p>	<p>Healthy male subjects aged between 18 and 53 years, inclusive (N=14).</p>
<p>Investigational Drug</p>	<p>Prasugrel: 10 mg tablets, lot number CT518313. Warfarin: 5 mg tablets, lot number 514716.</p>
<p>Dosage and Administration</p>	<p>Period 1: a single dose of 15 mg warfarin was administered on Day 1. Period 2: a single dose of 60 mg prasugrel was administered on Day 1 followed by 10 daily doses of 10 mg prasugrel on Days 2 to 11. On Day 6, a single dose of 15 mg warfarin was co-administered with 10 mg prasugrel. Washout period of 14 days.</p>
<p>Blood Sampling:</p>	<p>PK: Blood samples to measure plasma R- and S-warfarin concentrations collected at predose, 0.5, 1, 2, 4, 6, 8, 12, 16, 24, 36, 48, 72, 96 and 120 hours</p>

	<p>after the warfarin dose given on Day 1 for Sequence 1 and on Day 6 for Sequence 2.</p> <p>PD, international normalized ratio (INR) and prothrombin time (PT): Blood samples were collected at predose, 6, 12, 24, 30, 36, 48, 72, 96 and 120 hours after the warfarin dose given on Day 1 for Sequence 1 and on Day 6 for Sequence 2.</p> <p>PD, platelet aggregation: Blood samples for Sequence 1 were collected at predose, 4 and 12 hours (on Day 1), and at 24 hours (on Day 2). For Sequence 2 samples were collected at predose, 4 and 12 hours (on Day 1, 5 and 6), and at predose (on Day 2, 4, 7, 9, and 11).</p> <p>PD, bleeding time: Blood samples for Sequence 1 were collected at predose, 12, 24 and 48 hours (on Day 1). For Sequence 2 samples were collected at predose (on Day 1, 7 and 8), and at predose and 6 hours (on Day 6).</p>
Assay	Plasma concentrations of R- and S-warfarin were measured using validated LC/MS/MS method.
PK Assessment	C_{max} (ng/mL), T_{max} (hr), AUC_{0-t} (ng·hr/mL), $AUC_{0-\infty}$ (ng·hr/mL), CL_p/F (L/hr), V_z/F (L), $T_{1/2}$ (hr) were calculated for R- and S-warfarin (WinNonlin).
PD Assessment	Platelet aggregation: turbidometric method with 20 μ M ADP as the agonist. Prothrombin time. Bleeding time.
Statistical methods	<p>Log-transformed C_{max} and AUC_{0-8} of R- and S-warfarin were evaluated separately to estimate ratios of geometric means of warfarin in the presence and in the absence of prasugrel and the corresponding 90% CI by a linear mixed effect model with treatment as a fixed effect, subject as a random effect, and a random error term. The values of T_{max} were analyzed with the Wilcoxon signed rank test.</p> <p>A lack of interaction was indicated if the 90% CI for the geometric mean ratios in both AUC_{INR} and INR_{max} fell completely within the pre-defined no effect boundary of 0.8 to 1.25. The AUC_{INR}, INR_{max}, and predose warfarin measurement were log-transformed prior to analysis. Time to reach the maximum response of INR or PT was assessed with the Wilcoxon signed rank test. One-way analysis of variance (ANOVA) was used to compare the mean maximum platelet aggregation (MPA) across the two treatment periods.</p>

Results

Demographics:

A total of 14 healthy male caucasian subjects, aged 18 to 53 years, inclusive, participated in the study. Summary of demographics is presented in Table 131.

Table 131 Summary of subject demographics.

Subject number	Age (years)	Gender	Race	Height (cm)	Weight (kg)	BMI (kg/m ²)
101	53	Male	Caucasian	183	99.6	29.7
102	25	Male	Caucasian	182	91.4	27.6
103	19	Male	Caucasian	178	73.4	23.2
104	24	Male	Caucasian	172	70.8	23.9
105	46	Male	Caucasian	175	85.6	28.0
106	23	Male	Caucasian	166	68.5	24.8
107	36	Male	Caucasian	174	77.8	25.7
108	43	Male	Caucasian	169	75.3	26.4
109	46	Male	Caucasian	167	83.4	29.9
110	26	Male	Caucasian	175	73.3	23.9
111	25	Male	Caucasian	172	74.6	25.2
112	32	Male	Caucasian	179	74.5	23.3
113	18	Male	Caucasian	171	56.8	19.4
114	33	Male	Caucasian	179	80.0	25.0
Mean	32			174	77.5	25.4
SD	11			5	10.4	2.8

Assay:

The samples were analyzed for R- and S-warfarin using a validated liquid chromatography with tandem mass spectrometric detection (LC/MS/MS) method. The lower and upper limits of quantification were 10 ng/mL and 2500 ng/mL, respectively.

