administration with clopidogrel LD and MD along with atorvastatin. Epistaxis was resulted in 1 subject during administration of atorvastatin. A serious adverse event resulted in liver failure during coadministration of prasugrel LD and MD along with atorvastatin.

**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 LLOQ for R-138727, R-119251, R-106583, R-95913 were 0.5, 1, 1, 1 ng/ml respectively.

**Table 108 Validation parameters for plasma metabolites of prasugrel and clopidogrel.**

| | **Plasma R-138727** |
|---|---|
| linearity | 0.5 to 250 ng/ml |
| Precision (RSD) | 2.59 to 4.56% |
| Accuracy (RE) | -7.20 to 7.00% |
| LLOQ | 0.5 ng/ml |
| | **Plasma R-119251** |
| linearity | 1 to 500 ng/ml |
| Precision (RSD) | 3.57 to 5.12% |
| Accuracy (RE) | -3.25 to 4.00% |
| LLOQ | 1 ng/ml |
| | **Plasma R-106583** |
| linearity | 1 to 500 ng/ml |
| Precision (RSD) | 2.73 to 5.31% |
| Accuracy (RE) | -3.75 to 2.00% |
| LLOQ | 1 ng/ml |
| | **Plasma R-95913** |
| linearity | 1 to 500 ng/ml |
| Precision (RSD) | 2.89 to 4.75% |
| Accuracy (RE) | -3.20 to 2.80% |
| LLOQ | 1 ng/ml |
| Reviewer Comment | This assay characteristics and specificity are satisfactory, and representative MS chromatograms are presented. |

**Pharmacokinetics:**
**Pharmacokinetics of active metabolites prasugrel and clopidogrel in the presence and absence of atorvastatin:**
Figure 98 compares the plasma concentration time profile of R-138727 for all treatment arms.. There was no change in the plasma concentration with time ($AUC_{0-24}$) for R-138727 with atorvastatin administration after 60 mg of prasugrel LD. However there was an increase in the plasma concentration with time ($AUC_{0-8}$) for R-138727 with atorvastatin administration during prasugrel MD.

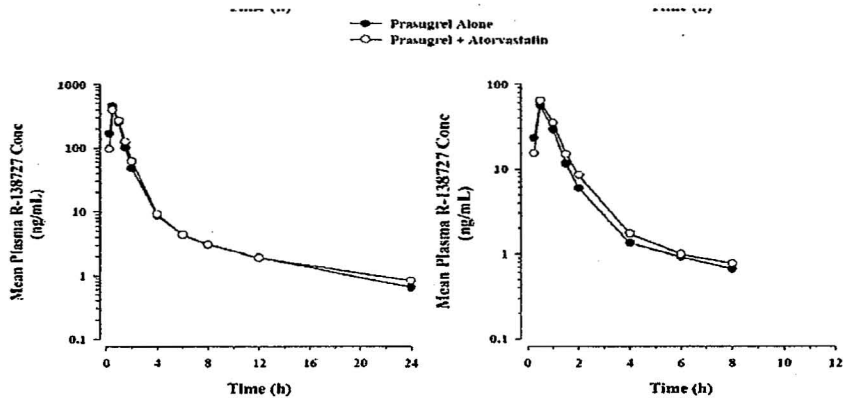



**Figure 98 Plasma concentrations of R-138727 after a 60-mg prasugrel loading dose (A) and after the tenth daily 10-mg prasugrel maintenance dose (B) alone and with atorvastatin.**

Figure 99 compares the plasma concentration time profile of R-130964 following 300 mg clopidogrel LD and during 75 mg MD on Day 10 in the absence and presence of atorvastatin administration. There was no change in the plasma concentration with time ($AUC_{0-4}$) for R-130964 with atorvastatin administration after 300 mg of clopidogrel LD. However there was an increase in the plasma concentration with time ($AUC_{0-2}$) for R-130964 with atorvastatin administration during clopidogrel MD.

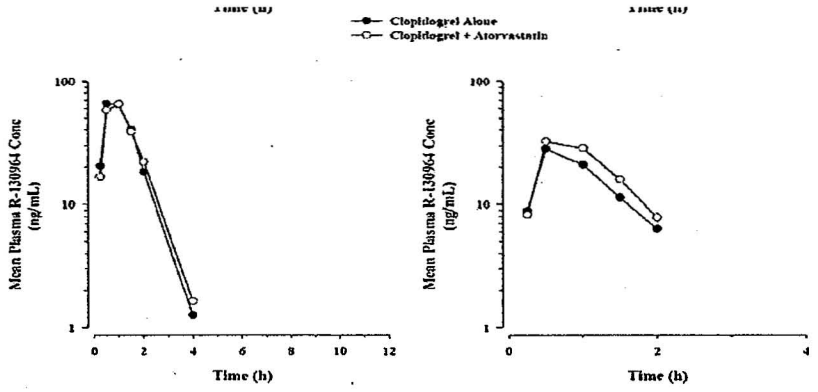



**Figure 99 Plasma concentrations of R-130964 after a 300-mg clopidogrel loading dose (A) and after the tenth daily 75-mg clopidogrel maintenance dose (B) alone and with atorvastatin.**

