- Clopidogrel pharmacokinetics was significantly affected by dose. Whereby, the relative bioavailability was reduced by 50% after a 600-mg LD compared to the 75-mg MD indicating that an 8 times difference in dose of 600-mg LD to 75-mg MD resulted in active metabolite exposures that were only 3.9 times higher. In addition, dose was a significant covariate on the first-order absorption rate constant of R-130964 and explained the earlier time of peak concentration (30 minutes) of R-130964 after a 75-mg MD dose compared to the 600-mg loading dose.
- The PK/PD analysis described the relationship between concentration-time profiles of prasugrel and clopidogrel active metabolites and the time-course of MPA. Following LD of clopidogrel and prasugrel, a rapid decline in MPA is observed with the median MPA achieved being lower following prasugrel (33.2%) compared to clopidogrel (56.8%) at 24 hours postdose. The median predose MPA tended to be higher during prasugrel MD (42.1%) compared to that at 24 hours after LD and remains relatively stable throughout the sampling interval. Comparatively, the MPA following clopidogrel LD and MD (53.7%) although consistent across regimens does not provide the same extent of MPA suppression as prasugrel, albeit the difference is less pronounced following MD. The details of the PK/PD analysis can be found in the sponsor report H7T-MC-TABR (\\Cdsesub1\evsprod\NDA022307\0000\m5\53-clin-stud-rep\533-rep-human-pk-stud\5335-popul-pk-stud-rep\h7t-mc-tabr-pop-pk).

Study TAAL

Objectives

The objective of the population pharmacokinetic analysis was to characterize the population pharmacokinetics of R-138727 in subjects with ACS that underwent PCI.

Data

Data for population pharmacokinetics were available from 1159 subjects receiving prasugrel. The patient population predominantly consisted of Caucasians (N=1107). Other demographic characteristics of the patient population are provided in the Table 6.

Table 6: Summary of baseline demographics in the pharmacokinetic subset of Study TAAL
(per sponsor report H7T-MC-TAAL; Table TAAL.9.1)

	Age (yrs)	Weight (kg)	CGCL (mL/min)	Gender		Diabetes	
				Male	Female	Yes	No
Range	28–93	45–158	20–379	875	284	285	874
Mean (CV as %)	61 (18)	83 (19)	105 (36)				

Abbreviations: CGCL = Cockcroft-Gault Creatinine Clearance; CV = coefficient of variation; yrs = years.

Plasma samples for the determination of concentrations of prasugrel's inactive metabolites (R-106583, and R-119251) were collected after administration of the 60-mg LD and/or following 10-mg MD administration. Collection and measurement of prasugrel active metabolite (R-138727) could not be achieved in Study TAAL due to the complexities of handling samples at the study sites, including complicated and labor intensive blood collection, difficult processing procedures, and reagent requirements. Therefore, a multilinear regression correlation model was used to quantitatively predict R-138727 concentrations from its 2 downstream inactive metabolites (R-119251 and R-106583). The predicted R-138727 concentration versus time data combined with dosing information and pre-specified subject factors of clinical and demographic interest were analyzed, using population techniques, to characterize R-138727 pharmacokinetics.

Methods

Multi-Linear Regression Correlation Model:

A structural multi-linear regression correlation model for the prediction of prasugrel's active metabolite, R-138727, was developed using concentration-time data from the two downstream inactive metabolites of R-138727, R-119251 and R-106583. Log transformed concentrations were used in the assessment of correlation.

Estimates of the model parameters and error terms were obtained by fitting the concentration-time data by means of the nonlinear mixed-effects modeling program, NONMEM (version V) with PRED.

Patient factors were examined for a reduction in variability or bias in the prediction of R- 138727 and included: dose, age, Cockcroft-Gault creatinine clearance, serum creatinine, sex, smoking status, body weight, and co-administration with food or ketoconazole.

The correlation model was qualified by predicting the concentrations of R-138727 from the concentrations of R-119251 and R-106583 for studies TAAD and TABR. The predictive performance of the model was further tested with data from studies TABW, TACG, TAAN and TABZ.

Population Pharmacokinetics:

A three-compartment model with zero-order absorption, proportional between-patient variability on apparent clearance of active metabolite and proportional residual error was selected as the structural model for prasugrel active metabolite. As the R-138727 concentrations utilized in the pharmacokinetic model themselves reflected predicted values from the multi-linear regression correlation model, the potential influence of subject-specific factors using pharmacostatistical methods for covariate screening and selection were not applied. Rather, any influence on the posthoc derived R-138727 systemic exposures was assessed descriptively.

Details of the methods can be found in the sponsor report H7T-MC-TAAI Population Pharmacokinetics Report (\\Cdsesub1\evsprod\NDA022307\0000\m5\53-clin-stud-rep\533-rep-human-pk-stud\5335-popul-pk-stud-rep\h7t-mc-taal-pop-pk)

Results

- The correlation model for predicting the active metabolite concentrations is represented by the equation below. Log-transformed concentration of R-11925 and R-106583 were used to perform the analysis.

$$R\text{-}138727 = A^* R\text{-}119251 + B^*R\text{-}106583^*EXP(-C^*TIME)+D$$

- The model showed good correlation with only a minor deviation ~6% from the line of unity and described the variability within ~4.5%.
- Age, dose, co-administration of ketoconazole and food were identified as significant factors relating to the differences between R-138727 and R-106853. Final parameter estimates of the correlation model are shown in the table.