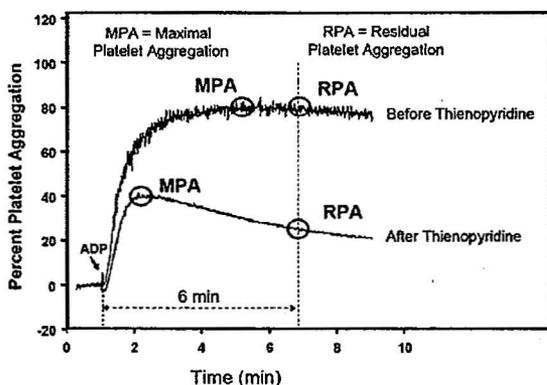


Figure 117 Light transmission aggregation tracings from pre and post administration of a thienopyridine.

Figure 117 represents aggregation tracings from pre and post administration of thienopyridine. After ADP addition, light transmission / aggregation increases due to the platelet aggregation that is recorded. Maximal platelet aggregation is defined as the maximum aggregation (increase in the light transmission) seen during the monitoring period. Residual platelet aggregation is the percent aggregation presented after 6 minutes following addition of ADP.

Pharmacokinetics:

Warfarin pharmacokinetics in the presence and absence of prasugrel:

Figure 118 compares the plasma concentration time profile of R-warfarin following a single 5 mg dose of warfarin with and without prasugrel treatment. The plasma concentration vs time profiles of both treatments look similar.

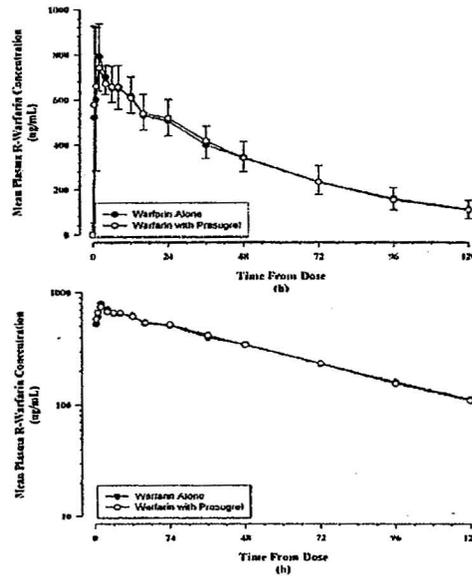
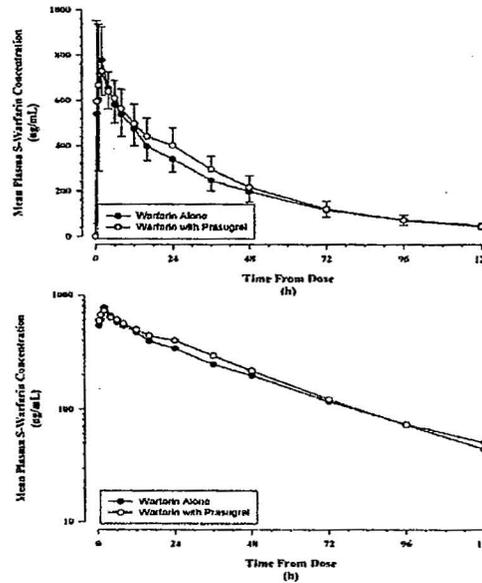


Figure 118 Plasma concentrations of R-warfarin following administration of warfarin alone and with prasugrel.

Error! Reference source not found. compares the plasma concentration time profile of S-warfarin following single 5 mg dose of warfarin with and without prasugrel treatment. The plasma concentration vs time profiles of both treatments look similar. The PK parameters of R-



and S-warfarin are shown in Table 132.

Figure 119 Plasma concentrations of S-warfarin following administration of warfarin alone and with prasugrel.