**Table 109 Noncompartmental Pharmacokinetic Parameter Estimates for R-138727 after a Single 60-mg Loading Dose and After the 10th Daily 10-mg Maintenance Dose of Prasugrel Alone and with Atorvastatin**

| | Geometric Mean (%CV) | | | |
|---|---|---|---|---|
| | R-138727 LD | | R-138727 MD | |
| Parameter | Prasugrel alone (N=34) | Prasugrel + Atorvastatin (N=31) | Prasugrel alone (N=32) | Prasugrel + Atorvastatin (N=28) |
| $C_{max}$ | 453 | 393 | 56.5 | 62.4 |
| (ng/mL) | (35) | (52) | (48) | (54) |
| $t_{max}$[a] | 0.50 | 0.50 | 0.50 | 0.50 |
| (h) | (0.25-1.00) | (0.25-1.50) | (0.25-1.00) | (0.25-2.00) |
| AUC(0-$t_{last}$) | 460 | 441 | 54.5 | 62.8 |
| (ng•h/mL) | (21) | (40) | (26) | (32) |

Table 109 compares the pharmacokinetic parameters of R-138727 following 60 mg prasugrel LD and during 10 mg MD in the absence and presence of atorvastatin administration. When co-administered with atorvastatin, the $C_{max}$ and $AUC_{0-8}$ values of R-138727 decreased by 13 and 4% after a loading dose of prasugrel and these values increased by 10 and 15% during the maintenance dosing of prasugrel.

**Table 110 Statistical Analysis of the Effects of Atorvastatin on R-138727 Following 60-mg Prasugrel LD.**

| | LS geometric means (90% CI) | | vs. Prasugrel alone |
|---|---|---|---|
| Parameter (unit) | Prasugrel alone (N=34) | Prasugrel + Atorvastatin (N=31) | Ratio of Geometric Mean (90% CI) |
| AUC(0-$t_{last}$) (ng•h/mL) | 460 (421, 502) | 441 (402, 483) | 0.959 (0.870, 1.06) |
| $C_{max}$ (ng/mL) | 453 (402, 511) | 393 (347, 445) | 0.866 (0.744, 1.01) |

Note: Pre-defined no effect boundary is (0.72, 1.38) for AUC; (0.70, 1.43) for $C_{max}$.
This table was generated from a linear mixed effect model.

**Table 111 Statistical Analysis of the Effects of Atorvastatin on R-138727 after the Tenth Daily 10-mg Prasugrel MD**

| | LS geometric means (90% CI) | | vs. Prasugrel alone |
|---|---|---|---|
| Parameter (unit) | Prasugrel alone (N=34) | Prasugrel + Atorvastatin (N=31) | Ratio of Geometric Mean (90% CI) |
| AUC(0-$t_{last}$) (ng•h/mL) | 54.1 (49.9, 58.7) | 63.1 (58.0, 68.6) | 1.17 (1.10, 1.24) |
| $C_{max}$ (ng/mL) | 56.5 (49.0, 65.1) | 62.4 (53.7, 72.6) | 1.11 (0.917, 1.33) |

Note: Pre-defined no effect boundary is (0.72, 1.38) for AUC; (0.70, 1.43) for $C_{max}$.
This table was generated from a linear mixed effect model.

The tables above show the statistical analysis of R-138727 following 60 mg prasugrel LD and during 10 mg MD in the absence and presence of atorvastatin administration. The treatment arms are not statistically different.

**Table 112** Statistical Analysis of the Effects of Atorvastatin on R-130964 After a 300-mg Clopidogrel Loading Dose

| | LS geometric means (90% CI) | | vs. Clopidogrel alone |
|---|---|---|---|
| Parameter (unit) | Clopidogrel alone (N=34) | Clopidogrel + Atorvastatin (N=31) | Ratio of Geometric Mean (90% CI) |
| AUC(0-$t_{last}$) (ng•h/mL) | 90.2 (77.8, 105) | 86.3 (74.4, 100) | 0.956 (0.868, 1.05) |
| $C_{max}$ (ng/mL) | 70.1 (60.7, 81.0) | 62.9 (54.5, 72.6) | 0.897 (0.800, 1.01) |

Note: Pre-defined no effect boundary is (0.80. 1.25) for AUC; (0.70, 1.43) for $C_{max}$.
This table was generated from a linear mixed effect model.