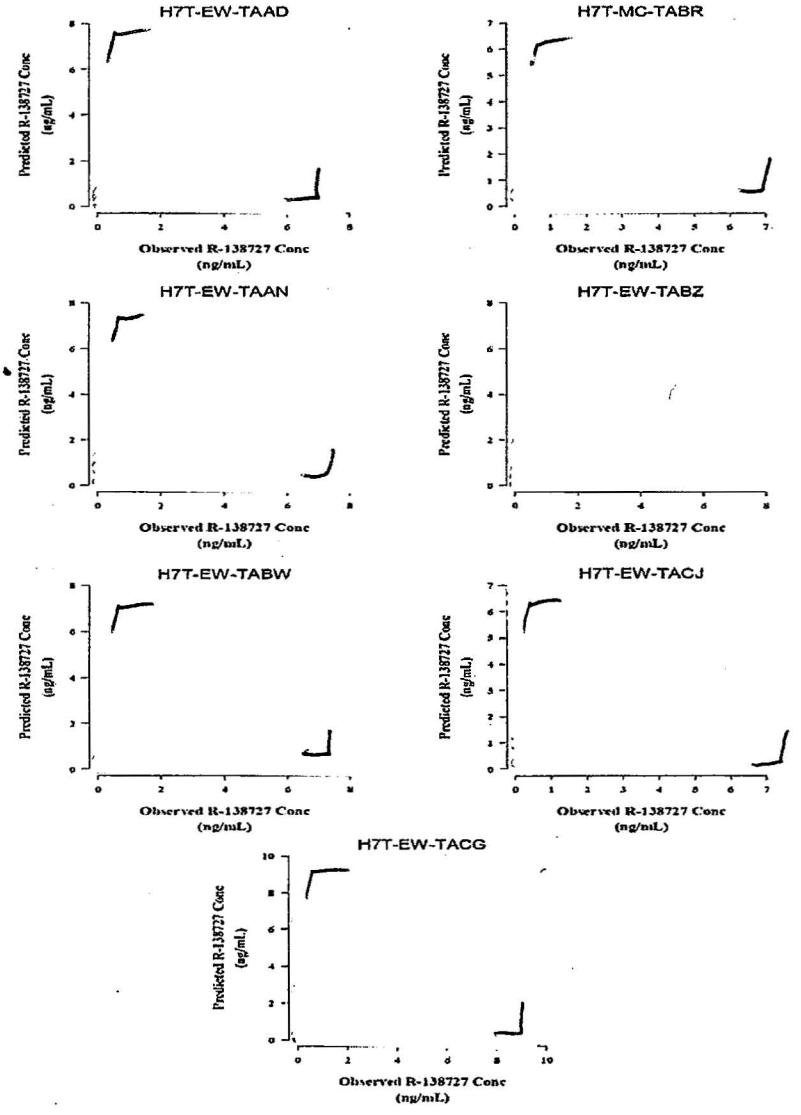
Table 7: Final correlation analysis model
(per sponsor report H7T-MC-TAAI; Table 2, page 116)

Parameter	Estimate	%Standard Error of Estimate
Correlation of R-119251 to R-138727 (A)	0.896	1.70
Correlation of R-106583 to R-138727 (B)	0.354	6.98
Correction of Correlation of R-106583 to R-138727 over Time (C)	0.807	5.34
Intercept to Correct between Loading and Maintenance Doses (D)	-0.305	9.34
Effect of Ketoconazole on the Correction of Correlation of R-106583 to R-138727 over Time (Effect on C)	-0.586	4.81
Effect of Food on the Correction of Correlation of R-106583 to R-138727 over Time (Effect on C)	-0.477	8.53
Effect of Dose on the Correlation of R-106583 to R-138727 (Effect on B)	-0.218	16.2
Effect of Age on the Correction of Correlation of R-106583 to R-138727 over Time(Effect on C)	0.0103	23.0
Proportional Residual Error	34.8%	10.0

Proportional residual error represented as %CV: calculated as %CV = SORT(SIGMA(N))*100%.

- The prediction was within 6% of the observed data across different studies thus establishing the predictive ability of the model as shown in **Figure 18.** The details of the multilinear correlation regression analysis can be found in the sponsor report H7T-MC-TAAL; Appendix TAAL.4 (\\Cdsesub1\evsprod\NDA022307\0000\m5\53-clin-stud-rep\533-rep-human-pk-stud\5335-popul-pk-stud-rep\h7t-mc-taal-pop-pk)

Figure 18: The correlation model performs reasonably well across different studies.
(per sponsor report H7T-MC-TAAL; Figure 5, page 119)



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- The pharmacokinetics of R-138727 was adequately described by a three compartment model with zero-order absorption. The final population pharmacokinetic parameter estimates are shown in the table

Table 8: Final population pharmacokinetic parameter estimates for Study TAAI.