Table 132 Noncompartmental pharmacokinetics of R- and S-warfarin following warfarin administration in the presence of prasugrel.

Parameter	Geometric Mean (%CV)			
	R-Warfarin		S-Warfarin	
	Warfarin alone (N=14)	Prasugrel + warfarin (N=14)	Warfarin alone (N=14)	Prasugrel + warfarin (N=14)
C _{max} (ng/mL)	915 (17.3)	843 (21.7)	912 (21.0)	842 (23.4)
t _{max} ^a (h)	2.00 (0.50-4.00)	1.52 (0.50-12.00)	2.00 (0.50-4.00)	1.52 (0.50-6.00)
AUC(0-t _{max}) (ng•h/mL)	38300 (15.6)	38200 (18.7)	24800 (18.4)	26600 (19.5)
AUC(0-∞) (ng•h/mL)	45700 (21.2)	44900 (24.2)	27300 (20.3)	28500 (20.7)
CL/F ^b (L/h)	0.164 (21.2)	0.167 (24.2)	0.275 (20.3)	0.263 (20.7)
V/F ^b (L)	10.5 (12.3)	10.2 (13.3)	14.0 (17.0)	11.5 (17.6)
t _{1/2} (h)	44.5 (21.0)	42.2 (21.1)	35.4 (14.8)	30.3 (11.7)

^a t_{max}: median (range)

^b Dose used to calculate CL/F and V/F was 7.5 mg since the 15 mg dose of warfarin was racemic

Table 132 presents the PK parameter estimates for R- and S-warfarin for all the treatment arms. The PK parameters for R- and S-warfarin with and without coadministration with prasugrel were similar.

Pharmacodynamics:

The inhibition of platelet aggregation was measured using turbidometric methodology at 20 μM concentration of ADP.

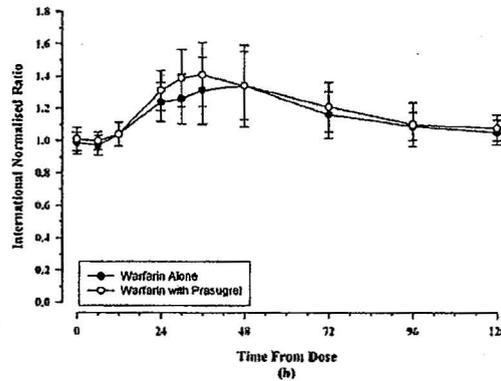


Figure 120 International normalized ratio following warfarin administration in the presence of prasugrel.

Figure 120 compares the international normalized ratio (INR) following warfarin administration alone and with prasugrel. The INR was similar in both treatment arms.

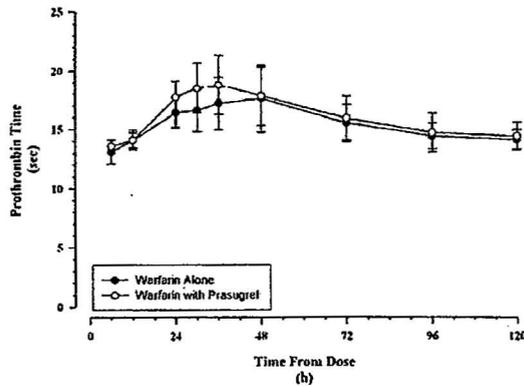


Figure 121 Prothrombin times after warfarin administration in the presence of prasugrel.

Figure 121 compares the prothrombin time for all treatment arms. The prothrombin time was similar during co-administration of prasugrel with warfarin compared to warfarin alone.

Platelet Aggregation Study:

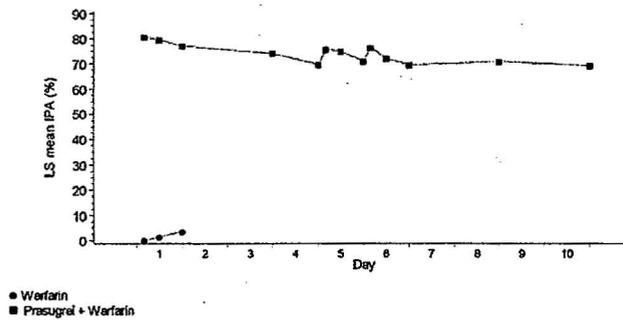


Figure 122 Least squares mean IPA to 20 µM ADP time profile following warfarin administration in the presence of prasugrel.