**Table 113 Statistical Analysis of the Effects of Atorvastatin on R-130964 after the Tenth Daily 75-mg Clopidogrel Maintenance Dose.**

| | LS geometric means (90% CI) | | vs. Clopidogrel alone |
|---|---|---|---|
| Parameter (unit) | Clopidogrel alone (N=34) | Clopidogrel + Atorvastatin (N=31) | Ratio of Geometric Mean (90% CI) |
| AUC(0-$t_{last}$) (ng•h/mL) | 28.5 (24.6, 33.1) | 36.7 (31.6, 42.5) | 1.28 (1.16, 1.42)* |
| $C_{max}$ (ng/mL) | 27.8 (23.8, 32.5) | 33.3 (28.5, 38.9) | 1.20 (1.04, 1.38) |

Note: Pre-defined no effect boundary is (0.80, 1.25) for AUC; (0.70, 1.43) for $C_{max}$.
*Outside the pre-defined range.
This table was generated from a linear mixed effect model.

The tables above show the statistical analysis of R-130964 following 300 mg clopidogrel LD and during 75 mg MD in the absence and presence of atorvastatin administration.

**Pharmacodynamics:**

**Inhibition of platelet aggregation was measured using turbidometric methodology at 20 μM concentration of ADP:**

Figure 100 compares the % IPA response to 20 μM ADP following prasugrel administration alone, clopidogrel administration alone, co-administration of prasugrel LD and MD with 80 mg atorvastatin, and co-administration of clopidogrel LD and MD with 80 mg atorvastatin. The sponsor concluded that the IPA (%) response were similar when prasugrel LD administered alone compared to co-administration of prasugrel LD along with atorvastatin, and when clopidogrel LD administered alone compared to co-administration of clopidogrel LD along with atorvastatin. Based on the sponsor's data in figures represent IPA to time, the SD error bars represented were high indicating large variability in the data.

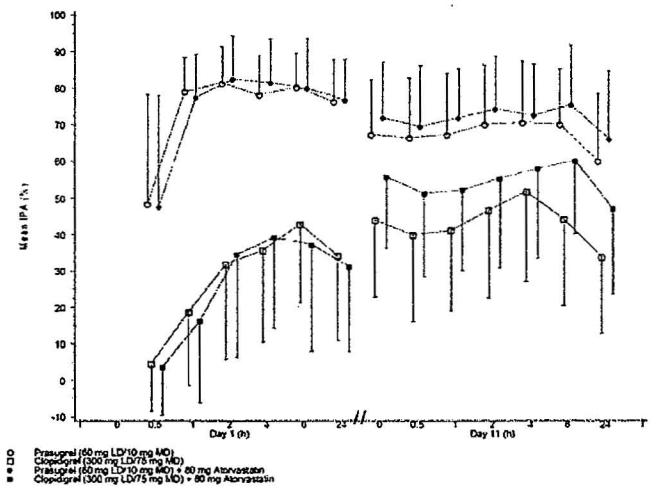



**Figure 100 Mean (SD) IPA to 20 μM ADP following a loading dose (Day 1) and maintenance dose (Day 11) of prasugrel and clopidogrel administered alone and with atorvastatin.**

**Table 114 Statistical Comparison of IPA Response to 20 μM ADP Following Administration of Prasugrel Alone and with Atorvastatin.**

| | | LS mean IPA (90% CI) | | (Prasugrel + Atorvastatin) – Prasugrel | |
|---|---|---|---|---|---|
| Dose Phase (Day) | Time (h) | Prasugrel (60 mg LD/ 10 mg MD) | Prasugrel (60 mg LD/10 mg MD) + Atorvastatin (80 mg) | Difference (90% CI) | p-value |
| LD (Day 1) | 0.5 | 48.4 | 47.5 | -0.91 (-14.57, 12.75) | 0.912 |
| | 1 | 79.1 | 78.0 | -1.11 (-8.69, 6.47) | 0.809 |
| | 2 | 81.3 | 82.7 | 1.42 (-6.16, 8.99) | 0.757 |
| | 4 | 78.2 | 81.9 | 3.74 (-3.62, 11.11) | 0.402 |
| | 6 | 80.3 | 80.1 | -0.21 (-7.57, 7.15) | 0.962 |
| | 24 | 76.3 | 76.3 | 0.03 (-7.33, 7.39) | 0.995 |
| MD (Day 11) | 0 | 67.5 | 71.6 | 4.14 (-3.27, 11.54) | 0.357 |
| | 0.5 | 66.4 | 68.8 | 2.40 (-5.01, 9.80) | 0.593 |
| | 1 | 67.2 | 71.4 | 4.14 (-3.27, 11.54) | 0.357 |
| | 2 | 70.2 | 73.7 | 3.47 (-3.94, 10.87) | 0.440 |
| | 4 | 70.7 | 71.9 | 1.25 (-6.15, 8.66) | 0.780 |
| | 6 | 69.9 | 74.9 | 5.00 (-2.42, 12.42) | 0.267 |
| | 24 | 60.0 | 65.0 | 5.02 (-2.39, 12.42) | 0.264 |