(per sponsor report H7T-MC-TAAL; Table TAAL.9.2)

Parameter Description	Population Estimate (%SEE)	Between-Subject Variability[a] (%SEE)
Duration of Absorption	0.0865	--
D1 (hr)	(94.9)	
Rate Constant for First-Pass Formation of R-138727	5.77	--
K12 (hr^{-1})	(57.2)	
Fraction of First Pass Formation of R-138727	55.0 FIXED	--
FFP (%)		
Apparent Clearance of R-138727	120	52.7
CL20/F (L/hr)	(2.47)	(10.2)
Apparent Volume of Distribution for R-138727	74.3	--
V2/F (L)	(6.82)	
Rate of R-138727 Formation from R-95913	0.0517	--
K32 (hr^{-1})	(5.51)	
Proportional Residual Error for R-138727[b]	65.9% (2.81)	

Abbreviations: CV = coefficient of variation; SEE = standard error of the estimate.

[a] %CV = (SQRT(EXP(OMEGA(variance estimate))-1))*100%

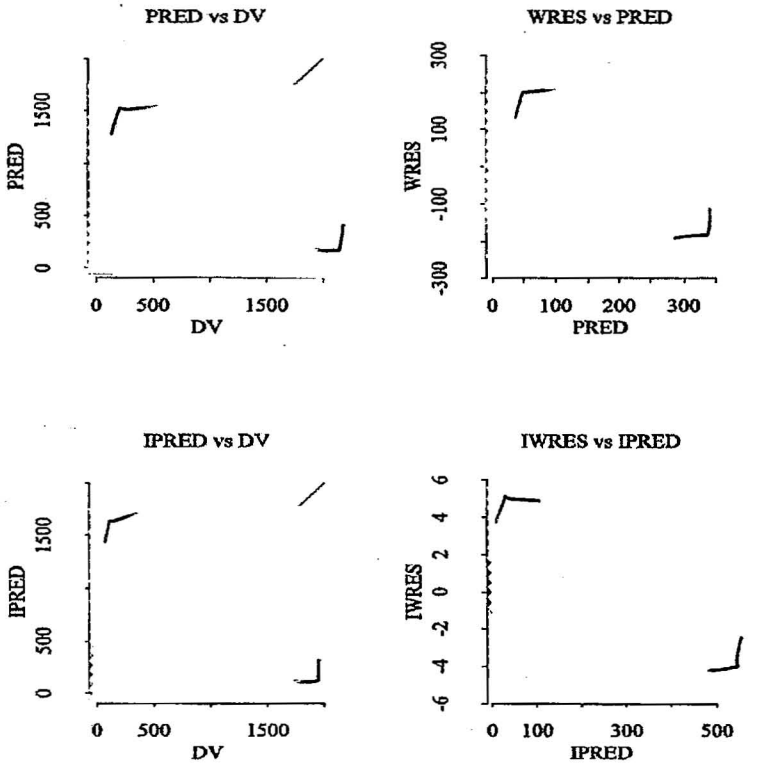
[b] %CV = SQRT(SIGMA(variance estimate))*100%

- The systemic exposure increased with decreasing body weight; whereby median exposure in subjects weighing <60 kg were approximately 35% higher compared to subjects having a mean body weight of 84 kg.
- The systemic exposure of R-138727 was not appreciably affected by age, body mass index, gender, diabetes, smoking, and renal impairment.
- The exposure of prasugel active metabolite is comparable between healthy subjects, subjects with stable atherosclerosis and the target population; therefore, properties observed in healthy subjects are applicable to subjects with acute coronary syndromes and stable atherosclerosis.

Reviewer's Comments

- The population pharmacokinetic and the PK/PD analyses for studies TAAD and TABR are acceptable. The sponsor has done a commendable job of characterizing the concentration-IPA relationship for both prasugrel and clopidogrel.
- The sponsor chose an exponential function to describe the relationship between the clearance of R-138727 and body weight in studies TAAD and TABR based on the data. This relationship was predominantly driven by a single extremely high body weight (>140 Kg). Such a relationship is not physiologically representative as unusually high clearances will be achieved at the higher body weights.
- The multilinear correlation model developed for the prediction of the R-138727 concentration of the downstream inactive metabolites is acceptable and the predictive performance of the model is reasonable.
- Given the systematic under prediction of individual predictions (IPRED) and large weighted residuals associated with high concentration (see **Figure 19**), the population pharmacokinetic model for study TAAL is not acceptable.

Figure 19: Goodness-of-fit for final prasugrel PK model for Study TAAL.
(per sponsor report H7T-MC-TAAL; Appendix TAAL.3)



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/s/

Elena Mishina
5/23/2008 01:53:27 PM
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Raj, we are signing without Sripal, Patrick knows that.

Rajnikanth Madabushi
5/23/2008 02:09:14 PM
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