Figure 122 compares the IPA response vs time to 20 µM ADP in all treatment arms. The platelet aggregation was not inhibited in subjects who received only warfarin. The co-administration of the warfarin with prasugrel did not affect the IPA response to 20 µM ADP compared to warfarin alone.

Table 133 Statistical comparison of IPA to 20 µM ADP following warfarin administration in the presence of prasugrel

Time (h)	LS mean IPA (90% CI)		Difference (90% CI)	P-value
	Prasugrel + warfarin (N=14)	Prasugrel alone ^a (N=14)		
4	76.3 (73.1, 79.5)	75.7 (72.5, 78.9)	0.613 (-2.71, 3.93)	0.761
12	72.1 (68.9, 75.3)	74.9 (71.7, 78.1)	-2.85 (-6.17, 0.472)	0.158
24	69.5 (66.3, 72.7)	70.9 (67.7, 74.1)	-1.41 (-4.73, 1.91)	0.484

^a Prasugrel alone = after Day 5 dose of prasugrel alone

Table 133 compares the IPA response to 20 µM ADP for all treatment arms.

Bleeding Time:

Table 134 compares the bleeding time ratios following warfarin administration in the presence or absence of prasugrel dosing. There was significant increase ($p < 0.01$ at 12, 24 and 48 hours post-dose) in the bleeding time when prasugrel is co-administered with warfarin compared to warfarin alone. The increase in the bleeding times were 40%, 68% and 73% at 12, 24 and 48 hours respectively following co-administration of prasugrel with warfarin

Table 134 Statistical comparison of bleeding time ratios following warfarin administration in the presence of prasugrel

Time (h)	Geometric mean bleeding time ratio (90% CI) ^a		(Prasugrel + warfarin) / (warfarin alone)	
	Prasugrel + warfarin (N=14)	Warfarin alone (N=14)	Ratio (90% CI)	P-value
12	1.47 (1.29, 1.66)	1.05 (0.924, 1.19)	1.40 (1.17, 1.67)	0.003
24	1.71 (1.51, 1.94)	1.02 (0.896, 1.16)	1.68 (1.41, 2.01)	<0.001
48	2.04 (1.80, 2.32)	1.18 (1.04, 1.34)	1.73 (1.44, 2.06)	<0.001

^a Bleeding time ratio = bleeding time at time t / bleeding time at baseline (predose on Day 1)

Table 135 compares the bleeding time ratios for all treatment arms. There was a significant increase in the bleeding time when prasugrel was co-administered with warfarin compared to prasugrel alone. Warfarin prolonged the bleeding time by 36% at 48 hours post dose to prasugrel administration.

Table 135 Statistical Comparison of Bleeding Time Ratio following prasugrel administration in the presence of warfarin.

Time (h)	Geometric mean bleeding time ratio (90% CI) ^a		(Prasugrel + warfarin) / (predose ^b)	
	Prasugrel + warfarin (N=14)		Ratio (90% CI)	P-value
Predose ^b	1.50 (1.32, 1.71)			
12	1.47 (1.29, 1.66)		0.974 (0.815, 1.16)	0.804
24	1.71 (1.51, 1.94)		1.14 (0.951, 1.36)	0.235
48	2.04 (1.80, 2.32)		1.36 (1.14, 1.62)	0.005

^a Bleeding time ratio = bleeding time at time t / bleeding time at baseline (predose on Day 1)

^b Predose = prior to Day 6 dose of prasugrel + warfarin = 24 hours after Day 5 dose of prasugrel alone

COMMENTS:

1. The changes in R- and S-warfarin pharmacokinetics were minor after co-administration of MD of prasugrel with warfarin. The INR and PT caused by warfarin were similar when warfarin alone and warfarin with prasugrel treatments were compared. The difference in the IPA response at each time point between the subjects who received prasugrel alone and co-administration of prasugrel with warfarin were not statistically significant.
2. There was a significant increase in the bleeding time when prasugrel was co-administered with warfarin compared to prasugrel alone. Warfarin prolonged the bleeding time by 36% at 48 hours post dose to prasugrel administration.
3. Labeling Comment: in the Precaution Section it should be stated that warfarin and prasugrel should not be administered cautiously due to the bleeding time prolongation.