Table 114 presents the statistical comparison of % IPA response to 20 μM ADP following prasugrel administration alone, and co-administration of prasugrel LD and MD with 80 mg atorvastatin. The differences in the IPA (%) response in both treatment arms were not statistically significant.

Figure 101 compares the VASP (platelet reactivity index) following prasugrel LD alone, clopidogrel LD alone, co-administration of prasugrel LD with 80 mg atorvastatin, and co-administration of clopidogrel LD with 80 mg atorvastatin. Co-administration of atrovastatin did not influence VASP phosphorylation for both prasugrel and clopidogrel arms.

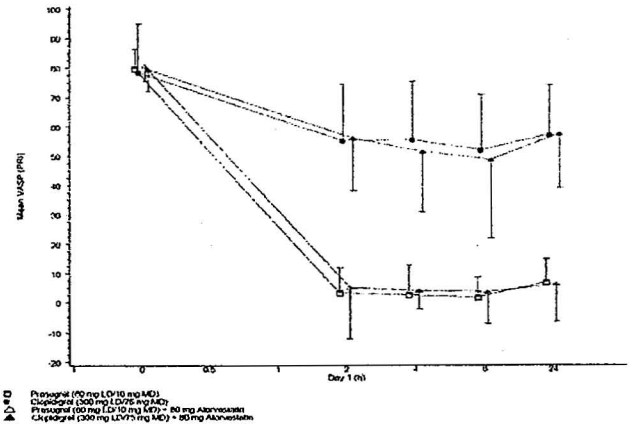



**Figure 101 Mean (SD) VASP (PRI) following a loading dose (Day 1) of prasugrel and clopidogrel administered alone and with atorvastatin.**

**COMMENTS:**

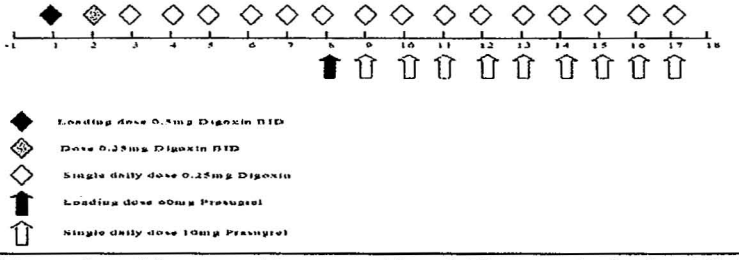
1. The $C_{max}$ and $AUC_{0-8}$ of R-138727 (active metabolite of prasugrel) decreased to 13% and 4% respectively with 80 mg of atorvastatin administration following 60 mg of prasugrel LD. The $C_{max}$ and $AUC_{0-8}$ of R-138727 increased to 10% and 15% respectively with atorvastatin administration during prasugrel MD.

2. The IPA responses were similar when prasugrel LD administered alone compared to co-administration of prasugrel LD along with atorvastatin, however, due to the high variability of the method, it might not be discriminative enough to evaluate the differences between the treatments.

3. The pharmacokinetic interactions between atorvastatin and prasugrel are minimal and the restriction of the coadministration these drugs is not needed.

### 4.2.18 Effect of Prasugrel on the Disposition of Digoxin in Healthy Subjects (H7T-EW-TAAX)

Principal Investigator: Diane Kleinermans, MD, Douglas Lee, MBChB
Study center: Covance Clinical Research Unit Ltd., Springfield House, Hyde Street, Leeds, LS2 9LH, UK.
Study period: 06 October 2005 to 28 November 2005.
Phase of development: Phase I