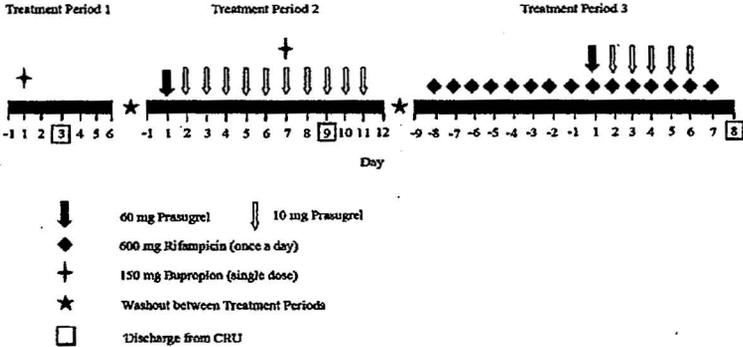
4.2.23 Effect of Rifampicin on the Pharmacokinetics and Pharmacodynamics of Prasugrel Metabolites and the Effect of Prasugrel on the Disposition of Bupropion in Healthy Male Subjects (H7T-EW-TAAS)

Principal Investigator: Steven MD, FRCP, FFPM

Study center: Hammersmith Medicines Research Middlesex Hospital, Park Royal, London, NW10 7NS, UK.

Study period: 7 July 2005 to 26 October 2005

Phase of development: Phase I

Objectives	<p>Primary: To assess the effect of potent CYP3A4 induction on the of R-138727, the prasugrel active metabolite, after a loading dose (LD) and during maintenance dosing (MD), To assess the extent of CYP2B6 inhibition with prasugrel. Secondary: To assess the effect of potent CYP3A4 induction on the pharmacodynamics (IPA to 5 and 20 μM ADP) of prasugrel To assess the effect of potent CYP3A4 induction on the LD and MD PK of prasugrel inactive metabolites (R-95913, 106583 and R-119251) To assess the safety and tolerability of prasugrel given alone and in combination with rifampicin or bupropion.</p>
Study Design	<p>This was an open-label, multiple dose, three-period, fixed sequence study.</p>  <p>The diagram illustrates a 30-day study timeline. Treatment Period 1 (Days -11 to -6) includes a single 150 mg bupropion dose on Day -11 and a discharge from CRU on Day -6. Treatment Period 2 (Days -1 to 12) includes a 60 mg prasugrel loading dose on Day -1, followed by 10 mg prasugrel maintenance doses on Days 1-11, and a single 150 mg bupropion dose on Day 7. Treatment Period 3 (Days -9 to 7) includes daily 600 mg rifampicin doses from Day -9 to Day 7. Washout periods are indicated by stars between Period 1 and 2, and between Period 2 and 3. A legend defines symbols: downward arrow for 60 mg Prasugrel, double arrow for 10 mg Prasugrel, diamond for 600 mg Rifampicin (once a day), plus sign for 150 mg Bupropion (single dose), star for Washout between Treatment Periods, and square for Discharge from CRU.</p>
Study Population	Healthy male subjects, aged 18 to 53 years, inclusive (N=32)
Investigational Drugs	<p>Prasugrel: 10 mg tablets, lot number CT522027 and CT520876. Bupropion: 150 mg SR tablets. Rifampicin: 300 mg capsules.</p>
Dosage and Administration	<p>Period 1: Single 150-mg dose of bupropion was administered on day 1. Period 2: Single 60-mg LD of prasugrel on Day 1. Ten 10-mg MD of prasugrel on Days 2 to 11. On Day 7, a single 150-mg dose of bupropion. Period 3: Daily 600-mg doses of rifampicin on Day -8 to Day 7. Day 1: a single 60-mg prasugrel. Days 2 to 6: 10-mg of prasugrel. Washout period: at least 7 days.</p>
Blood Sampling:	<p>PK of Bupropion – predose, 1, 2, 3, 4, 5, 6, 7, 8, 12, 24, 48, 72, 96, and 120 hours after the bupropion dose on Day 1 in Period 1 and Day 7 in Period 2, and for the measurement of prasugrel metabolites – 0.25, 0.5, 1, 1.5, 2, 4, 8, 12, and 24 hours after the prasugrel dose on Day 1 and on Day 6 in Periods 2</p>