| | |
|---|---|
| Objectives | Primary: To assess the effect of a 60 mg loading dose (LD) of prasugrel and 9 days of a 10 mg maintenance dose (MD) on the disposition of digoxin in healthy subjects.<br>Secondary: To assess the safety and tolerability of digoxin given alone and in combination with prasugrel in healthy subjects. |
| Study Design | This was a single-centre, open-label, one-period, single-sequence study.<br>  <br> |
| Study Population | Healthy male subjects aged between 19 and 50 years, inclusive (N=18). |
| Investigational Drug | Prasugrel: 10 mg tablets, lot number CT522561.<br>Digoxin: 0.25 mg tablets, lot numbers DG281, DG289 and DG292. |
| Dosage and Administration | Digoxin was administered in two LD of 0.5 mg approximately 12 hours apart on Day 1 (total daily dose of 1 mg), and two doses of 0.25 mg digoxin were administered approximately 12 hours apart on Day 2 (total daily dose of 0.5 mg). Single daily doses of 0.25 mg digoxin were administered for the next 15 days (Days 3 to 17). A single LD of 60 mg prasugrel was coadministered with digoxin on Day 8, and single daily MDs of 10 mg prasugrel were coadministered with digoxin for the next 9 days (Days 9 to 17). |
| Blood Sampling: | PK: Blood samples to measure serum digoxin concentrations collected on Day 7, 8 and 17 at predose, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12 and 16 hours post dose, and on Day 9 and 18 at 24 hours after coadministration of dioxin and prasugrel. Urine output was collected over the intervals of 0 to 12 hours and 12 to 24 hours after digoxin on Day 7 and after coadministration of digoxin + prasugrel on Days 8 and 17. |
| Assay | Serum and urine concentrations of digoxin were measured using validated LC/MS/MS method. |
| PK Assessment | $C_{max}$ (ng/mL), $T_{max}$ (hr), $AUC_{0-t}$ (ng·hr/mL), $CL_{r,ss}$ (L/hr), $Ae_{0-t,ss}$ (mg), $F_e$ (%) were calculated for both serum and urinary digoxin (WinNonlin). |
| Statistical methods | The pharmacokinetic parameters were statistically analyzed for digoxin on Day 7, 8 and 17: area under the serum concentration-time curve over one 24-hour ($AUC_{0-t}$), maximum observed serum concentration ($C_{max}$) and renal |

| | |
|---|---|
| | clearance ($CL_{r,ss}$). These parameters were log transformed and analyzed with a linear mixed-effects model allowing for the fixed effect of treatment and the random effect of subject. The 90% confidence intervals (CI) for the ratio of the geometric means between the test and reference treatments were calculated. A comparison of $T_{max}$ values between the treatments was performed using the Wilcoxon sign rank test. In these analyses, the test treatment was digoxin + prasugrel on Days 8 and 17, and the reference treatment was digoxin on Day 7. Pharmacokinetic parameter estimates for digoxin were calculated using non-compartmental methods of analysis using the log-linear trapezoidal method of WinNonlin Enterprise version 5.0.1. |

**Results**

**Demographics:**

A total of 18 healthy male subjects, aged 18 to 53 years, inclusive, participated in the study. Summary of demographics is presented in Table 115.

**Table 115 Summary of subject demographics**

| Subject Number | Age (years) | Gender | Race | Height (cm) | Weight (kg) | BMI (kg/m²) |
|---|---|---|---|---|---|---|
| 1 | 20 | Male | Caucasian | 176 | 70.8 | 22.9 |
| 2 | 34 | Male | Caucasian | 179 | 73.7 | 23.0 |
| 3 | 22 | Male | Caucasian | 178 | 92.2 | 29.1 |
| 4 | 36 | Male | Caucasian | 172 | 73.2 | 24.7 |
| 5 | 38 | Male | Caucasian | 181 | 89.6 | 27.3 |
| 6 | 22 | Male | Caucasian | 188 | 78.8 | 22.3 |
| 7 | 33 | Male | Caucasian | 173 | 80.6 | 26.9 |
| 8 | 29 | Male | Caucasian | 176 | 80.8 | 26.1 |
| 9 | 23 | Male | Caucasian | 182 | 83.1 | 25.1 |
| 10 | 23 | Male | Caucasian | 164 | 78.9 | 29.3 |
| 11 | 38 | Male | Caucasian | 172 | 76.0 | 25.7 |
| 12 | 19 | Male | Caucasian | 175 | 68.0 | 22.2 |
| 13 | 22 | Male | Mixed (Caucasian/Oriental) | 163 | 76.3 | 28.7 |
| 14 | 50 | Male | Caucasian | 181 | 102.4 | 31.3 |
| 15 | 23 | Male | Caucasian | 176 | 73.1 | 23.6 |
| 16 | 28 | Male | Caucasian | 164 | 66.5 | 24.7 |
| 17 | 21 | Male | Caucasian | 176 | 68.6 | 22.1 |
| 18 | 24 | Male | Caucasian | 178 | 73.0 | 23.0 |

**Assay:**

The serum and urinary samples were analyzed for digoxin using a validated liquid chromatography with tandem mass spectrometric detection (LC/MS/MS) method. The lower and upper limits of quantification for serum were 0.1 ng/mL and 20 ng/mL, and for urine were 5 ng/mL and 1000 ng/mL respectively. The accuracy and precision for the digoxin method is presented in Table 116.

**Table 116 Method validations (Intra day) for serum and urinary digoxin using LC/MS assay.**

| **Parameter** | **Serum** |
|---|---|
| linearity | 0.1 to 20 ng/ml |
| Precision (RSD) | 6.25 to 9.42% |
| Accuracy (RE) | -2.86 to 2.83% |
| LLOQ | 0.1 ng/ml |
| **Parameter** | **Urinary** |
| linearity | 5 to 1000 ng/ml |

| | |
|---|---|
| Precision (RSD) | N/A |
| Accuracy (RE) | -8.25 to 5.50% |
| LLOQ | 5 ng/ml |
| Reviewer Comment | This assay characteristics and specificity are satisfactory, representative MS chromatograms are presented. |

**Pharmacokinetics:**

**Digoxin pharmacokinetics in the presence and absence of prasugrel:**

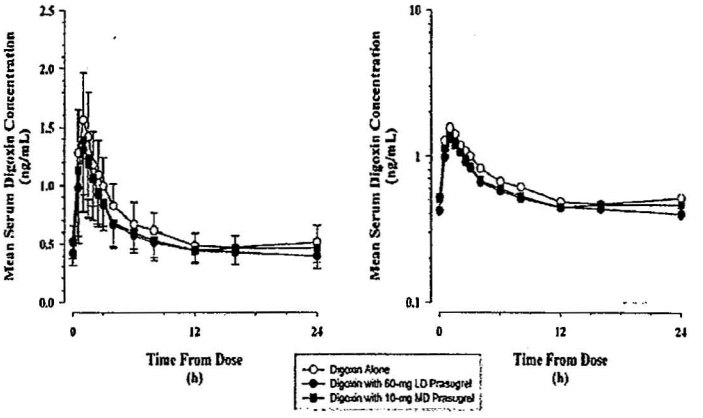



**Figure 102 Digoxin serum concentrations for all treatment arms.**

The figure above compares the serum concentration vs time profile of digoxin for all treatment arms. The exposure to digoxin decreased when it was co-administered with prasugrel.

**Table 117 Noncompartmental pharmacokinetic parameters for all treatment arms.**

| | Geometric mean (%CV) | | |
|---|---|---|---|
| Parameter | Digoxin alone (N=18) | Digoxin + prasugrel (LD) (N=18) | Digoxin + prasugrel (MD) (N=18) |
| $C_{max}$ (ng/mL) | 1.69 (21.7) | 1.50 (32.7) | 1.40 (38.7) |
| $t_{max}$[a] (h) | 1.00 (0.50-1.50) | 1.00 (0.50-2.00) | 1.01 (0.50-3.00) |
| AUC(0-τ) (ng•h/mL) | 14.9 (23.0) | 13.3 (26.1) | 13.0[b] (24.8) |
| $Ae_{0-\tau,ss}$ (mg) | 0.173 (18.3) | 0.160 (23.1) | 0.140 (28.8) |
| Fe (%) | 69.1 (18.3) | 63.9 (23.1) | 56.0 (28.8) |
| $CL_{r,ss}$ (L/h) | 11.6 (19.9) | 12.0 (23.2) | 11.1[b] (22.7) |

Abbreviations: $Ae_{0-\tau,ss}$ - mass of digoxin excreted in urine over one 24-hour dosing interval at steady-state; AUC(0-τ) - area under the serum concentration-time curve over one 24-hour dosing interval; $C_{max}$ - maximum observed serum concentration; $CL_{r,ss}$ - renal clearance of digoxin at steady-state; Fe - fraction of dose excreted unchanged; $t_{max}$ - time of $C_{max}$.

Table 117 compares the pharmacokinetic parameters for all treatment arms. $AUC_{0-24}$, $C_{max}$, $A_{e0-t,ss}$ and $\%F_e$ were decreased by 13%, 17%, 19% and 19% respectively in subjects following co-

administration with the 10 mg MD of prasugrel with digoxin compared with the subjects following digoxin administration alone.

**Table 118 Statistical comparisons of pharmacokinetics following digoxin administration in the presence of prasugrel.**

| | Least squares geometric mean (90% CI) | | | Ratio of least squares geometric mean (90% CI) | |
|---|---|---|---|---|---|
| Parameter | Digoxin + prasugrel (LD) (N=18) | Digoxin + prasugrel (MD) (N=18) | Digoxin alone (N=18) | Digoxin + prasugrel (LD) vs digoxin alone | Digoxin + prasugrel (MD) vs digoxin alone |
| AUC(0-τ) (ng•h/mL) | 13.3 (12.1, 14.7) | 12.8 (11.5, 14.1) | 14.9 (13.5, 16.5) | 0.895 (0.850, 0.943) | 0.857 (0.813, 0.903) |
| $C_{max}$ (ng/mL) | 1.50 (1.33, 1.70) | 1.40 (1.24, 1.59) | 1.69 (1.50, 1.91) | 0.888 (0.786, 1.00)[a] | 0.829 (0.734, 0.936)[a] |
| $CL_{\tau,ss}$ (L/h) | 12.0 (11.0, 13.1) | 11.1 (10.2, 12.1) | 11.6 (10.6, 12.7) | 1.03 (0.964, 1.10) | 0.957 (0.893, 1.03) |
| | Median (approx 90% CI) | | | Median difference (approximately 90% CI) [Wilcoxon sign rank test p-value] | |
| $t_{max}$ (h) | 1.00 (1.00, 1.00) | 1.01 (1.00, 1.50) | 1.00 (1.00, 1.00) | 0.000 (-0.500, 0.500) [0.835] | 0.0150 (0.000, 1.00) [0.0872] |

[a] Exceeds the bounds of the "no effect boundary" of 0.8 to 1.25, as described by regulatory guidances.

Table 118 shows the statistical comparison of the pharmacokinetic parameters for all treatment arms. $AUC_{0-24}$, $C_{max}$ and $CL_{\tau,ss}$, were decreased by 13%, 17% and 4% respectively in subjects following co-administration with the 10 mg MD of prasugrel with digoxin compared with the subjects following digoxin administration alone.

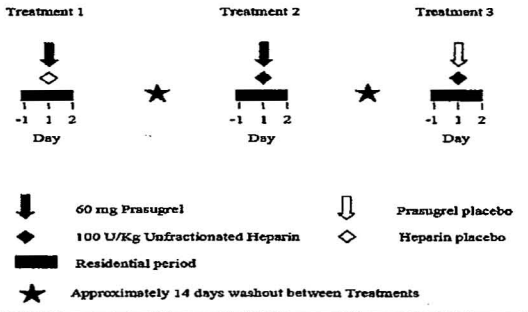
**COMMENTS:**

1. When digoxin is co-administered with prasugrel, the decrease in the systemic exposure to digoxin was only 13%. Although digoxin has a narrow therapeutic window, this change in exposure is not deemed to be clinically important and the dose adjustment of digoxin is not required.

2. The renal clearance of digoxin is dependent on the p-glycoprotein expression. When co-administered with prasugrel MD, the renal clearance of digoxin at steady state was not affected; and therefore, prasugrel does not seem to inhibit the p-glycoprotein.

### 4.2.19 Effect of Prasugrel on the Pharmacodynamic Response of Unfractionated Heparin in Healthy Subjects (H7T-EW-TAAT)

Principal Investigator: Joseph Chiesa, MD FFPM
Study center: Phase 1 Clinical Trials Unit Ltd. Old Convent of Notre Dame, 119, Looseleigh Lane, Derriford, Plymouth, PL6 5HH, UK.
Study period: 30 June 2005 to 06 September 2005
Phase of development: Phase I

| | |
|---|---|
| Objectives | Primary: To evaluate the effect of a 60 mg loading dose (LD) of prasugrel on the activated partial thromboplastin time (APTT) response following an intravenous (*i.v*) bolus dose of unfractionated heparin (UFH) in healthy subjects.<br>Secondary: To determine the degree of platelet aggregation after dosing prasugrel 60 mg alone and in combination with UFH.<br>To evaluate the effect of a prasugrel 60 mg LD on the degree of factor-Xa inhibition and change in the activated clotting time (ACT) observed after dosing with UFH.<br>To determine the safety of a prasugrel 60 mg LD in combination with UFH. |
| Study Design | A single blind (subject only), randomized three-period, three-treatment crossover study.<br>  <br> |
| Study Population | Healthy male and female subjects, aged 18 to 60 years, inclusive (N=18) |
| Investigational Drug | Prasugrel: 10 mg tablets, lot number CT520474.<br>UFH (Sodium heparin): 1000 U/mL, lot number BN 625636. |
| Comparator drug | Placebo matching prasugrel as tablets, lot number CT520475.<br>Placebo matching UFH. |
| Dosage and Administration | In Treatment 1: Single oral 60 mg prasugrel, 2 hours later, single *i.v* bolus of saline (placebo matching UFH) was administered.<br>In Treatment 2: Single oral 60 mg prasugrel, 2 hours later, single *i.v* bolus of 100 U/kg UFH was administered.<br>In Treatment 3: Single oral placebo (matching prasugrel), 2 hours later, single *i.v* bolus of 100 U/kg UFH was administered.<br>A 14 days washout period was incorporated between treatments. |
| Blood Sampling: | PD, APTT: pre-prasugrel / placebo dose, pre-UFH / saline dose, 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 7, 8, 12 and 24 hours post-UFH / saline dose. |

| | |
|---|---|
| | PD, anti factor-Xa: pre-prasugrel / placebo dose, pre-UFH / saline dose, 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 12 and 24 hours post-UFH / saline dose.<br>PD, ACT: pre-prasugrel / placebo dose, pre-UFH / saline dose, 0.5, 1, 2, 4, 6 and 8 hours post-UFH / saline dose.<br>PD, platelet aggregation: pre-prasugrel / placebo dose, 1, 2, 2.25, 3, 4, 8 and 12 hours post-prasugrel / placebo dose.<br>PD, bleeding time: pre-prasugrel / placebo dose, 4 and 6 hours post-prasugrel / placebo dose for each treatment period. |
| Assay | Blood samples for the determination of APTT and ACT values and factor Xa inhibition were assayed using standard coagulation analysis. Platelet aggregation in platelet-rich plasma was measured using the turbidometric method with 5 and 20 μM ADP as the agonist. |
| PD Assessment | Noncompartmental parameter like area under the curve of APTT ($AUC_{APTT}$), anti-Xa ($AUC_{anti\text{-}Xa}$), and ACT ($AUC_{ACT}$) were calculated from zero to time t, where time zero was time of UFH / saline dose and time t was last time point (WinNonlin). |
| Statistical methods | ACT and anti-Xa ratios were assessed using linear mixed effect models to provide ratios, and 90% CI, between the treatments. Maximum platelet aggregation (MPA), inhibition of platelet aggregation (IPA) and bleeding time ratios assessed using linear mixed effect models to provide differences or ratios, and 90% CIs, between the treatments. |

**Results**

**Demographics:**

A total of 18 healthy male Caucasian subjects, aged 18 to 50 years, inclusive, participated in the study (Table 119).

**Table 119 Subject Demographics.**

| Subject number | Age (years) | Gender | Race | Height (cm) | Weight (kg) | BMI (kg/m²) |
|---|---|---|---|---|---|---|
| 101 | 36 | Male | Caucasian | 173 | 77.2 | 25.8 |
| 102 | 30 | Male | Caucasian | 182 | 76.2 | 23.0 |
| 103 | 22 | Male | Caucasian | 178 | 73.9 | 23.3 |
| 104 | 23 | Male | Caucasian | 178 | 64.3 | 20.3 |
| 105 | 50 | Male | Caucasian | 175 | 89.9 | 29.4 |
| 106 | 19 | Male | Caucasian | 175 | 65.9 | 21.5 |
| 107 | 25 | Male | Caucasian | 178 | 67.9 | 21.4 |
| 108 | 22 | Male | Caucasian | 184 | 93.4 | 27.6 |
| 109 | 41 | Male | Caucasian | 176 | 81.9 | 26.4 |
| 110 | 22 | Male | Caucasian | 191 | 84.1 | 23.1 |
| 111 | 22 | Male | Caucasian | 190 | 82.1 | 22.7 |
| 112 | 25 | Male | Caucasian | 182 | 79.6 | 24.0 |
| 113 | 19 | Male | Caucasian | 184 | 75.8 | 22.4 |
| 114 | 18 | Male | Caucasian | 181 | 74.4 | 22.7 |
| 115 | 19 | Male | Caucasian | 184 | 76.1 | 22.5 |
| 116 | 31 | Male | Caucasian | 183 | 72.5 | 21.6 |
| 117 | 31 | Male | Caucasian | 173 | 67.2 | 22.5 |
| 118 | 42 | Male | Caucasian | 188 | 105.0 | 29.7 |

**Pharmacodynamics:**

**Activated Partial Thromboplastin Time, Factor Xa Inhibition and Activated Clotting Time:**

Activated Partial Thromboplastin Time, Factor Xa Inhibition and Activated Clotting Time Values of anti-Xa were below the quantification limit of 0.06% in predose, placebo, and